AN INTRODUCTION

TO

Chemical Pharmacology

Pharmacodynamics in Relation to Chemistry

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PREFACE

Before the foundation of a science is definitely laid, many facts must be established, analyzed and correlated. In obtaining these facts many methods may be used and many fields studied. This is especially true of the science of pharmacology, the foundation of which rests on anatomy, physiology, chemistry and physics. It is natural therefore, in the development of pharmacology, that research should have proceeded in waves, during which anatomy, physiology, physics or chemistry, played the predominant rôle. The sequence of such waves may be due to the investigator following the line of least resistance or to the influence of a dominant character in the science. Finally however, such waves are spent, and new methods of attack are developed, often in a new field.

The period of pure physiological methods in which changes in blood pressure, respiration or heart rate have been recorded, for the present seems spent, and many are convinced that chemistry now offers the most hopeful method for the solution of many problems of pharmacology.

The changes in blood pressure, respiration, secretion or metabolism, after the administration of drugs are fundamentally due to a chemical reaction between the drug and the tissue. Physical changes also result, and it is often difficult to separate the purely physical from the purely chemical. The fact that we know little of the chemistry involved in many cases where the dynamic reaction is most pronounced cannot be used as an argument against the importance of a study of the Chemical Pharmacology. Rather our ignorance of such a reaction should stimulate chemical investigation concerning many life processes. The dictum of the great physiologist who said "Ignoramus, Ignorabimus," must apparently remain true, until chemical investigation gives the explanation.

The field of Chemical Pharmacology is so immense that it is possible to present only a small part of it within accepted

limits. However, much of it is co-extensive with Biological Chemistry and the aim of this work is to select for emphasis those chemical reactions, which, in the various branches, have an especial relation to pharmacology.

The following facts, therefore, have been collected and are presented from the point of view of pharmacology, in the belief that students of chemistry, pharmacy, biology, and medicine should become more familiar with this branch of the subject. The writer is also of the opinion that in the teaching of pharmacology, the chemical side should receive much more attention than it does at present. In this way the student will have an opportunity to review and add to his previous work in chemistry, and enter the clinical years better equipped and with a fuller appreciation of the most promising avenue of advance.

In the preparation of this work many sources of information have been used. Original papers are not quoted because in an elementary work the student wishes a general survey of the field and when he attains the stage in which he is able to digest literature the sources are readily found. The following works among others have been freely used and contain the original references: Frankel's Arzneimittel Synthese; The Chemical Basis of Pharmacology—Francis and Fortescue—Brickdale; Cushny, Text-book of Pharmacology; Sollmann, Manual of Pharmacology; Richter's Organic Chemistry; Mathews, Physiological Chemistry; Henry's Plant Alkaloids; Barger, Simpler Natural Bases; Kobert's Lehrbuch der Intoxikationen; Armstrong, Carbohydrates and Glucosides; Haas and Hill, Chemistry of Plant Products. I am especially indebted to my colleague in the department, Harry Victor Atkinson, for help in proof reading and for many suggestions.

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CHEMICAL PHARMACOLOGY

I. INTRODUCTION

Pharmacology is the science which deals with drugs and the reactions of living matter brought about by drugs. The term, "drug" is derived from the Dutch or Anglo-Saxon word, "drugan," meaning to dry, and was formerly applied to dried medicinal plants. At that time materia medica was entirely of plant origin, at present the term includes all substances used as remedial agents.

It is often desirable to define foods, drugs, and poisons; but the distinctions at best are unsatisfactory and arbitrary. Foods are substances, which, when taken into the alimentary tract are digested, build up tissue, supply energy, repair waste, and do not injure health. A poison is anything that, in amounts of fifty grams or less, injures or destroys life, when taken by mouth. There is, however, no satisfactory definition of a poison, and fifty grams is an arbitrary amount; some set the limit at one gram. Drugs and poisons are relatively little acted on by the body, are but little digested or hydrolyzed, and as a rule do not supply energy, and do not repair waste. Some substances, may be remedies, foods, or poisons, according to the method of administration; *e.g.* egg albumen and peptone, are foods when taken by mouth, but they are violent poisons if given intravenously. Iron salts too, when taken by mouth are valuable remedies in some cases of chlorosis, but they also may exert a toxic action if given by vein. Some foods such as milk, fish and strawberries produce most violent toxic symptoms, when taken even in small amounts, in some persons who are said to have an idiosyncrasy for those particular substances.

Classifications.—Drugs may be classified as:

1. Inorganic or mineral

2. Organic $\begin{cases} \text{Animal} \\ \text{Vegetable} \end{cases}$

or as was done by chemists about the middle of the 17th Century, as animal, vegetable, and mineral.

When it was discovered that certain compounds are found in both animals and plants, the distinction between animal and vegetable chemistry disappeared and to include both the broader term "organic" was substituted. It was believed then that "vital force" was necessary for the formation of organic compounds, and that these could not be produced by the chemist. In 1828, however, Wöhler prepared the organic substance, "urea" from the so-called inorganic compound, ammonium isocyanate:

$$NH_4\,CNO = CO\underset{NH_2}{\overset{NH_2}{\diagdown}}$$
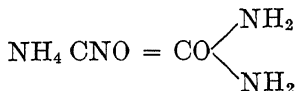
Ammonium isocyanate   urea

Since this discovery a sharp distinction between organic and inorganic compounds cannot be made. Yet, the term "organic" has survived, and includes not only those substances formed in plants and animals, but also most carbon compounds. Many synthetic drugs which contain carbon, are in reality no more organic than calcium carbonate, but are included in organic chemistry because of relationship, or of historical interest.

The term vital force or vital activity is still used by physiologists and pharmacologists especially in discussing absorption and secretion. It means simply that the known physics and chemistry is inadequate to explain all the phenomena, and that the explanation of some life processes is still unknown.

In addition to carbon, the chemistry of drugs includes other important elements. Twelve elements are necessary for life and are consequently found in varying amounts in all organic matter. These elements are: C, H, N, O, S, P, Na, Mg, Ca, Fe, Cl, and K. If any of these elements be extracted from living matter, death results.

If the amount of each element in a substance is determined, we say that the analysis is *ultimate*. The elements however do not exist in a free state in plants or animals, but are combined to form fats, proteins, carbohydrates, volatile oils, gums, gum resins, alkaloids, glucosides, salts, etc. These, when they are definite chemical compounds, are called proximate principles, and the determination of the amount of these substances is *proximate* analysis.

Proximate principles because of their reaction are divided into acid, neutral, and basic principles. The following scheme is illustrative:

Organic Drugs

Animal   Vegetable

Proximate Principles

1. Proteins

2. Lipoids or ether extracts............... $\begin{cases} \text{Fats} \\ \text{oils} \\ \text{cholesterines} \\ \text{waxes} \end{cases}$

3. Carbohydrates..................... $\begin{cases} \text{Celluloses} \\ \text{dextrin} \\ \text{gums} \\ \text{sugars} \\ \text{pectins} \\ \text{starches} \\ \text{glycogen} \end{cases}$

4. Alkaloids
5. Glucosides—which include saponins and sapotoxins.
6. Volatile, ethereal, or essential oils.

7. Stearoptenes..................... $\begin{cases} \text{Camphor} \\ \text{menthol} \\ \text{thymol} \end{cases}$

8. Resins $\begin{cases} \text{oleoresins} \\ \text{gum resins} \\ \text{balsams} \end{cases}$
9. Organic acids.

10. Coloring matter or pigments.......... $\begin{cases} \text{Chlorophyll} \\ \text{carotin} \\ \text{xanthophyll} \end{cases}$

11. Ash or inorganic residue which remains when drugs or plants are ignited to constant weight at red heat.

While according to their reaction these bodies are acid, basic, or neutral; the term "neutral principle" is often used in a different

sense. It is applied especially to those neutral physiologically active bodies that do not belong to a more definite chemical class; *e.g.* picrotoxin *is a neutral principle* and is known only by that term. Glucosides are also neutral, but are rarely referred to as such, because the term, "glucoside" is more specific than "neutral principle." An alkaloidal salt may be neutral in reaction but is never referred to as a neutral principle, but is always classified with alkaloids.

Proximate principles, when acted upon by bacteria, yeasts, enzymes, heat or chemical agents, give rise to pure chemicals of simpler composition such as paraffins, alcohols, ethers, acids, etc., and these form the basis of organic chemistry. Many of these chemicals are used in medicine, and a knowledge of the structure of the simple organic bodies is essential for a study of the more complicated proximate principles, and for the study of pharmacology. Pharmacology in the last analysis is applied organic chemistry, or the chemistry and reactions of living matter, as modified by changes in environment. The cause of these changes whether due to noxious gases, decomposition products of foods, impurities in water, bacterial toxins or other injurious or modifying agent in the widest sense comes under the term "drug." However, the study of pharmacology is usually limited to those drugs that are used in therapeutics, or that are especially valuable in investigative work.

THE COMPOSITION OF DRUGS
CARBON

Carbon in the elemental condition, and in the form of CO, CO_2 and the carbonates is included in inorganic chemistry. All other carbon compounds are, for convenience, classified under organic chemistry.

The word, "carbon" is derived from the Latin, "carbo," meaning coal, and the ordinary test for carbon is the carbonizing action or the becoming coal-like on burning. If we partially burn a piece of wood, paper, or almost any organic substance it chars. There is a similar action, if we add strong sulphuric to it. The acid extracts the water part of the molecule leaving carbon partially free, or charred. If enough oxygen is present in the

molecule, or if burning continues, the carbon is completely oxidized and disappears as a gas, CO or CO_2, but always as CO_2 if enough oxygen be present. Most carbon compounds when taken into the body are oxidized in a similar way, but the oxidative potential of the body is not sufficiently high to oxidize elementary carbon, nor even such compounds as cellulose.

Not all organic compounds carbonize on heating. If oxalic acid, COOH. COOH, be heated, it breaks down into CO_2, CO and H_2O without charring. The reason being that it contains enough oxygen in the molecule, to completely oxidize the carbon present. The form in which carbon occurs in the molecule is also an important factor in determining whether or not it will carbonize on heating. When present in the form of carboxyl, as it is in the case of oxalic acid, it is already oxidized and in a bound or

gaseous form $-C\diagup^O_{\diagdown OH}$ so that carbonization is impossible

since it is already past that state. It may break either as

$H-C\diagup^O_{\diagdown OH} \rightarrow H_2O + CO$ in which case, the water is split

directly from the molecule; or in oxalic acid it may break into CO_2 and H_2O, the H in the acid being oxidized to water by the oxygen of the air;

$$\begin{array}{l} COOH \\ | \\ COOH + O = 2CO_2 + H_2O \end{array}$$
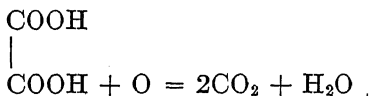
There is a general tendency of organic acids, especially when heated under the influence of strong dehydrating agents, to break up, giving off CO_2 or CO from the carboxyl group: *e.g.*

Formic acid $\quad HCOOH + H_2SO_4 = CO + H_2O$
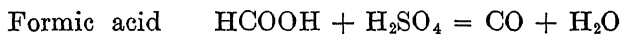
Malonic acid heated to 140° yields acetic acid and CO_2

$$\begin{array}{l} COOH \\ | \\ CH_2 = CH_3COOH + CO_2 \\ | \\ COOH \end{array}$$
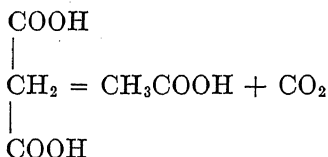
In case of aliphatic compounds, the tendency to yield CO_2 is greater where two carboxyl groups are attached to one carbon atom.

COOH

Gallic acid when heated
yields pyrogallic acid and
carbon dioxide

$+ CO_2$

OH   OH   OH   OH

OH   OH
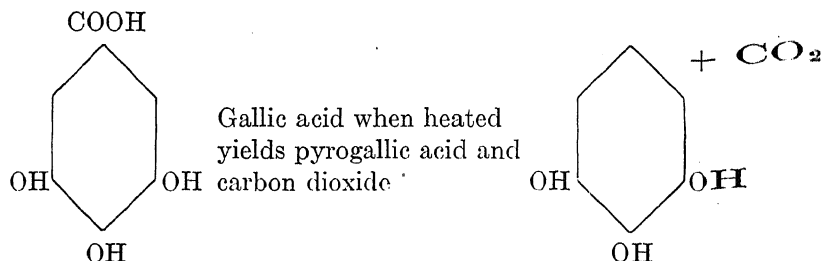
For these reasons carbonization is not a general test for organic substances. The formation of CO_2 is a more definite test.

The presence of carbon can be shown in those cases that do not char, if the gas evolved on heating be collected in $NaOH$ or $Ca(OH)_2$; this results in the formation of a carbonate

$$2NaOH + CO_2 = Na_2CO_3 + H_2O$$
$$\text{or } Ca(OH)_2 + CO_2 = CaCO_3 + H_2O$$
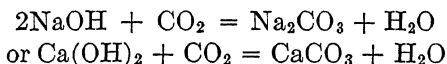
The presence of CO_2 in the respired air can be shown this way. The formation of a carbonate is a general proof of the presence of carbon whether or not there be carbonization.

Carbon, prepared by heating bone—bone charcoal, or wood—wood charcoal, in absence of air or oxygen, is used in medicine in some cases of stomach disease, and in other cases, as an absorbent of gases. It will also absorb toxins as in diphtheria, and has been sometimes applied locally for this purpose. It is used in chemical analysis as a clarifying agent to absorb colors. When carbon is wet its value as an absorbent for gases is greatly lessened, for this reason, its value when given to absorb gases in the stomach is questionable.

Carbon dioxide in the body is the specific stimulus of the respiratory centre. It is generated by the oxidation of the carbon of the food. The fate of carbon and hydrogen is very important since in the body the oxidation of the carbon and hydrogen of the food is the exclusive source of heat and therefore of body temperature. The calorific value of foods in the body is the same as they yield in the calorimeter, but in the body oxidation pro-

ceeds at about 40°C. while in the calorimeter high temperatures are necessary to complete the oxidation.

Test for Hydrogen

The presence of carbon and hydrogen together in drugs or organic compounds can be shown by heating the dried material with desiccated copper oxide in a glass tube. The copper oxide is reduced in the presence of organic matter and the free O oxidizes the C and H to CO_2 and H_2O. The CO_2 is detected in the usual way with lime water. The water formed will condense in the cold part of the tube in which the substance is heated. The formation of water is proof of the presence of hydrogen. If desired, the water so formed may be collected in sulphuric acid and weighed as is done in ultimate analysis. Hydrogen in the free form is not used in medicine.

NITROGEN

Nitrogen as a free gas is characterized by its chemical inertness. A burning splinter immersed in a vessel containing nitrogen gas is immediately extinguished. Animals and plants die if confined in an atmosphere of nitrogen. For this reason, it was formerly called Azote (against life). It is a constant constituent of all plants and in combination is an indispensible food. It is also essential in the air as a diluent of oxygen, since life in pure oxygen is impossible. Because of its inertness, the gas has been used in therapeutics, in the pleural cavity, to collapse one lung in case of tuberculosis of that organ; the idea being to rest the lung by collapse and so permit healing, also by preventing movement, to lessen the tendency to spread the diseased condition. Nitrogen in plants exists mainly in the form of:

1. Proteins
2. Amino acids
3. Amines
4. Alkaloids
5. Phosphatides
6. Nitrates
7. Cyanides
8. Ammonia
9. Some glucosides
10. Mixed compounds, etc.

To determine whether or not, a drug or any organic matter contains nitrogen, the following tests may be used:

Test for Nitrogen

1. In many cases, when an organic substance is burned, an odor like burnt feathers is given off; this is characteristic of the presence of N.

2. Lassaigne's test: Organic bodies always contain carbon, therefore if a small amount of the substance be heated in a dry test tube to redness, with Na, or K, and the test tube be immediately plunged into water in a beaker, the C and N, if present, will combine with the Na, or K to form KCN or NaCN, which may be detected by treating with a mixture of ferric and ferrous salts, Prussian blue being formed.

Freshly prepared ferrous sulphate with a drop or two of ferric chloride added, is a suitable reagent. During the operation some ferrous hydrate is converted into ferric hydrate, which when acidified with HCl is converted into ferric chloride. The reactions may be illustrated as follows:

1. $2C + 2N + 2K \rightarrow 2KCN$
2. $6KCN + FeSO_4 \rightarrow K_4Fe(CN)_6 + K_2SO_4$
3. $Fe_2Cl_6 + FeSO_4 + 8NaOH \rightarrow Fe_2(OH)_6 + Fe(OH)_2 + 6NaCl + Na_2SO_4$
4. $2Fe_2(OH)_6 + 3K_4Fe(CN)_6 + 12HCl \rightarrow Fe_4\{(Fe)(CN)_6\}_3 + 12KCl + 12H_2O$

Or

1. $FeSO_4 + 2KOH = Fe(OH)_2 + K_2SO_4$
2. $Fe(OH)_2 + 2KCN = Fe(CN)_2 + 2KOH$
3. $Fe(CN)_2 + 4KCN = K_4Fe(CN)_6$
4. $2Fe_2Cl_6 + 3K_4(Fe(CN)_6) = Fe_4\{Fe(CN)_6\}_3 + 12KCl$
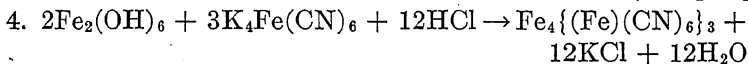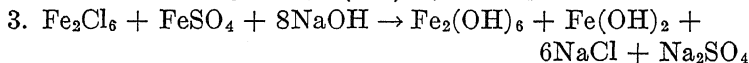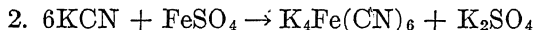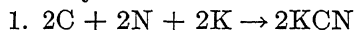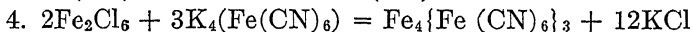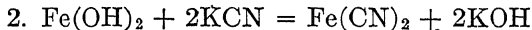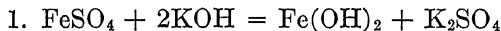
If the blue or green color does not quickly develop, a drop of ferric chloride should be added. It often happens that not enough Prussian blue is formed to give the blue color. The formation of a green solution is sufficient proof.

Nessler's Test.—Nessler's reagent produces a brown precipitate of $NHg_2I. H_2O$ in solutions containing ammonia. If only a trace of ammonia be present a yellow or reddish yellow color is produced. This reaction is used to determine ammonia in water.

3. Kjeldahl's Test for Nitrogen.—Also the estimation of the amount of nitrogen. This test consists essentially in boiling the organic substance with strong H_2SO_4 which destroys the organic matter and converts the nitrogen into $(NH_4)_2SO_4$; this is then tested for NH_3 which if present, proves the presence of nitrogen. The method here described is the most used one for determination of the amount of nitrogen and protein material in drugs, foods, and other products. It is carried out as follows:

Place 1 to 5 grams of the dry material, accurately weighed in a Kjeldahl flask of about 500 cc. capacity. Add 30 cc. H_2SO_4 conc. and about 0.5 gram mercuric oxide, or pure mercury. The mercury acts as a catalytic agent and hastens oxidation. Boil over a free flame until the solution is a pale straw color, white or clear water color. Sometimes the substance, on boiling, bumps; to prevent this, kaolin, zinc or other finely divided inert material is added, which prevents bumping by stirring the mixture so that the heat is uniformly distributed and no point of the glass becomes heated to a much greater extent than the rest. Many substances foam so much on heating that paraffin or some other substance is added to lessen this. After the substance has boiled until it is milky or water color, the flask is removed and about 0.5 gram of $KMnO_4$ added, to complete the oxidation. The nitrogen is now in the form of $(NH_4)_2SO_4$, which has been proved by isolation and analysis of the crystals. An excess of strong $NaOH$ added to this solution liberates NH_3, which may be distilled and caught in a solution of acid of a known strength and titrated, e.g., $(NH_4)_2SO_4 + 2NaOH = Na_2SO_4 + 2NH_4OH$. If we collect this, say in 50 cc. of $N/10$ H_2SO_4 we know how much NH_3 is present by titrating the excess of the acid with $N/10$ $NaOH$. 1 cc. of $N/10$ H_2SO_4 = .0017 grams NH_3 or .0014 grams N. For example: one gram of a substance treated as above, with H_2SO_4 was made strongly alkaline and distilled into 50 cc. $N/10$ H_2SO_4. When this distillate was titrated with $N/10$ $NaOH$ it was found that it took 20 cc. $NaOH$ to neutralize. Therefore, the nitrogen in one gram of the substance is equivalent to 50 cc. $N/10$ − 20 cc. $N/10$ = 30 cc. $N/10$ acid. Since 1 cc. $N/10$ acid = .0014 grams N, 30 cc. = 0.042 grams N or the amount in one gram of the substance and the percentage is 100 times 0.042 = 4.2 per cent.

Since protein contains on the average of 16 per cent. N, it is customary to multiply the amount of N by 6.25 to obtain the per cent. of protein (6.25 times 16 per cent. = 100 per cent.). All protein, however, does not contain exactly 16 per cent. nitrogen, so that in some cases the factor 6.25 is not exact.

Various non-essential details in the method are used in some cases, such as the addition of potassium sulphate to raise the boiling point and the addition of other catalytic agents.

OXYGEN

Oxygen.—In addition to carbon, hydrogen and nitrogen most organic compounds also contain oxygen. Because these elements occur so universally in organic matter, they have been called organogens. This term has also been used to include the other essential ingredients of plants. The well known chemical properties of oxygen in the gaseous form cannot be demonstrated in organic bodies. There is no simple practical method for its direct determination. Its quantity is usually calculated in analyses by the difference between 100 per cent. and the sum of the percentage of the other elements present, after the other elements have been determined. Ever since the importance of oxygen became known, attempts have been made to use it in failing respiration. As a rule, however, it is of little value, because in most cases the asphyxiation that suggests its use, is really due to a failure of the heart. Again the hemoglobin of the blood, which is the oxygen carrier to the tissues, is in most cases saturated, so that the administration of pure oxygen can aid but little. In cases of severe hemorrhages or of poisoning carbon monoxide, nitrites, chlorates, nitrobenzol, etc. which destroy the oxygen carrying power of the blood, it has been shown that when pure oxygen is administered the oxygen content of the red cells and serum is increased somewhat, and this slight increase may be very beneficial. If the gas be administered under tension there may be sufficient oxygen increase in the blood to cause convulsions in animals. Hilarity and other nervous influences have been observed in man. There is some increase in metabolism but not sufficient to be of benefit in any given case.

Ash.—If an organic substance contains C, H, N, and O only, it will leave no residue or ash on burning. Plant drugs leave

an ash which contains varying amounts of Na, K, Mg, Ca, Cl, P, S, Si and Fe, as necessary ingredients. Depending on the soil on which they were grown, plants may also contain As, Ba, Mn, I, Zn or any other element, not as essential, but as accidental elements.

Before testing for these elements, it is necessary to reduce the plant or drug to an ash. The organic matter must be completely destroyed because the inorganic elements react only as ions and ionization is prevented and masked by organic matter.

To aid in the "ashing" some oxidizing agent which can be driven off by heat may be used, e.g., H_2O_2 — HNO_3, etc. or, in case we do not wish to test for K, or Cl, $KClO_3$ may be used. A small amount of any of these agents aids oxidation and the reduction of the substance to a white or grey white ash. The ash of plants is rarely pure white because of the presence of iron, and other elements. After the ash has been prepared, it is dissolved usually in dilute HCl and tests for the elements made with the solution. The following scheme will show how to prepare the ash of plants for analysis.

Weigh out 5 grams of the root, leaves, or whatever is to be determined, and place in a platinum or porcelain crucible or dish. Heat it gradually on a thin sheet of asbestos over a Bunsen burner. In order to avoid loss by volatilization, tilt the dish or crucible, and at the beginning keep it covered. The material first chars, then glows beginning at the top and gradually extending to the bottom. Carefully regulate the heat to a dull redness (about 700°C.). If heated higher than this, there is a loss of alkali chlorides by volatilization and the phosphates fuse about the particles of carbon, so that this cannot be oxidized completely. A muffle furnace may be used to complete the oxidation. Finally, when the ashing is complete, weigh and calculate the amount.

In an actual determination, several weighings are made, and the substances heated between these weighings, until the weight keeps constant. We know then that oxidation is complete.

The ash of plants contains considerable carbon dioxide, which may be found with sodium, potash, or any of the other elements, in the form of a carbonate and imparts to the ash an alkaline reaction. The use of plant ash in earlier times for the formation

of soap, is due to this fact. In the analysis of an ash, therefore, we determine the amount of CO_2, sand, *silica*, Fe, Al, Ca, Mg, and acid radicals, SO_3, P_2O_5, etc. These are in very small amounts and while absolutely essential to the life of the plant, and in the main, essential ingredients of foods, they are not present in sufficient amount to be important as drugs.

II. PARAFFINS

The paraffins are prepared from crude petroleum or rock oil (petros-rock) which in turn is the result of the decomposition of organic matter. Because of their inertness the name paraffin has been applied (parum-small, affinis-affinity). The series is known by a number of names:

1. Fatty or aliphatic because the best known fats belong chemically to it (aliphos, fat).

2. The limit series because the valences of the carbon atoms are saturated to the limit.

3. It is called the chain series or acyclic because the carbon atoms are supposed to be arranged in the form of a chain

$$-\overset{|}{C}-\overset{|}{C}-\overset{|}{C}-$$
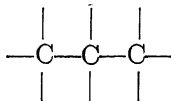
in contra-distinction to the ring, or benzene series.

4. Since methane, CH_4, is the first member, it is also known as the *methane series*. Because methane is found in nature in marshes, the term *marsh gas series* is also used. Members of from 1 to 60 carbon atoms are known.

All hydrocarbon compounds are grouped under three heads, namely:

1. *Fatty* or acyclic, or chain-like carbon derivatives.

2. *Carbocyclic,* or aromatic compounds.

3. *Heterocyclic* compounds.

Properties of the Hydrocarbons of the Paraffin Series. Those containing from 1 to 4 carbon atoms are gases; from 5 to 16 liquids; and those containing more than 16 carbon atoms are solids. This statement refers to ordinary temperatures and

pressures. All of them may be converted into gas, or all into solids, if the temperatures and pressure conditions are controlled.

The paraffins are saturated, therefore, they do not absorb bromine or hydrogen and are not absorbed by sulphuric acid. They are insoluble in water; the lower and intermediate members are readily soluble in alcohol and ether. They are noted for their chemical and pharmacologic inertness. Their action in the body is mainly physical. However, such light distillates as naphtha and benzine, are excellent solvents for fats, oils, lipoids, resins, and their volatility aids absorption. These light distillates often produce toxic effects that can be ascribed to their action on the nervous system, probably due to a solvent action on lipoids. Following their administration, headache, nausea, giddiness, unconsciousness, muscular tremors, convulsions, cyanosis and death, have been observed.

The irritant effect of the lighter members may also produce gastritis and gastro-enteritis. When the boiling point reaches that of kerosene, the toxicity is greatly diminished. Gastro-enteritis and narcotic effects similar to alcohol have been observed after kerosene, but no deaths have been reported, although cases are reported where as much as a liter was swallowed. Liquid petrolatum has an emollient effect. The solids are inert.

A few hydrocarbons, benzine, gasoline, kerosene, vaseline, liquid petrolatum, and solid paraffin are used in medicine. One should carefully distinguish between benzine, and benzene. Benzine is a light paraffin, a mixture of C_6H_{14} and C_7H_{16}, while benzene or benzol, C_6H_6, is an aromatic compound. It (benzol) has recently had considerable vogue in the treatment of leukæmia. Small amounts of it (1 cc. dose) reduce the number of white cells in the blood, but its continued use is fatal. Kerosene is used especially in dispensary practice to rid the hair of nits and lice.

The hydrocarbons above mentioned differ mainly in their physical properties, but there is some chemical basis for this difference. The source of all these is crude petroleum.

CRUDE PETROLEUM

This is a most important source of the paraffin hydrocarbons. When distilled at varying temperatures, the different fractions

have a varying and mixed composition, but are approximately as follows:

Distillation at temperature of:	Gives as a resulting substance:
$0°$	Gases, which may be liquified under pressure, CH_4 to C_4H_{10}
$18°$	Rhigolene, $C_5H_{12}—C_6H_{14}$
$50°$ and $60°$	Petroleum ether, or naphtha, $C_6H_{14}—C_7H_{16}$
$70°$ and $90°$	Benzine, a mixture of C_6H_{14} and C_7H_{16}
$90°$ and $120°$	Ligroin, C_7H_{16} and C_8H_{18}
$120°$ and $150°$	Petroleum benzine, $C_8H_{18}—C_{10}H_{20}$
$150°$ and $300°$	Burning oil distillate kerosene

From the residue left after distillation at $300°$, liquid paraffin, vaseline, and solid paraffin are prepared. These are essentially paraffins that distil between $300°$ and $390°$C.

LIQUID PETROLATUM

Liquid petrolatum may be obtained from petrolatum after the fractions distilling under $330°$ have been removed. The remaining liquid, when distilled between $330°$ to $390°$, gives *liquid petrolatum* which is purified by treating with sulphuric acid, and then by caustic soda, and by filtering while hot through some decolorizing agent, like animal charcoal or Fuller's earth. It is used in medicine as a cathartic and as a vehicle for other drugs.

Petrolatum, U. S. P. or petroleum jelly, is a soft paraffin or vaseline obtained from the liquid paraffin distillate. The part solidifying at $38°–54°$ is called petrolatum or vaseline.

Paraffin durum, or hard paraffin, is chemically similar to vaseline, but has a higher melting point, $50°–57°$, hence it will crystallize out of the distillate before vaseline. It is prepared in the cakes of commerce by pressure, and on account of its inertness is used in the laboratory around the stoppers of acid and alkali bottles. It has been used by "beauty specialists" to remedy minor deformities by injecting under the skin, a procedure which is not recommended.

Light liquid petrolatum (petrolatum levis) is used as a vehicle

especially for nasal and throat sprays. It is itself an emollient and as such serves to soothe, and to protect inflamed mucous membranes, and at the same time mild antiseptics like menthol or eucalyptol are incorporated with it. A popular nasal spray or nebula consists of one per cent. each of menthol and eucalyptol in light liquid petrolatum.

Liquid petrolatum (heavy-Petrolatum ponderosum or gravis) is used as a cathartic and is very servicable where a cathartic has to be given continuously as in chronic constipation and certain diseases of the intestine. It acts mechanically. Any non-absorbable fluid may act in the same way. It is valuable in these cases, because it does not cause griping, and does not become inert through continual use. The physical difference between light and heavy petrolatums is mainly a difference of viscosity.

The following tables show how the boiling point changes as the molecular weight increases.

Substance	Molecular formula	Boiling point
Methane	CH_4	$-164°$
Ethane	C_2H_6	$-84°$
Propane	C_3H_8	$-45°$
Butane	C_4H_{10}	$1°$
Pentane	C_5H_{12}	$36°$
Hexane	C_6H_{14}	$70°$
Eicosane	$C_{20}H_{42}$	$330°$
Penta tria contane	$C_{35}H_{72}$	$331°$
Dimyricyl	$C_{60}H_{122}$	

OCCURRENCE IN NATURE

Methane, or marsh gas, CH_4, the first of the series, is found in marshes and coal mines in varying amounts, and wherever decomposition of vegetable matter in lack of oxygen occurs. Mixed with air, methane is known as the fire damp of mines. It is one of the gases of the intestine, and in smaller amounts may be found in respired air. It may be prepared synthetically in a number of ways. These methods have little direct interest in pharmacology, but since they are fundamental and illustrate how

paraffins may be formed from the elements they are briefly indicated:

SYNTHESIS OF METHANE

I. Hydrogen sulphide and carbon bisulphide passed through a red hot tube containing copper, yield CH_4.

$$2H_2S + CS_2 + 4Cu = 4CuS + CH_4$$
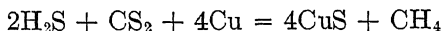
II. By passing carbon monoxide and hydrogen over reduced nickel at 200°C.

$$CO + 3H_2 = CH_4 + H_2O$$
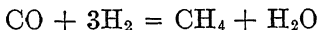
III. At 250°C., CO_2 is also reduced in the presence of finely divided nickel.

$$CO_2 + 4H_2 = CH_4 + 2H_2O$$
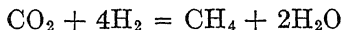
IV. Methyl alcohol or wood spirit can be converted into methane by changing to methyl iodide and then (a) the iodide nascent hydrogen:

$$CH_3OH + I_2 + 2H = CH_3I + H_2O + HI \qquad \text{or } (b)$$
$$CH_3I + 2H = 2CH_4 + HI$$
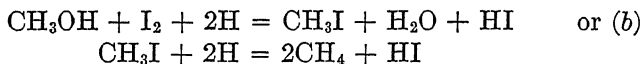
These and many other methods are used for preparing methane. Methane itself has no uses in medicine. The most important derivatives of methane from a pharmacological point of view, are methyl alcohol because of its toxicity and as a source of formaldehyde. The latter is used because of its antiseptic action.

ETHANE

This is the second member of the paraffin or methane series. It occurs in small quantities in natural gas and crude petroleum. Its derivatives only are important. It may be prepared synthetically in a number of ways, which show that it is made up of two methyl (CH_3) groups, as the following reaction shows:

$$2CH_3I + 2Na = CH_3.CH_3 + 2NaI$$
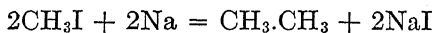
Ethane is also formed when ethylene is treated with nascent hydrogen:

$$C_2H_4 + 2H = C_2H_6$$
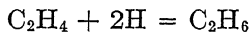
or when ethyl iodide is treated with hydrogen

$$C_2H_5I + 2H = C_2H_6 + HI$$
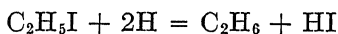
while ethane is not used in medicine its derivatives are exceedingly important.

IMPORTANT DRUGS OF THE METHANE SERIES
III. ALCOHOLS

The drugs of the methane series includes alcohols, ethers, ketones, and many derivatives which are used as narcotics or hypnotics.

Alcohols are hydroxyl derivatives of the marsh gas series (*cf.* phenols). According to the number of hydroxyls in the molecule they are classified as:

1. Monatomic or monhydric
2. Diatomic or dihydric, etc.

No gaseous alcohols are known. Up to $C_{12}H_{25}OH$ with few exceptions they are neutral, colorless liquids with a pleasant odor and burning taste. The more important members of the monhydric alcohols with their boiling point and specific gravity are as follows:

Substance	Chemical formula	B. P.	Spec. Grav.	Relative toxicity (Baer)
Methyl alcohol................	CH_3OH	66°	0.812	0.8 (?)
Ethyl alcohol.................	C_2H_5OH	78°	0.806	1.
Propyl alcohol................	C_3H_7OH	97°	0.817	2.
Butyl alcohol.................	C_4H_9OH	117°	0.823	3.
Amyl alcohol.................	$C_5H_{11}OH$	131°	0.825	4.

Ethyl alcohol is the only one that is used in medicine to any degree. Methyl and amyl alcohols are of importance because of their toxicity. The relative toxicity given by Baer does not hold good for all forms of life. It is only approximate at best. For man, it is incorrect, methyl being more toxic than ethyl. As we ascend in the alcoholic series, the members soon become more solid, and much less soluble, hence less toxic. A drug that is insoluble in the tissues or fluids of the body is inert. However, many substances that are insoluble in water dissolve readily in the body fluids. Next to water, alcohol is the solvent that will dissolve the greatest number of substances.

Methyl alcohol, or wood spirit, is prepared on a large scale by the dry distillation of wood. It is important in medicine chiefly because many cases of poisoning have arisen from its use. Its

actions in general are the same as ethyl alcohol, and are exerted mainly on the central nervous system. It seems to have a selective action on the optic nerve, and blindness often follows its use; even one dose of about 60 cc. has caused permanent blindness. Many such cases have been reported recently. In repeated doses it is much more toxic than ethyl alcohol. It has been used in patent medicines because it is cheaper than ordinary alcohol. Its use, however, should be condemned unhesitatingly.

The main differences in the intoxication of methyl and ethyl alcohols are: The coma produced by methyl alcohol may last for several days, as compared with a few hours in case of ethyl alcohol. Methyl alcohol readily attacks the optic nerve and may cause the blindness, which is absent in the action of ethyl alcohol. The oxidation products of methyl alcohol, formaldehyde and formic acid, are prone to irritate the kidneys and bladder, consequently nephritis and cystitis are frequent after wood alcohol poisoning.

Tests for Methyl Alcohol

1. It burns with a luminous flame. In this it resembles ethyl alcohol. In the body however, it is not so readily oxidized.

2. It dissolves fats, oils, resins, etc. and is extensively used for this purpose being a better solvent for these than ethyl alcohol. This greater solvent power for lipoids may be the cause of its greater toxicity.

3. It is miscible with water in all proportions, the same as ethyl alcohol.

4. Methyl alcohol may be converted into methyl salicylate (oil of Wintergreen) as follows:

To some sodium salicylate in a test tube, add an equal volume of methyl alcohol and concentrated sulphuric acid. Heat gently. The odor is that of methyl salicylate; which is an important antirheumatic remedy.

$$C_6H_4\begin{matrix} OH \\ COONa \end{matrix} + CH_3OH = C_6H_4\begin{matrix} OH \\ COOCH_3 \end{matrix} + NaOH$$
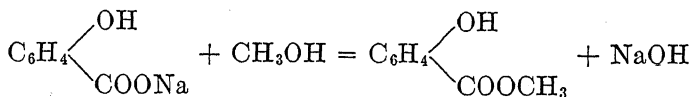
Sodiumsalicylate   methylalcohol   methylsalicylate.

Oleum betulæ (oil of birch) is also methyl salicylate.

5. Methyl alcohol readily yields formaldehyde on oxidation. Heat a small copper spiral to redness and drop it quickly into a test tube containing two or three drops of methyl alcohol. Note the odor of formalin. This same reaction takes place in the body when methyl alcohol is taken.

$$H-\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}}-H \rightarrow \quad H-\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}}-OH \rightarrow \quad H-C\underset{H}{\overset{O}{\diagup}}$$

Methane   Methyl alcohol   Formaldehyde
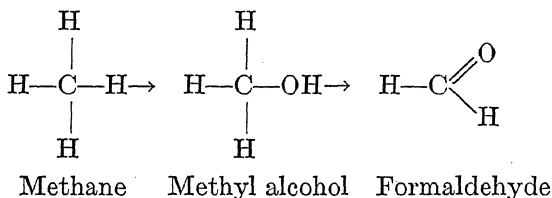
An oxidation of the hydrocarbons has not been observed in the body.

ETHYL ALCOHOL

Ethyl alcohol, C_2H_5OH, grain alcohol, or alcohol, is the next higher homologue in the methyl series, and is the result of fermentation of the sugars, of fruits and certain plants. Sugar and consequently alcohol may be prepared from any plant that contains starch. The U. S. P. (IX) requires that the ordinary commercial alcohol contain not less than 92.3 per cent. by weight and 94.9 per cent. by volume of C_2H_5OH. When a specific kind of alcohol is not mentioned, ethyl alcohol is always understood.

Alcohol dilutum contains alcohol, one-half, and distilled water one-half by volume.

Alcohol dehydratum or absolute alcohol is obtained by treating 96 per cent. alcohol with quicklime, and distilling. The lime holds all but the last traces of water which are taken out with anhydrous copper sulphate. When rectified again, it contains 0.5 per cent. water in which form it is used commercially, but the pure absolute alcohol can be obtained by treating the latter with barium oxide and re-distillation. Absolute alcohol is so hygroscopic that as a rule it is not found on the ordinary market. It contains 0.5 to 1 per cent. water. To prove the presence of water in alcohol, drop a small piece of anhydrous copper sulphate into 5 cc. of alcohol. Shake and let it stand. If the

slightest trace of water be present, a light blue color develops. Also if a few drops of liquid paraffin be added to the same amount of alcohol and shaken, a cloudiness due to the formation of an emulsion by the water, indicates the presence of water.

Whiskey, is prepared from fermented grain, potatoes, or anything containing starch. The starch is hydrolyzed to glucose and this on fermentation yields alcohol. Whiskey contains about 45 to 55 per cent. alcohol.

Gin, containing about 40 per cent. alcohol, is also made from grain and in its final distillation, juniper berries, anise seed, etc., are added.

Rum, prepared from fermented molasses, contains from 45 to 55 per cent. alcohol.

Brandy, prepared from fermented juices of such fruits as grapes, apples, peaches, etc. contains about 45 to 55 per cent. of alcohol.

Wine, champagne, and beer, are obtained by direct fermentation and are not distilled. Wine and champagne contain about 8 to 10 per cent. alcohol.

Beer is produced by fermenting malted grain with the addition of hops, for the taste. It contains from 3 to 5 per cent. alcohol.

Alcohol is important because of:

1. Its local irritant action.
2. Its action on the central nervous system.
3. Its destructive action on the tissues.
4. Its supposed food value.

A study of these properties places alcohol among drugs and poisons rather than among foods.

When alcohol over 60 per cent. is applied to the skin it tends to unite with the living protoplasm and the reaction produces redness, itching and a sense of heat. On mucous membranes and especially on abrasions the irritant action is much greater. If applied to blood or protein solution, alcohol over 60 per cent. will cause precipitation on standing. This union with protein confers astringent properties on alcohol. Alcohol, however, even in strong solutions (90 per cent.) may be slowly injected into the blood stream without causing precipitation, since the circulation causes it to be rapidly diluted. On the cerebrum

alcohol depresses progressively the psychic, sensory and motor functions. It attacks the brain functions in the reverse order of their evolution. The sense of judgment, attention, perception, reflection, and logical sequence are first to be depressed. The apparent stimulation being due to depression of the controlling function. There is no stimulation of the intellectual faculties, as shown by psychological tests of accuracy, rapidity, or mental exercise. There is no stimulation of the motor areas of the brain as shown by response to electrical stimulation of the areas. There is no stimulation of the medulla as judged by effect on blood pressure, heart and respiration. There is no stimulation of the cord as judged from the condition of the reflexes. The peripheral nerves and nerve endings are depressed and neuritis may be produced by continued use of alcohol. Bacterial toxins and heavy metals such as lead and arsenic may cause a similar neuritis.

The destructive action on the tissues is shown by:

The antiseptic action. The growth of microörganisms is retarded by all concentrations over 10 per cent. The greatest effect being manifested by about 70 per cent. This is apparently due to the fact that stronger solutions cause a precipitation film on the surface of the organism which retards absorption.

The gastro-intestinal tract especially of the stomach of alcoholics frequently shows a chronic inflammatory condition. Nephritis and hepatitis are very common, and neuritis due to alcohol is relatively frequent.

Alcohol as a food—a great deal can be oxidized in the body and to that extent it is a food. A dog weighing 25 lbs. is known to have oxidized 95 per cent. of 16 grams absolute alcohol in $5\frac{1}{2}$ hours. It can also replace fat and carbohydrates to a certain degree and spare protein waste, but it cannot build up tissue. Since it is easily oxidized and can supply energy, and prevent tissue destruction, it may be used as a medicinal food. Its destructive action on the tissues and its proneness to result in the formation of a vicious habit, prevent its being classified with foods.

Offer gives the following experiment on a healthy man to show the effects of alcohol, as a food:

Gram Nitrogen

Period 1.	Diet alone	Loss, 0.3441	Body nearly in nitrogenous equilibrium
Period 2.	Diet 100 grams of alcohol	Loss, 1.1689	Toxic action on tissues
Period 3.	Diet 100 grams of alcohol	Gain, 0.2335	Tolerance beginning to be established, and alcohol acting as a protein-sparing foodstuff
Period 4.	Diet alone	Loss, 0.0110	
Period 5.	Diet with added fat equivalent to 100 grms. of alcohol	Gain, 1.5654	

The Fate of Alcohol in the Body.—Alcohol is readily absorbed. Even from the stomach from which absorption is usually slight, about 20 per cent. of ingested alcohol is absorbed. After absorption the greatest amounts are found in the blood and central nervous system. When the blood contains 0.12 per cent. there is stupor, but as much as 0.72 per cent. has been found in a case of fatal intoxication. More than six parts per one-thousand in the blood invariably proves fatal. It is said that if stupor or unconsciousness after a drinking bout last over 10–12 hours recovery rarely takes place. Traces remain in the blood for twenty-four hours, but over 95 per cent. of the amount ingested is oxidized. Whether the blood normally contains traces of alcohol is a disputed question. Traces have been found in normal blood but there is a question whether or not this was formed by an abnormal fermentation of carbohydrates in the intestine, rather than as a normal product of digestion.

B. Fischer reports the following analysis of the alcoholic content of the organs of a man who died from alcoholic intoxication:

Weight	Organ	Alcohol
2720 grams	Stomach and intestines	30.6 grams
2070 grams	Blood—heart and lungs	10.85 grams
1820 grams	Kidneys and liver	7.8 grams
1365 grams	Brain	4.8 grams

Ethyl alcohol is recognized by its odor and by chemical tests.

Since it distils easily from water solution, if it is in dilute solutions, as beer, or in colored solutions, as wines, it should be distilled before testing.   The first part of the distillate should be used for the test.

Chemical Tests for Ethyl Alcohol

1. To a small portion of the distillate add a crystal of potassium bichromate and a few drops of H_2SO_4 and warm.   The alcohol is oxidized to the aldehyde and acetic acid with the characteristic odor, and the chromate is reduced giving a green color.   Do not use too much bichromate.

1. $K_2Cr_2O_7 + H_2SO_4 = K_2SO_4 + H_2Cr_2O_7\ (H_2O + 2CrO_3)$
2. $3C_2H_5OH + 2CrO_3 + 3H_2SO_4 = 3CH_3CHO + Cr_2(SO_4)_3 + 6H_2O$
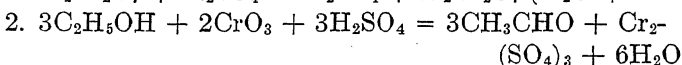
2. **Lieben's Iodoform Test.**—To a few drops of dilute alcohol in a test tube add a crystal of iodine.   Warm gently and add drop by drop KOH until the red color just disappears.   Note the odor.   When the sediment has settled examine under the microscope.

$C_2H_5OH + 4I_2 + 6KOH = CHI_3 + HCOOK + 5KI + 6H_2O.$

Bromoform can be prepared in the same way by using bromine instead of iodine.   Acetone also gives this test but differs from alcohol in that it will give it when NH_4OH is used instead of KOH or NaOH.

3. **Ethyl Acetate Test.**—Mix equal volumes of alcohol or the liquid to be tested and concentrated sulphuric acid: About 2 cc. each.   To this add about 0.1 gram dry sodium acetate and heat. Ethyl acetate is formed if alcohol is present and is recognized by its odor:

1. $C_2H_5\ OH + H_2SO_4 \Rightarrow O_2S \begin{smallmatrix} OC_2H_5 \\ OH \end{smallmatrix} + H_2O$

2. $CH_3COONa + C_2H_5.O.SO_2OH = CH_3COOC_2H_5 + NaHSO_4$
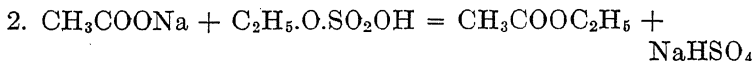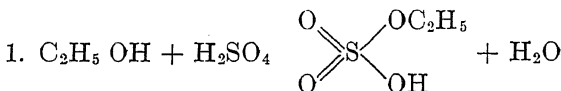
There is no evidence that any substance formed in making these tests is ever formed from alcohol in the body.

To Determine the Amount of Ethyl Alcohol in Liquors

Place 100 cc. of the liquid in a flask of about 300 cc. capacity. Add 50 cc. of water. Connect with a condenser and distil over 100 cc. This contains all the alcohol in a water solution. Determine the specific gravity of the distillate by means of a pycnometer, Westphal balance, or a delicate hydrometer. Read the per cent. of alcohol from tables prepared for this purpose. See U. S. P. IX, page 633. These tables were prepared as follows: Water has a specific gravity of 1.0000. Absolute alcohol has a specific gravity of 0.79365, consequently between 0 per cent. alcohol and 100 per cent. we have a range of sp. gr. of 0.20635. By mixing known amounts of water and alcohol and carefully measuring the sp. gr. of such mixtures, the tables were prepared.

Propyl and Butyl Alcohols

Propyl and butyl alcohols are not used in medicine and are of interest only as impurities in preparations of ethyl alcohol. Propyl is more powerful in its action than ethyl and butyl still stronger than propyl. The toxic action increases with increasing molecular weight. This is known as the Rule of Richardson. There are two propyl alcohols—the normal and the isopropyl.

THERE ARE FOUR BUTYL ALCOHOLS. C_4H_9OH

	B. P.	Specific gravity at 20°
$CH_3—CH_2—CH_2—CH_2OH$ Normal butyl alcohol (primary carbinol)	117°	.810
$(CH_3)_2CH—CH_2OH$ Isobutyl alcohol (primary isopropyl carbinol)	117°	.806
$\begin{matrix} CH_3—CH_2 \\ CH_3 \end{matrix}\rangle CHOH$ Normal secondary butyl alcohol (methyl ethyl carbinol)	100°	.808
$(CH_3)_3COH$ Tertiary butyl alcohol (trimethyl carbinol)	83°	.786

The normal alcohol when oxidized gives propionic aldehyde and acid, while oxidation of isopropyl alcohol gives acetone.

$$CH_3—CH_2—CH_2OH \rightarrow CH_3—CH(OH)—CH_3$$
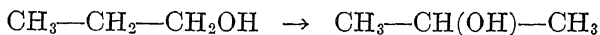
Primary propyl alcohol (normal) Secondary propyl alcohol (isopropyl alcohol)

Normal butyl occurs in traces in fusel oil. It is also produced by Bacillus butylicus when grown on glycerine and various sugars, but it has little biological importance. The toxicity of these and other alcohols on fish has been studied by Picaud who gives the relative toxicity as follows:

Methyl	.66
Ethyl	1.00
Propyl	2.00
Butyl	3.00
Amyl	10.00

On the isolated mammalian heart Hemmedter found that the pumping power as measured by the amount expelled in 30 seconds was reduced by the various alcohols as follows:

Methyl	19 cc.
Ethyl	17 cc.
Propyl	79 cc.
Butyl	161 cc.
Amyl	323 cc.

Isopropyl is more toxic than normal, but normal butyl is more toxic than isobutyl. Alcohols with branched chains are less toxic than those with straight chains.

Amyl alcohols:

Only primary isobutyl carbinol and secondary butyl carbinol, are important in pharmacology. Ordinary amyl alcohol is a mixture of these. Both occur in fusel oil, and are formed through the life processes of the yeast cell and are derived from proteins. Consequently where a fermentation mash contains proteins, as when grain and potatoes are used, more amyl alcohol is produced, than in the preparation of rum or brandy where the mash contains less protein. Yeast may

Amyl Alcohol or Pentyl Alcohol
(Amylum-starch)
THERE ARE EIGHT AMYL ALCOHOLS

		B. P.	Specific gravity at 20°
1. Normal primary (butyl carbinol)	$CH_3{-}CH_2{-}CH_2{-}CH_2{-}CH_2OH$	138°	.817
2. Isobutyl carbinol (primary)	$\begin{array}{c}CH_3\\\ \diagdown\\ \ \ \ \ CH{-}CH_2{-}CH_2OH\\\ \diagup\\ CH_3\end{array}$	130°	.810
3. Secondary butyl carbinol (primary) (active amyl alcohol)	$\begin{array}{c}CH_3\\\ \diagdown\\ \ \ \ \ \ CH{-}CH_2OH\\\ \diagup\\ CH_3{-}CH_2\end{array}$	128°	.816
4. Tertiary butyl carbinol (primary)	$\begin{array}{c}CH_3\\\ \diagdown\\ CH_3{-}C{-}CH_2OH\\\ \diagup\\ CH_3\end{array}$	113°	
5. Methyl propyl carbinol (secondary)	$\begin{array}{c}CH_3\\\ \diagdown\\ \ \ \ \ \ \ CHOH\\\ \diagup\\ CH_3{-}CH_2{-}CH_2\end{array}$	119°	
6. Methyl isopropyl carbinol (secondary)	$\begin{array}{c}CH_3\\ CH_3\diagdown\\ \ \ \ \ CH{\diagup}\ \ CHOH\\ CH_3\end{array}$	112°	.819
7. Diethyl carbinol	$\begin{array}{c}CH_3{-}CH_2\\\ \diagdown\\ \ \ \ \ \ \ CHOH\\\ \diagup\\ CH_3{-}CH_2\end{array}$	117°	
8. Dimethyl ethyl carbinol (tertiary)	$\begin{array}{c}CH_3\\ CH_3{-}C{-}OH\\ CH_3{-}CH_2\end{array}$	102°	

produce amyl alcohol from its own protein consequently, all yeast alcohols may contain amyl alcohol. The specific constituent of the protein from which amyl alcohol is prepared appears to be leucine and isoleucine. Ehrlich, using a pure culture of yeast, found that when this acted on a sugar solution containing leucine it readily yielded isoamyl alcohol and isoleucine yielded amyl alcohol. The reactions are represented as follows:

(1) $(CH_3)_2.CH.CH_2CH(NH_2).COOH + H_2O = (CH_3)_2.CH.$
$$CH_2CH_2.OH + CO_2 + NH_3$$

      Leucine   Isoamyl alcohol

(2) $CH_3.CH(C_2H_5).CH.(NH_2).COOH + H_2O = CH_3.CH(C_2H_5.$
$$CH_2OH + CO_2 + NH_3$$

         Isoleucine   d-amyl alcohol
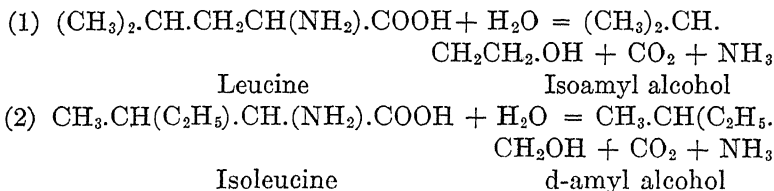
The amyl alcohols are colorless oily liquids insoluble in water,

with a disagreeable characteristic odor and acrid taste. Their action in general resembles ethyl alcohol but they are about four times as toxic. They are more locally irritant, and some authorities state that the effect of chronic use is more deleterious than in the case of pure ethyl alcohol.

Fusel oil is to some extent used in the preparation of essences and perfumes, and exerts an influence on other perfumes. The essential oils and aromatic substances develop their finest odors in alcohol from a special source. In some cases such alcohols are treated with charcoal which removes most of the fusel oil, the remaining traces act with other aromatic bodies to produce a harmony which cannot be reached by any other alcohol. Ehrlich points out that "the great variety of the bouquets of wine and aromas of brandy, cognac, arrak, rum, etc. may be very simply referred to the manifold variety of the proteins of the raw materials (grapes, corn, rice, sugar cane, etc.) from which they are derived."

When oxidized, amyl alcohol is converted into valerianic acid

$$(CH_3)_2CH.CH_2COOH$$

which may be recognized by its odor.

TESTS

1. To test ordinary alcohol for fusel oil constituents: Mix 10 cc. of alcohol with 5 cc. of water and 1 cc. of glycerine and allow the mixture to evaporate spontaneously from a piece of filter paper. No odor should be perceptible when the last traces of alcohol leave the paper. Compare this with a similar solution to which 1 cc. of amyl alcohol has been added.

2. Warm 1 cc. of amyl alcohol with 2 cc. of concentrated H_2SO_4. A rose red color is produced.

3. Heat 1 cc. of amyl alcohol with 1 cc. H_2SO_4 and a little sodium acetate. Amyl acetate is produced which has a strong smell of pears and is known as pear oil.

4. Heat 1 cc. of amyl alcohol with 1 cc. H_2SO_4 and a small crystal of potassium bichromate; valerianic aldehyde

$$CH_3(CH_2)_3C{\diagup O \atop \diagdown H}$$ is formed. This has a peculiar characteristic odor.

Valeric or valerianic acid ($CH_3(CH_2)_3COOH$) is the acid corresponding to amyl alcohol, just as acetic is the acid of ethyl alcohol. There are four possible isomerides of valeric acid. The normal valeric acid is N. propyl-acetic acid $CH_3CH_2CH_2.$ $CH_2.COOH$.

Valerian, which is used in medicine in cases of hysteria and other functional nervous trouble contains valerianic acid as the active or odoriferous principle. The action in these cases is psychic, and due to the impression made by the odor.

DIHYDRIC ALCOHOLS

These are of no pharmacologic interest except in illustrating the influence of the change of the molecule on its physical and physiological actions. The only dihydric alcohol that is used at all is glycol or ethylene glycol,

$$\begin{array}{l} CH_2OH \\ | \\ CH_2OH \end{array}$$
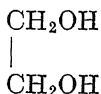
Do not confuse this with glycocoll (p. 67). The two hydroxyls here render the substance more soluble in water and less soluble in other liquids, hence lessen the physiological activity (See Meyer and Overton theory of narcosis). The introduction of OH groups in this series also increases the sweetness of the substance. Glycerine contains three OH groups and glucose five, and they are sweeter in about this proportion. This is still more strongly emphasized under trihydric or triatomic alcohol-glycerine.

Glycerine, which contains three hydroxyl groups is still less active, and glucose, which is an hexatomic alcohol, is not toxic. In fact, sugars are classified as foods rather than drugs.

Ethylene glycol is a thick, colorless, syrupy liquid with a sweet taste (Greek, "glykys" meaning, sweet, and "ol," alcohol). It boils at 197.5° and mixes with water and alcohol in all proportions. It was formerly recommended in the treatment of tuberculosis, but is now considered worthless for this purpose.

Glycol is formed when choline is heated:

$$
\begin{array}{ccc}
\underset{CH_3}{\overset{CH_3\ \ CH_2.CH_2OH}{\diagdown\ \ \diagup}} & & \\
CH_3-N-OH \ \longrightarrow \ & CH_3-N \ + \ CH_2OH \\
\diagup & \diagup & | \\
CH_3 & CH_3 & CH_2OH
\end{array}
$$

Choline   Tri-methylamine. Glycol

Nitric acid oxidizes glycol to oxalic acid:

$$
\begin{array}{cccc}
CH_2OH & CHO & CHO & COOH \\
| \quad \rightarrow & | \quad \rightarrow & | \quad \rightarrow & | \\
CH_2OH & CH_2OH & CHO & COOH
\end{array}
$$

Glycol   glycolaldehyde   glyoxal   oxalic acid
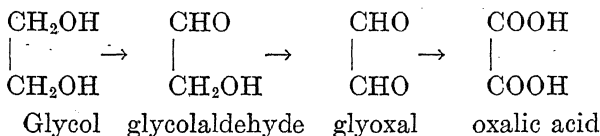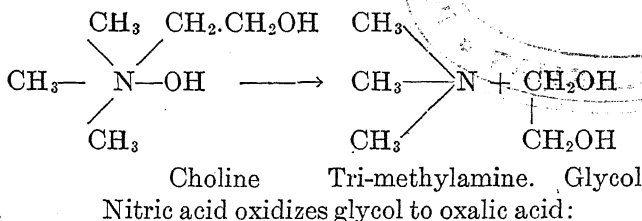
These products are formed when glycol is oxidized in the body. Oxalic acid is also formed from cellulose on treatment with caustic potash, but it is doubtful if any such action occurs in the animal body.

Glycolaldehyde is one of the products of the oxidation of dextrose with alkalies and is thought by some to be formed in the oxidation of sugars in the body.

TRIHYDRIC ALCOHOLS

Of trihydric or triatomic alcohols, glycerine only is important. It is used extensively in medicine.

$$
\begin{array}{c}
CH_2OH \\
| \\
CHOH \\
| \\
CH_2OH
\end{array}
$$
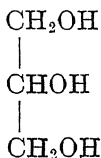
It has a strong avidity for water, and because of this when applied to mucous membranes it is irritating. All ordinary fats are esters of glycerine and a fatty acid. Glycerine is sweeter than glycol and is the only trihydric alcohol found in nature.

Chemical Tests

1. Test the solubility of glycerine in water, alcohol, and ether. The increase in hydroxyl groups, as a rule, decreases the solubility in ether, and increases the solubility in water. Compare this with other alcohols.

2. Taste alcohol, glycol, glycerine, and glucose. The hexc are alcoholic compounds. Increasing the hydroxyl groups is some way connected with the sweet taste, though not absolut essential to the taste, for benzosulphinidum, lead acetate, (which have no (OH) groups may be five hundred times swee than sugar (see p. 210).

3. Heat a few drops of glycerine with a small crystal of KHS over a free flame. It is dehydrated with the formation of ac lein ("Acer," acrid, and "oleum," oil).

$$C_3H_5(OH)_3 = C_3H_4O + 2H_2O \text{ or } C_3H_5(OH)_3 = CH_2 : CH.Cl + 2H$$
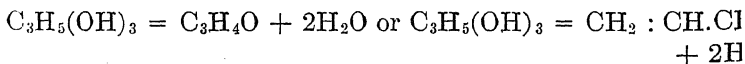
Glycerine is used to a considerable degree in medicine. was formerly recommended in the treatment of diabetes, as sweetening agent to replace sugar. It has been found, howev to be of little use in these cases. In larger doses (5–20 cc.) is a laxative, but may produce gastro-enteritis. It is used suppositories as rectal enemata in cases of constipation; as vehicle or solvent for many drugs, and especially in the glyceri of tannic acid, starch, and boroglycerine. It has some power a germicide, and is used to preserve vaccine lymph. The use it in skin diseases combined with substances like benzoin, i chapped hands, lips, or other parts is common. It has ma other uses in medicine.

HIGHER ALCOHOLS

Cetyl alcohol, $C_{16}H_{33}OH$, is found in spermaceti, and myric alcohol, $C_{30}H_{61}OH$, in waxes. These alcohols in waxes corr spond to the glycerine of ordinary fats; this is the main diff ence between the fats and waxes (q.v.). In waxes the fatty ac also is higher in the series (more C atoms) than the palmit stearic or oleic acids of the ordinary fats.

SULPHUR ALCOHOLS OR MERCAPTANS

The sulphur alcohols correspond to the ordinary alcohols which (S) takes the place of (O). Ethyl mercaptan is form from ethyl chloride and potassium sulphydrate in alcohol sol tion: $C_2H_5Cl + KSH = C_2H_5SH + KCl$

The sulphur confers greater chemical reactivity and also great

pharmacological activity on the alcohols. While the OH in ordinary alcohols is replaceable only with Na, or K, the mercaptans react also with heavy metals. The name comes from their reaction with mercury (mercurium captans):

$$2C_2H_5.SH + HgO = (C_2H_5S)_2.Hg + H_2O$$
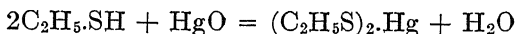
The sulphur alcohols are not used directly in medicine, but are used in the manufacture of some medicinal agents. Ethyl mercaptan is important because it was the first discovered mercaptan, and because it forms the basis for the manufacture of the sulphone group of hypnotics, of which sulphonal or sulphonmethane is the most important.

THE PHARMACOLOGY OF THE ALCOHOLS IN RELATION TO THEIR CHEMISTRY

The relative inertness of the paraffins is markedly activated by the introduction of the OH groups. The monhydric alcohols are pronounced narcotics, which action, seems to depend on the hydrocarbon radical. Thus, CH_4 is inert, CH_3OH, narcotic. Further oxidation destroys the CH_3 groups, and the narcotic action is lost. Ethane CH_3CH_3 is inert, ethyl alcohol CH_3CH_2OH is narcotic, while if both CH_3 groups in ethane are oxidized giving glycol, CH_2OHCH_2OH, it is inactive. All hydrocarbons are relatively inert except those that are volatile liquids and have a solvent action.

Propyl alcohol, $CH_3CH_2CH_2OH$, is more toxic than ethyl, but when two more OH groups are substituted for H, as in glycerol, $CH_2OH.CH.OHCH_2OH$, it loses its soporific and toxic action. In large doses it may produce restlessness, tremors, and even tetanus. These actions, however, are less than those of propyl alcohol, and are apparently more on the motor than on the sensory side of the nervous system.

As the number of carbon atoms in alcohols increases, the toxicity increases. The six carbon alcohols or aldehydes corresponding to the hexanes are highly toxic, while the corresponding sugars are foods. Thus, normal hexane $CH_3CH_2CH_2CH_2CH_3$ is actively intoxicant, producing excitement followed by deep anesthesia when inhaled. Glucose, $CH_2OH (CHOH)_4CHO$, has no toxic properties in any amount. Secondary alcohols are more toxic than primary, and tertiary more than secondary.

The action of the alkyl radical of the alcohol is especially noticeable in the tertiary alcohols where it is found that the larger the alkyl radical attached to the carbon carrying the hydroxyl, the more pronounced is the action, *e.g.*,

4 grams of tri-methyl carbinol (tertiary butyl alcohol)
$(CH_3)_3COH$, or

2 grams of dimethyl ethyl carbinol $(CH_3)_2$ $\mathord{>}COH$, or C_2H_5

1 gram of tri-ethyl carbinol $(C_2H_5)_3COH$ have about the same sleep-producing power. A similar characteristic has been observed in other compounds.

Glycol, $\begin{matrix} CH_2OH \\ | \\ CH_2OH \end{matrix}$ the dihydric primary alcohol, is inert, but if

alkyl groups are introduced, in place of the hydrogen attached to the carbon, substances known as pinacones are formed (Gr. pinax, pinak tablet). It has been found that 10 grams of methyl pinacone

$\begin{matrix} (CH_3)_2COH \\ \overset{\cdot}{(CH_3)_2COH} \end{matrix}$ or 1.5 grams of ethyl pinacone, $\begin{matrix} (C_2H_5)_2COH \\ \overset{\cdot}{(C_2H_5)_2COH} \end{matrix}$
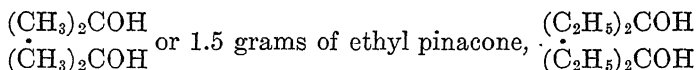
have about the same sleep-producing or depressing action.

These examples show clearly the pharmacological action of alkyl radicals, which are hypnotics or depressants of the central nervous system, and the greater the molecular weight the greater the depression produced.

IV. ANESTHETICS, NARCOTICS, SOPORIFICS, HYPNOTICS

The alkyl radicles are nerve depressants, and affect the cerebrum especially. According to the degree of depression produced, several terms are used to define the condition.

Hypnotics, soporifics or somnifacients are used to produce sleep. Alcohol, ether, or chloroform, in the proper dose may be used, but more often milder bodies such as chloral, paraldehyde, the sulphones, veronal, or similar drugs are used.

Narcotics produce a condition of narcosis or coma. The depressant action is more profound than the hypnotic state and

may be produced by larger amounts of the same drugs. In addition to the aliphatic narcotics mentioned, urethane and morphine readily produce narcosis. The aliphatic anesthetics most used are ether, ethyl chloride, and chloroform. Nitrous oxide, although not an aliphatic preparation is usually studied with them. The action of each of these is practically the same as alcohol, but the stages of the action are more prolonged in alcohol intoxication. Some stages in general anesthesia produced by ether or chloroform may be so fleeting that they are difficult to observe.

Four distinct stages may be observed following the administration of the aliphatic narcotics and hypnotics.

Dixon gives the stages with the symptoms of ether anesthesia as follows:

Stage I.

Disorganized consciousness and analgesia	Irritant action of the vapour on the nasal and bronchial mucous membrane.
	Reflex effects—coughing, salivation, respiratory, cardiac.
	Disturbances of judgment.
	Loss of memory and self-control.
	Emotional tendencies.
	Disturbances of special senses.
	Analgesia.
	Vertigo and ataxia.
	Quickened pulse and rise in blood-pressure.
	Increased respiration.
	Dilated pupils.

Stage 2.

Excitement and Unconsciousness	Coughing, retching, vomiting.
	Delirium varying from shouting to inarticulate muttering.
	Tonic, and clonic muscular spasm.
	Reflexes diminished.
	Unconsciousness.
	Respiration irregular from the struggling.
	Pulse accelerated and pupil dilated, both from excitement.

Stage 3.

Surgical Anesthesia	Muscular relaxation.
	Loss of reflexes.
	Breathing regular, often "snoring."
	Decrease of respiratory exchange.
	Fall of temperature.
	Fall of blood pressure.
	Pupil small; does not react to light.

Stage 4.

Leading to Bulbar paralysis	Loss of bladder and rectal reflexes.
	Paralysis of vaso-motor centre (great fall of blood-pressure).
	Paralysis of respiratory centre.
	Widely dilated pupils.
	Great depression of cardiac muscle.

The amount of chloroform in the blood during light anesthesia is 25 to 35 mgs. per 100 cc. If the concentration is raised to 40–70 mgs. per 100 cc. respiration fails. During light ether anesthesia there are 100–110 mgs. per 100 cc., and 130 to 140 mgs. in deep anesthesia. 160 to 170 mgs. per 100 cc. causes failure of respiration. In deep alcoholic coma in man Sweisheimer found that the blood contained 2.25 parts per 1000 cc. Grehant found that 6 parts alcohol per 1000 cc. blood was invariably fatal to animals.

Whether the heart or respiration stops first depends on the method of administration. Large concentrations especially of chlorine containing anesthetics, if too quickly administered, paralyze the heart before respiration. When present in the respired air, in the per cent. given, Cushny tabulates the differences between ether and chloroform as follows:

Chloroform	Ether	
0.5–0.7 per cent.	1.5–2.5 per cent.	Insufficient to cause anesthesia.
1.0 per cent.	3–3.5 per cent.	Causes anesthesia on prolonged inhalation.
2.0 per cent.	6.0 per cent.	Arrests respiration after sometime.

The amount of anesthetic in 100 cc. of the blood shows the same proportion and is as follows:

Chloroform	Ether	
25–35 mgs.	100–140 mgs.	Anesthesia
40–70 mgs.	160–170 mgs.	Respiratory arrest.

According to the concentration of chloroform in the respired air, Rosenfeld gives the following series of experiments to show the effects:

RELATIONSHIP BETWEEN THE PERCENTAGE OF CHLOROFORM IN THE RESPIRED AIR AND THE DEPTH AND RAPIDITY OF THE ANESTHESIA (ROSENFELD, SPENZER)

(From Meyer & Gottlieb)

Chloroform percentage in respired air	Time necessary to induce anesthesia	Depth of anesthesia or narcosis	Remarks
0.54–0.69	2 hrs.	No narcosis	Somnolence only.
0.96–1.01	30–40 min.	Complete	Blood-pressure at first normal then gradual fall for 4 hrs. Respiration normal.
1.16–1.22	30 min.	Complete	Cessation of respiration at end of 2 hrs.
1.41–1.47	37 min.	Deep	As above after 1 hr.
1.63–1.65	12 min.	Deep	As above after 30 min.
Ether percentage in respired air			
1.5	2 hrs.	Hardly any	Slight somnolence only.
2.5		Very incomplete	Reflexes maintained.
3.2–3.6	25 min.	Complete	Respiration and cardiac function remained good for hours.
4.45	15 min.	Complete	Respiration slow and regular; pulse accelerated.
6.0			Respiration ceased in 8–10 minutes.

THEORIES REGARDING THE CAUSATION OF ANESTHESIA

Both chemical and physical theories have been advanced to explain the action of ether and chloroform in producing anesthesia.

1. **The Meyer-Overton Theory.**—Meyer and Overton think that anesthesia is due to the solvent action of the anesthetic on the lipoids of the central nervous system. The anesthetics are also somewhat soluble in water, and the anesthetic value depends on the distribution, coefficient, *i.e.* the ratio of the solubility in fats (S/F) to the solubility in water (S/W). The most powerful anesthetics are very soluble in fats and but little soluble in water. Meyer studied many aliphatic narcotics and arranged them in the order of their potency. These are expressed in the fractions of normal solutions, that will produce the first definite physiological effect, which he calls the liminal value.

	Liminal value in terms of normal solution	Distribution Coefficient $\frac{SF}{SW}$
Trional	0.0018	4.46
Tetronal	0.0013	4.04
Sulphonal	0.006	1.11
Butylchloral hydrate	0.002	1.59
Bromal hydrate	0.002	0.66
Chloral hydrate	0.02	0.22
Ethyl methane	0.04	0.14
Methyl methane	0.4	0.04
Monacetin	0.05	0.06
Diacetin	0.015	0.23
Triacetin	0.01	0.3
Chloralamide	0.04	
Chlorhydrin	0.04	
Dichlorhydrin	0.002	

While this theory is attractive, it merely explains how the drug gets to the place of action, and Cushny has pointed out that some benzene derivatives are good lipoid solvents and have a high distribution coefficient, yet are without narcotic action. Again cells rich in lipoid substances are not always attacked in relation to this substance. The peripheral nerves are much less

influenced than the central nervous system. Baumann and Kast give the following table to show that narcotic action depends on the presence of ethyl radicals.

	Action	Distribution Coefficient
Dimethyl-sulpho-methane	very slight	.106
Dimethyl-sulpho-ethane	slight	.151
Sulphonal (Diethyl sulphone dimethyl methane)	marked	1.115
Trional (Diethyl sulphone methyl ethyl methane)	more marked	4.46
Tetronal (Diethyl sulphone diethyl methane)	more marked	4.04

2. The Theory of Moore and Roaf.—They believe that the action of the anesthetic is due to a loose combination of the anesthetic with the cell proteins. A certain concentration of the anesthetic in the blood is necessary to maintain the combination. Lipoids may aid in keeping the necessary concentration of the anesthetic around the living protein, and to this extent the Meyer-Overton theory may hold.

3. Verworn's Theory.—He accepts the Meyer-Overton theory to some extent, but believes that the fundamental action is the prevention of oxidation by the cell. In the last step anesthesia is an asphyxiation. Due to the presence of the anesthetic the nerve cells cannot utilize the oxygen that may be present.

Many other theories have been presented but none are entirely satisfactory. In this connection it should be mentioned that physiologists have been unable to present a satisfactory theory to explain natural sleep.

The Hyderabad Commission—1889 and 1890

Because of the difficulty of handling ether in hot climates such as India, the Nizam of Hyderabad caused an investigation to be made of the relative values of ether and chloroform as anesthetics, especially with reference to the action on the heart. The commission concluded after numerous experiments that the only means by which the heart's safety is jeopardized is through paralysis of respiration. Accordingly respiration always stops first. This report is both right and wrong. According to

the conditions of their experiments, where the anesthetic in the respired air is dilute and gradually increased, respiration stops first. If, however, the concentration in the respired air is too great at the beginning, or is quickly increased, the heart may stop first due to direct action on and paralysis of the heart muscle. It is quite possible, therefore, to have either respiration or heart stop first, or both at the same time. Consequently, therefore, in giving an anesthetic, it is necessary to watch both heart and respiration.

The relative toxicity of ether and chloroform on the heart was found by perfusing the isolated heart through the coronary vessels. To stop the heart's action 0.015 per cent. chloroform or 0.4 per cent. of ether was required. This indicates that chloroform is about 25 times as toxic as ether. On the respiratory center chloroform is about 4 times as toxic as ether.

Ether and chloroform are excreted mainly by the lungs. Ether is excreted only in this way. Small amounts of chloroform have been found in the urine and milk, but the statement that some carbon monoxide is formed from chloroform in the body is erroneous. Chloroform may be detected in the breath for 24 hours after narcosis. Nicloux gives the following figures to show the disappearance from the blood.

CHLOROFORM CONTENT OF BLOOD AFTER TERMINATION OF ANESTHESIA

Time elapsed since termination of anesthesia	Per cent. of chloroform in blood	
	Exp. 1	Exp. 2
0 minutes	0.054	0.0595
5 minutes	0.0255	
15 minutes	0.0205	
30 minutes	0.018	0.023
1 hour	0.0135	0.018
3 hours	......	0.0075
7 hours	......	0.0015

Ether is eliminated somewhat more rapidly, which explains the more rapid recovery from ether narcosis.

ETHER CONTENT OF BLOOD AFTER TERMINATION OF ANESTHESIA

	Per cent. of ether in blood	
	Exp. 1	Exp. 2
0 minutes....................	0.115	0.159
3 minutes....................	0.071	0.108
5 minutes....................	0.063	0.080
15 minutes....................	0.052	0.058
1 hour....................	0.025	0.021
2 hours....................	.....	0.004

ETHER OR ETHYL OXIDE

Ether is prepared by mixing alcohol and sulphuric acid and distilling. The following formula indicates the reaction.

$$C_2H_5OH + {H \atop H}{>}SO_4 = {C_2H_5 \atop H}{>}SO_4 + H_2O$$

$$C_2H_5OH + C_2H_5{<}{H \atop SO_4} = {C_2H_5 \atop C_2H_5}{>}O + H_2SO_4$$
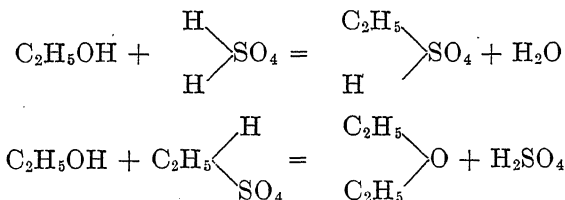
Ether used for anesthesia is chemically pure ethyl ether.

CHEMICAL TESTS

1. Specific gravity 0.713 to 0.716 at 25°C. Boils at 35°C. which is below body temperature (37°C.)

To show inflammability of ether apply a flame to 1 cc. of it in a small dish. Repeat this with chloroform.

2. Shake ether with an equal volume of CS_2. The mixture becomes turbid if the ether contains water, not otherwise. Ether will dissolve about 10 per cent. water. Anilin violet colors ether which is adulterated with alcohol, but does not the pure ether.

3. Shaken with $\frac{1}{10}$ volume of 5 per cent. KOH, no color should be developed in either liquid in the absence of aldehyde.

4. Ether is miscible with alcohol, benzine, chloroform, benzene, fixed and volatile oils, and lipoids in all proportions. Test the

solubility of oils, fats, lanolin, and other lipoids in ether. *Cf.* the
Overton-Meyer theory of Narcosis, p. 36.

5. Na will not act on dry ether due to the absence of hydroxyl.

6. Strong acids decompose ether with the formation of ethereal
salts.   The action of H_2SO_4 on alcohol is much more complete.
Similarly in the body, ether is excreted unchanged, while alcohol
is almost completely oxidized.

The replacement of the hydrogen hydroxyl in alcohol results
in marked physical and chemical changes. $C_2H_5OC_2H_5$ is much
more volatile than C_2H_5OH.   The more volatile a substance the
more quickly it penetrates, consequently it acts more quickly
when taken into the body.

In the body, alcohol is rapidly and almost completely oxidized.
Ether is not oxidized in the body, but is a catalytic poison, *i.e.*,
it causes a marked reaction by action in the body without itself
undergoing any change.   When oxidized outside the body it
yields the same products as alcohol.   Ethers of the marsh-gas
series are always more active than the corresponding alcohol.

Glycerine—$\begin{matrix} CH_2OH \\ CHOH \\ CH_2OH \end{matrix}$ is inert, but when converted into glycerine

ether

CH_2—O—CH_2
CH —O—CH
CH_2—O—CH_2
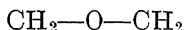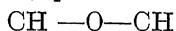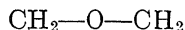
it becomes narcotic.   The narcotic action of the alkyl radical
is manifested in other compounds.   Phenol C_6H_5OH which is
antiseptic and stimulating to the motor side of the cord loses its
antiseptic and stimulating action when converted into phene-
tol, $C_6H_5.O.C_2H_5$.

NH_3, which is stimulating, loses its convulsant action as the
hydrogen atoms are replaced by alkyls and the quaternary
ammonium bases have a curara-like action.

Urea also becomes depressant when alkyl groups are sub-
stituted for H, as when $CO{<}^{NH_2}_{NH_2}$ becomes $CO{<}^{N(C_2H_5)_2}_{NH(C_2H_5)}$

These examples again show the depressant and hypnotic action
of the alkyl groups.

ETHYL CHLORIDE

Ethyl chloride, C_2H_5Cl, is prepared by passing HCl gas through alcohol in which anhydrous $ZnCl_2$ is dissolved, the $ZnCl_2$ acting as a catalytic and dehydrating agent. At ordinary temperatures it is a gas which boils at 12.5°C. It is freed from HCl by passing through water.

This compound, like chloroform, illustrates the influence of introducing Cl into the molecule. It is twice as soluble in water as in the blood, and is sometimes used as a general anesthetic, especially in nose and throat work. It has a greater paralytic action on the heart muscle than ether, but much less than chloroform. All anesthetics containing chlorine act strongly on the heart, as depressants.

Its main use is as a local anesthetic, the action being due to its rapid evaporation. Freezing with any other agent would have the same effect.

The most prominent action of the methane group as a whole is the anesthetic, hypnotic, and analgesic action. The members of the benzene series on the other hand have a more pronounced action on the motor side of the nervous system and are antiseptics.

HYPNOTICS AND ANALGESICS OF THE METHANE SERIES

(Hypnos—sleep)   (An. without—algos—pain)

These may be divided into:

      1. The chloroform group
      2. The urethane group
      3. The sulphone group

1. **The Chloroform Group.**—Chloroform, $CHCl_3$, is formed by the action of bleaching powder (a mixture of $CaCl_2$ and $CaOCl_2$) on dilute alcohol or acetone. The chloroform is distilled off, washed, and treated with concentrated H_2SO_4 to destroy other derivatives, and is then rectified. The bleaching powder supplies chlorine which is an oxidizing agent.

The reactions are complex, and probably as follows:

1. $C_2H_5OH + CaOCl_2 = CaCl_2 + CH_3CHO + H_2O$
2. $2CH_3CHO + 6CaOCl_2 = 3CaCl_2 + 3Ca(OH)_2 + 2C_2HCl_3O$
3. $2C_2HCl_3O + Ca(OH)_2 = 2CHCl_3 + Ca(CHO)_2$

4. with acetone:

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!\!>\!\!CO + 6CaOCl_2 = 2CHCl_3 +$$

$$2Ca(OH_2) + Ca(C_2H_3O_2)_2 + CaCl_2$$
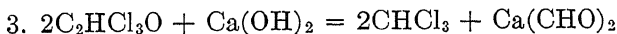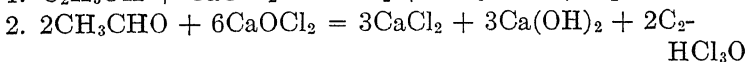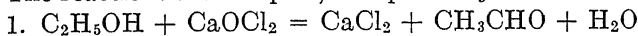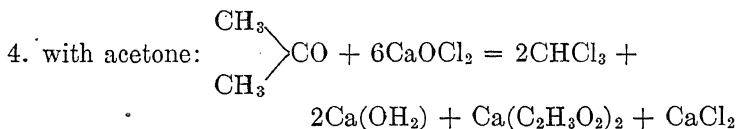
Chemical Tests

1. Place 2 cc. of chloroform in a dish and apply flame. Compare with ether and alcohol.

2. Add a few drops of $AgNO_3$ to chloroform. No precipitate if pure. Why? It contains chlorine. Make alkaline and again heat. Compare with chloral.

3. Evaporate 10 cc. from filter paper on a clean glass slide. No odor or residue should remain, if pure.

4. A paper dipped in chloroform burns with a green mantle and HCl is given off.

5. Test a few cc. of chloroform by boiling with a few drops of KOH and 0.1 gram of resorcinol. The intense red color is due to rosolic acid, a derivative of anilin. Chloral gives this same result.

Resorcinol $C_6H_4(OH)_2$ 1:3

Rosolic acid

$$C - C_6H_4OH \overset{\displaystyle C_6H_3\diagup CH_3}{\underset{\displaystyle \diagdown OH}{}}$$

$$\underset{\displaystyle C_6H_4 = O}{\diagdown\!\!\diagdown}$$
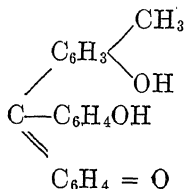
In the presence of air, chloroform decomposes slowly into carbonyl chloride (phosgene) and HCl.

$$CHCl_3 + O = COCl_2 + HCl.$$
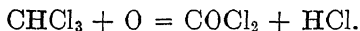
The carbonyl chloride is very poisonous. To prevent decomposition, it should be kept in the dark; and 1 per cent. alcohol added as a preservative. The action of the alcohol is as follows:

$$COCl_2 + 2C_2H_5OH = CO\!\!\!<^{OC_2H_5 \text{ (ethyl carbonate)}}_{OC_2H_5} + 2HCl$$
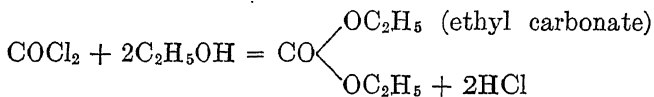
6. Chloroform is decomposed by passing its vapor through a hot tube. HCl is formed which can be recognized by testing with moist litmus paper, and by the precipitation of AgCl when passed into silver nitrate solution.

7. Phenyl Isocyanide Test.—Add 1–2 drops of aniline and a few drops of aqueous KOH to the chloroform. Heat gently. Phenyl isocyanide is produced. This has a characteristic indescribable repulsive odor. The reaction is:

$$CHCl_3 + C_6H_5NH_2 + 3KOH = C_6H_5NC + 3KCl + 3H_2O$$
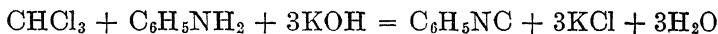
Chloral, chloralhydrate, bromoform, iodoform, and carbon tetrachloride also give this test. The test is sensitive 1 : 6000.

8. Chloroform will reduce Fehling's solution.

THE URETHANE GROUP OF HYPNOTICS

Urethane: Ethyl carbamate $CO{\Large<}{NH_2 \atop OC_2H_5}$
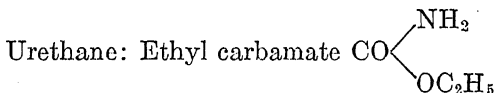
Urea and alcohol under proper conditions yield urethane.—

$$CO{\Large<}{NH_2 \atop NH_2} + C_2H_5OH \rightarrow CO{\Large<}{NH_2 \atop OC_2H_5} + NH_3$$
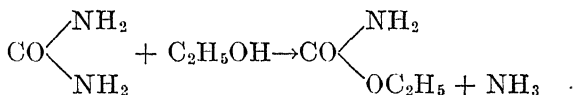
This is soluble in water, a weak hypnotic, and breaks down in the body to its components, probably by the following mechanism:

$$CO{\Large<}{NH_2 \atop OC_2H_5} + NH_3 = C_2H_5OH + CO{\Large<}{NH_2 \atop NH_2}$$
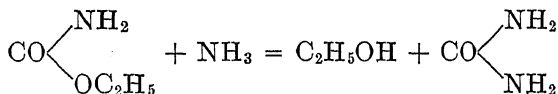
Nearly all substances in the body break down much more readily into their components than they can be synthesized. In the formation of urethane, indirect processes must be employed:

$$CO + 2Cl \text{ in sunlight} \rightarrow CO{\Large<}{Cl \atop Cl} \quad \text{carbonyl chloride}$$

$$CO{\Large<}{Cl \atop Cl} + C_2H_5OH \rightarrow CO{\Large<}{Cl \atop OC_2H_5} \text{ chloroformic ester} \quad + HCl.$$

$$CO{\Large<}{Cl \atop OC_2H_5} + NH_3 \rightarrow CO{\Large<}{NH_2 \atop OC_2H_5} \quad \text{Urethane} + HCl$$
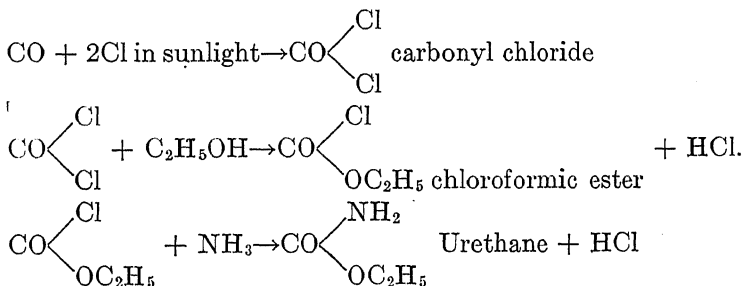
It has been found that the pharmacologic action of the urethanes, like the alcohols, increases with increased molecular weight, and with the size of number of the alcohol radicals, con-

sequently, diurethane, $CO\begin{smallmatrix}OC_2H_5\\OC_2H_5\end{smallmatrix}$ is a more powerful narcotic,

than urethane.

Hedonal, $CO\begin{smallmatrix}NH_2\\OCH\begin{smallmatrix}CH_3\\C_3H_7\end{smallmatrix}\end{smallmatrix}$ which is the ester of

urea and the amyl alcohol methyl propyl carbinol, is more power-ful than urethane. On account of both the urea and alcohol content, these drugs are strongly diuretic.

VERONAL

Diethyl malonyl urea, is made from urea, alcohol and malonic acid, by the introduction of esters of diethyl malonic acid with urea in the presence of metallic alcoholates. The following formulæ show the principles involved in the formation of veronal, and the basis for its chemical name:

$$CO\begin{smallmatrix}NH_2\\NH_2\end{smallmatrix} \quad CO\begin{smallmatrix}NH_2\\OC_2H_5\end{smallmatrix} \quad CO\begin{smallmatrix}OC_2H_5\\OC_2H_5\end{smallmatrix} + NH_3 \rightarrow$$

Urea   Urethane   ethyl carbonate

$$CO\begin{smallmatrix}NH_2\\OC_2H_5\end{smallmatrix} + C_2H_5OH$$

urethane   alcohol
or ethyl
carbamate

$$CH_2\begin{smallmatrix}COOH\\COOH\end{smallmatrix} + \begin{smallmatrix}C_2H_5\\C_2H_5\end{smallmatrix}C\begin{smallmatrix}COOH\\COOH\end{smallmatrix} + \begin{smallmatrix}H\\HN\\HN\\H\end{smallmatrix}C = O \rightarrow$$

Malonic acid   Diethyl malonic acid   urea

$$\begin{smallmatrix}C_2H_5\\C_2H_5\end{smallmatrix}C\begin{smallmatrix}CONH\\CONH\end{smallmatrix}CO + 2H_2O$$

Veronal   diethyl   malonyl urea

Chemical Tests

1. Prolonged boiling with sodium carbonate liberates NH_3.

2. In a solution acidulated with HNO_3 Millon's reagent produces a precipitate soluble in excess of the reagent.

3. The melting point of the crystals is 187°–188°C.

4. The presence of N is shown by fusing with KOH or NaOH and making the Prussian blue test, p. 8.

THE SULPHONE GROUP OF HYPNOTICS

Sulphuric acid may be written $\begin{array}{c} O \\ O \end{array} \!\!\!>\!\! S \!\!<\!\! \begin{array}{c} OH \\ OH \end{array}$. The replaceable hydrogen is not directly attached to the sulphur. When salts are formed, the replacing metal or radical is also not directly attached to the S, but to the oxygen: $\begin{array}{c} O \\ O \end{array} \!\!\!>\!\! S \!\!<\!\! \begin{array}{c} O-R \\ O-R \end{array}$
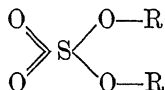
Similarly, in ethyl sulphuric $O_2S \!\!<\!\! \begin{array}{c} OC_2H_5 \\ OC_2H_5 \end{array}$

or phenyl sulphuric $O_2S \!\!<\!\! \begin{array}{c} OC_6H_5 \\ OC_6H_5 \end{array}$ (combined or etheral sulphates), the radical is not attached directly to the sulphur atom. These bodies are inert and phenyl sulphuric acid occurs normally in the urine up to 0.6 grams per day.

Sulphonic acids are compounds in which the carbon of the organic radical present is in direct union with the sulphur; the relation between ethyl sulphuric acid and ethyl sulphonic acid is shown by the formulæ:

$$\begin{array}{c} C_2H_5O \\ HO \end{array} \!\!\!>\!\! S \!\!<\!\! \begin{array}{c} O \\ O \end{array} \qquad \begin{array}{c} C_2H_5 \\ HO \end{array} \!\!\!>\!\! S \!\!<\!\! \begin{array}{c} O \\ O \end{array} \text{ or } \begin{array}{c} CH_3CH_2 \\ CH_3CH_2 \end{array} \!\!\!>\!\! S \!\!<\!\! \begin{array}{c} O \\ O \end{array}$$

ethyl sul-   ethyl sulphonic acid
phuric acid
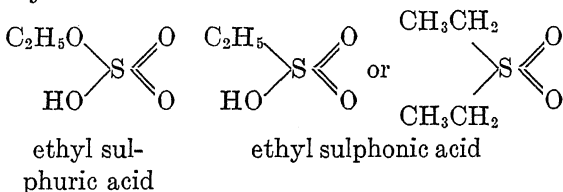
Where both OH groups of the sulphuric acid are replaced by radicals, the product is a sulphone: $\begin{array}{c} R \\ R \end{array} \!\!\!>\!\! SO_2$

The replaced radical may be methyl, ethyl, or any other alkyl group.

SULPHONAL

When acetone is mixed with mercaptan in the presence of HCl they condense:

$$\begin{array}{c} CH_3 \\ {\Large>} CO + H.SC_2H_5 = \\ CH_3 \end{array} \quad \begin{array}{c} CH_3 \quad S-C_2H_5 \\ {\Large>}C{\Large<} \\ CH_3 \quad S-C_2H_5 \end{array} + H_2O$$

$$H.SC_2H_5$$

Acetone   ethyl   acetone-ethyl mercaptol
           mercaptan
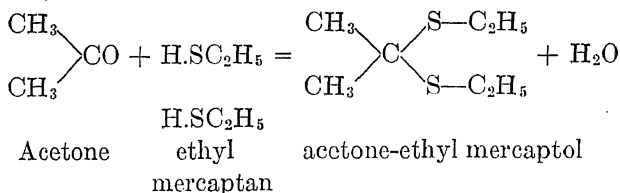
This can be oxidized by $KMnO_4$ to a sulphone:

$$\begin{array}{c} CH_3 \quad SC_2H_5 \\ {\Large>}C{\Large<} \\ CH_3 \quad SC_2H_5 \end{array} + 2O_2 = \begin{array}{c} CH_3 \quad SO_2C_2H_5 \\ {\Large>}C{\Large<} \\ CH_3 \quad SO_2C_2H_5 \end{array}$$
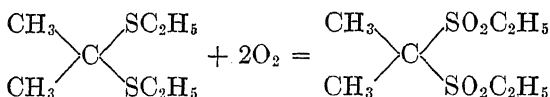
This is acetone diethyl sulphone or sulphone methane or diethyl sulphone dimethyl methane: The name is shown by the following steps:

1.
$$\begin{array}{c} H \quad\quad H \\ {\Large\diagdown}\;{\Large\diagup} \\ C \quad\quad (methane) \\ {\Large\diagup}\;{\Large\diagdown} \\ H \quad\quad H \end{array}$$

2.
$$\begin{array}{c} CH_3 \\ {\Large>}C = O \quad (acetone\ or\ dimethyl\ oxymethane) \\ CH_3 \end{array}$$

3.
$$\begin{array}{c} CH_3 \quad SC_2H_5 \\ {\Large>}C{\Large<} \\ CH_3 \quad SC_2H_5 \end{array}$$ (acetone ethyl mercaptol or dimethyl diethyl mercaptol methane)

4.
$$\begin{array}{c} CH_3 \quad SO_2C_2H_5 \\ {\Large>}C{\Large<} \\ CH_3 \quad SO_2C_2H_5 \end{array}$$ (dimethyl methane diethyl sulphone or sulphonal).

TRIONAL

This differs from sulphonal in that one of the CH_3 groups is replaced by ethyl C_2H_5:

$$\begin{array}{c} CH_3 \quad SO_2C_2H_5 \\ {\Large>}C{\Large<} \\ C_2H_5 \quad SO_2C_2H_5 \end{array}$$ consequently it is diethyl sulphone
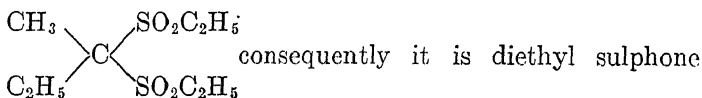
TETRANOL

This has all the replaceable hydrogen occupied by ethyl groups:

$$\begin{array}{c} C_2H_5 \\ \\ C_2H_5 \end{array}\!\!\!\!\!\!C\!\!\!\!\!\!\begin{array}{c} SO_2C_2H_5 \\ \\ SO_2C_2H_5 \end{array}$$ and is diethyl sulphone diethyl methane.
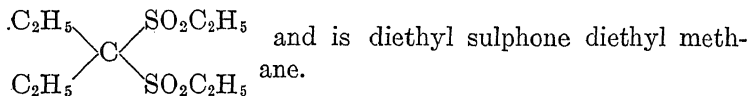
Since the pharmacological action of hydrocarbon radicals increases with the size of the molecule, we should expect trional to be more active than sulphonal. While this seems to be true for dogs, it does not seem to hold good for human beings. It should be emphasized that CH_3, or the first of the series, is nearly always an exception to the rule, both chemically and pharmacologically.

Sulphones are not true esters, but bodies of remarkable stability. They cannot be reduced to sulphides by nascent hydrogen. However, their stability outside the body is no criterion of their pharmacological activity; since some of those that are most stable are physiologically reactive and more or less decomposed in the body, while some less stable outside the body pass through it unchanged and are inert pharmacologically.

Ethylene diethyl sulphone:

$$\begin{array}{l} CH_2.SO_2C_2H_5 \\ | \\ CH_2.SO_2C_2H_5 \end{array}$$ and methylene di-ethyl sulphone $CH_2\!\!\!<\!\!\!\begin{array}{l} SO_2C_2H_5 \\ SO_2C_2H_5 \end{array}$ are easily decomposed

by alcoholic potash, but may be found unaltered in the urine, and are only slightly active physiologically, whereas, sulphonal, trional and tetronal, which are unacted on by alcoholic potash, acids, and many oxidizing and reducing agents, are decomposed in the body to some extent at least and are actively hypnotic.

Chemical Tests

Test solubility of each in water, alcohol, and ether.

Heat 0.1 gm. of each separately with an equal amount of charcoal in a dry test tube. Each one will be reduced to the sulphur alcohol which is recognized by its odor, which is similar to garlic.

Heat another portion of fusion in a test tube alone, SO_2 is given off and will bleach starch iodide, or methylene blue paper.

V. ALDEHYDES

Aldehydes are the first oxidation products of primary alcohols. Primary alcohols contain the group R, CH_2OH. Aldehydes contain the group $RC{<}^O_H$. Where R may be H, CH_3, C_2H_5, or any member of the marsh gas series. In the case of phenol groups with an aldehyde side chain, almost any complex may take the place of (R).

Aldehydes may be prepared:

1. By the oxidation of any primary alcohol;

$$CH_3CH_2OH + O = CH_3-C{<}^O_H + H_2O$$

2. $C_6H_5CH_2OH + O = C_6H_5-C{<}^O_H + H_2O$

    benzyl alcohol   benzaldehyde
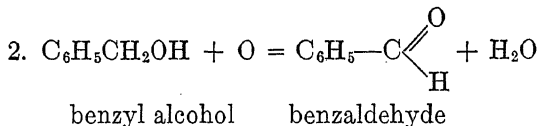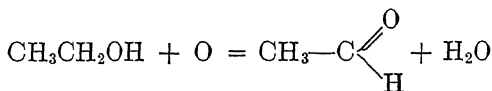
3. By dry distillation of a calcium salt, with calcium formate:

$Ca(CH_3COO)_2 + Ca(H.COO)_2 = 2CH_3CHO + 2CaCO_3$ or

$(C_6H_5COO)Ca + Ca(HCOO)_2 = C_6H_5COH + 2CaCO_3$
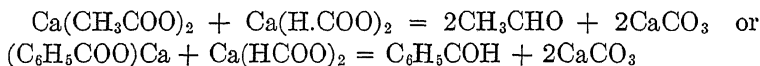
The mechanism of the reaction may be represented;

$$\frac{CH_3|COONa}{\overline{HCO}|ONa} \rightarrow CH_3C{<}^O_H + Na_2CO_3$$
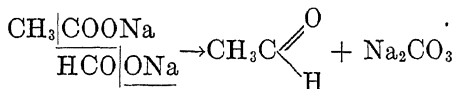
Any other method of oxidizing an alcohol or reducing an organic acid may yield an aldehyde.

General Properties of Aldehydes. Reactions.—The characteristic reactions are due to the group $-R-C{<}^O_H$ which shows exceptional chemical reactivity: the H atom in combination with $-C{<}^O_H$ can be readily oxidized, by the action of oxidizing

reagents. Since they are readily oxidized, aldehydes act as reducing agents; and when they are added to an ammoniacal solution in a test tube of silver nitrate the silver is precipitated as a silver mirror. For the same reason, they reduce Fehling's solution.

They form addition products readily. This is due to the $C = O$ group which opens up in the form: $C \!-\! O$ and the free valences add anything in the form of H and X as follows:

$$CH_3C\!\!<^O_H \ + \ HCN \rightarrow CH_3C\!\!<^{OH}_{\ \ CN}_H$$
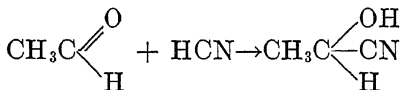
(a) For this reason, they are easily reduced by nascent hydrogen the same primary alcohol from which they were derived being formed—

$$CH_3C\!\!<^O_H \ + \ H_2 \rightarrow CH_3C\!\!<^{OH}_{\ \ H}_H$$
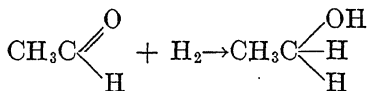
(b) When shaken with a saturated solution of sodium acid sulphite, a crystalline addition product is formed.

$$CH_3C\!\!<^O_H \ + \ NaHSO_3 \rightarrow CH_3\!-\!\overset{H}{\underset{SO_3Na}{C}}\!\!-\!OH$$
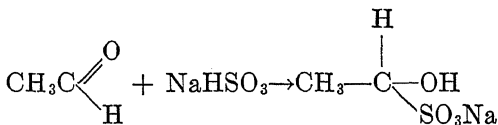
On heating this product with acid aldehyde is again liberated.

(c) Aldehydes unite with ammonia to form aldehyde ammonia

$$CH_3C\!\!<^O_H \ + \ NH_3 = CH_3\!-\!\overset{H}{\underset{NH_2}{C}}\!-\!O\!-\!H$$
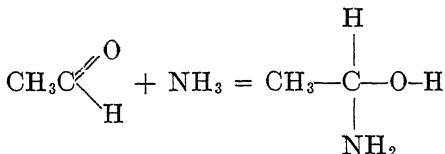
Similarily with hydroxyl amine, NH_2OH, hydrazines, etc., addition products are formed, the added product always breaking or ionizing into H and X. The H adds to the O of the aldehyde, and the X to the carbon.

4

Caustic alkalies differ from ammonia in their action on aldehydes. Instead of forming a definite compound they convert the lower aldehydes into resinous bodies of unknown composition.

Formaldehyde $H—C{<}^{O}_{H}$ (Methanal) is the aldehyde of methyl alcohol $CH_3OH + O = CHOH + H_2O$. At ordinary temperatures it is a gas and liquefies at (minus) $-21°C$. It may be prepared easily by heating a copper spiral and dropping it into methyl alcohol in a test tube. It may also be formed in the body from methyl alcohol. It can also be derived from hydrogen and carbon monoxide under the influence of an electric current. At $600°C$. it is dissociated into CO and H_2. Minute amounts of it are found in plants where it is highly important, from a theoretical point of view, in the formation of carbohydrates. The steps involved may be represented by the following reactions: (Baeyer)

1. $CO_2 \leftrightharpoons CO + O$
2. $H_2O \rightarrow H + OH$
3. $CO + H_2 \rightarrow CH_2O$
4. $6(CH_2O) \rightarrow C_6H_{12}O_6$

or carbon dioxide and water may react:

$CO_2 + H_2O = CH_2O + O_2$
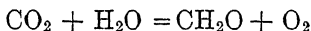
In combination with ammonia it forms hexamethylenamine or urotropine. When it is evaporated on a water bath, it polymerizes to form paraformaldehyde $(CH_2O)_2$. Trioxy methylene $(CH_2O)_3$ is a white crystalline compound that separates from formaldehyde on standing. It liberates formaldehyde again when it is heated.

Formaldehyde unites with amines, ammonia, sugars, dextrins, urea, tannic acid, proteins, and many other substances. It is therefore, a strong antiseptic, a local irritant and a general protoplasm poison, yet it is surprising how much of it may be injected intravenously into an animal without killing it. The reason being that it is oxidized or polymerized rapidly in the body. Even though it does not kill, it may produce a severe nephritis. The irritation is probably produced by the union with an amine group of the proteins.

The amine and aldehyde groupings may exist in the living protoplasm simultaneously. Loew explained the difference between living and dead protoplasm on a rearrangement of such a grouping. In the living or labile molecule or biogen he assumed the grouping to be:

$$\begin{array}{c} H \\ | \\ -C-NH_2 \\ \| \quad \diagdown \\ =C-C \diagup\!\!\diagdown O \\ \qquad H \end{array}$$ In the dead or stable form

$$\begin{array}{c} H \\ | \\ -C-N-H \\ \| \quad | \\ =C-C-OH \\ | \\ H \end{array}$$
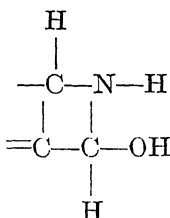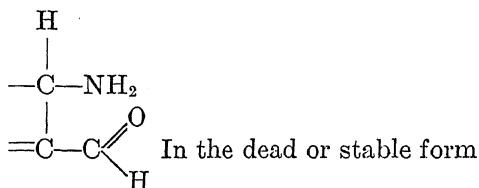
such a difference of course would be very difficult to prove.

Formaldehyde is valuable in medicine chiefly as an antiseptic, disinfectant, preservative and cauterizing agent. A solution of 37 per cent. by weight is known commercially as formalin.

On account of its relative physiological inertness and great antiseptic powers, in vitro, it was thought that formaldehyde might be injected into the veins with benefit in cases of tuberculosis and other infections. It is now known, however, that it is rather inert in the body because it is rapidly oxidized, and for this same reason it possesses relatively little antiseptic action in the body. In addition it shows no specificity. When the concentration in the body is sufficient to exert an antiseptic action, it will injure the tissues of the body just as readily as the bacteria within the tissues. Compounds of formaldehyde like hexamethylentetramine, that are decomposed in the body and excreted in the urine, are valuable in cases of infection of the genito-urinary tract and bladder. The concentration of the aldehyde in the urine is much greater than it is in the blood.

Tests for Formaldehyde

In solutions which are not clear, or in food products which are to be tested for its presence it is necessary in many cases to distil and test the distillate from 100 to 200 grams of the substance which has been acidified with phosphoric acid. Phosphoric acid is used because it is a non-volatile acid and will not appear in the distillate.

1. Add to the formalin solution, diluted if necessary, about 1 cc. of pure milk or a solution of peptone. Add 1–2 drops of 1 per cent. ferric-chloride solution. Carefully pour this solution into a test tube containing about 10 cc. of strong H_2SO_4. See that the two solutions do not mix. At the point of contact a violet or blue ring will appear. If the solution containing the formaldehyde is too strong, the result will not be so clear. If the milk contains less than 1:10,000 formaldehyde, the color may not appear for some time.

2. To the milk or peptone solution containing the formalin add double the volume of strong HCl containing 1 cc. of 10 per cent. Fe_2Cl_6 in each 500 cc. of acid. Heat to 80° to 90°C. in a white dish giving it a rotary motion to cause mixing. A violet color indicates formaldehyde. To test a suspected milk for formalin, use this same procedure. If the milk has stood for a long time, it may be necessary to distil it, as a firm combination of the formalin with the protein prevents the test to some extent.

3. **Lieberman's Test.**—Mix some of the watery solution of formalin with a drop of 1 per cent. phenol and pour cautiously, on some concentrated H_2SO_4 in a test tube. A crimson zone at point of contact indicates formaldehyde.

The Cannizzaro Reaction.—In the body, if formalin be given intravenously, there is both oxidation and reduction of it with the formation of methyl alcohol and formic acid:

$$2HC{\Large\diagup}^{\displaystyle O}_{\displaystyle H} + H_2O = CH_3OH + HCOOH$$
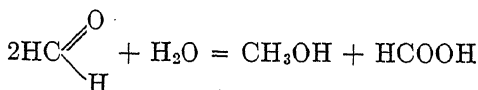
The presence of HCOOH may be shown by collecting the urine, reducing it with hydrogen and testing for formalin.

4. **Rimini's Method.**—To 15 cc. of the solution to be tested add 1 cc. of a dilute solution of phenyl hydrazine hydrochloride,

n a few drops of 1 per cent. ferric chloride solution and finally
icentrated HCl. A rose red color is given by formaldehyde.
lk can be tested without distillation by this method, but the
t is more delicate if a distillate is used. Acetic aldehyde or
izaldehyde do not interfere with the test.

5. **Phloroglucinol Test (Jorissen).**

Take phloroglucinol	0.1 gram
NaOH	2.0 gram
Aq. q.s.	10.0 cc. Make solution

10 cc. of milk or other fluid to be examined, add 2 cc. of this
gent by means of a pipette, placing the end of the pipette at
bottom of the tube in such a manner that the reagent will
n a separate layer. A bright red color, not purple, is formed
the zone of contact, if formaldehyde be present. Some other
ehydes, give a yellow color. The red color forms quickly and
n fades.

. **Phenylhydrazin HCl Method.**—Mix 5 cc. of the solution
e tested with 0.03 gram of phenylhydrazine hydrochloride and
5 drops of a 1 per cent. solution of ferric chloride. Keep the
tube containing this in cold water and add slowly with con-
it shaking to prevent heating, 1 to 2 cc. of concentrated
SO_4. A precipitate is formed which can be redissolved by the
ition of either alcohol or H_2SO_4; giving a red color. The
hol extract of anything to be tested will also give the
tion. This test has been found to give reliable reactions in
ilution of 1 to 150,000 formaldehyde. Acetic aldehyde or
zaldehyde, does not interfere.

. **Phenylhydrazine Hydrochloride and Ferrocyanic Method.**
s method can be applied directly to aqueous solutions or
eous alcoholic extracts. To from 3 to 5 cc. add the size of a
of phenylhydrazin hydrochloride and 2 to 4 drops (not more)
5 per cent. to 10 per cent. solution of potassium ferrocyanide
from 8 to 12 drops of 12 per cent. NaOH. A distinct green
luish green reaction is obtained in a dilution of 1–80,000
aldehyde.

cetic and benzaldehyde give a color from red to brown and
k the formaldehyde reaction. It is characteristic only when

a clear green color is obtained. The method is not applicable where blood coloring matter is present, but can be used with milk directly.

HEXAMETHYLENAMINE

Formaldehyde reacts with ammonia to form hexamethylenamine. The reaction is $6CH_2O + 4NH_3 = (CH_2)_6N_4 + 6H_2O$. This is represented as—
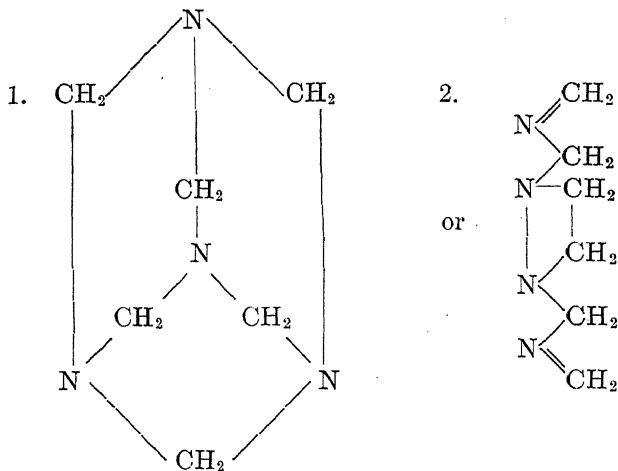
It is a feebly basic crystalline solid, which dissolves readily in water.

Hexamethylenamine is a valuable remedy in some cases of cystitis and infections of the urinary tract. It has also been used in laryngitis, pharyngitis, poliomyelitis, etc. It has but a slight irritating action, and only when taken in excessive amounts, does it cause nephritis or other untoward symptom. It is found on the market under a variety of names such as urotropin, cystogen, cystamine, hexamine, etc.

It has some solvent action on uric acid, and has been recommended in gout; but the concentrations that dissolve uric acid never obtain in the organism. It forms a number of additive products which have been introduced into medicine, such as amphotropin which is a combination with camphor; cystopurin, with sodium acetate; formurol with sodium citrate; cystazol,

with sodium benzoate. New urotropin, or helmitol, is anhydromethylene citric acid:

$$CH_2\text{---}O\text{---}CO$$
$$O\text{---------}C\text{---}CH_2\text{---}COOH$$
$$CH_2\text{---}COOH$$
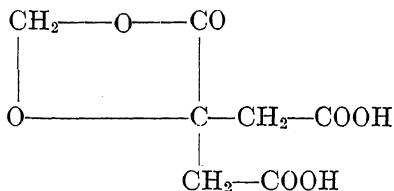
None of these compounds have any advantage over hexamethylenamine.

1. Mix 0.1 gram each of hexamethylenamine and salicylic acid. Add 5 cc. H_2SO_4 and heat moderately. A carmine-red color is produced.

2. An aqueous solution heated with dilute H_2SO_4 liberates formaldehyde. If the acid solution is made alkaline with NaOH and heated gently, NH_3 is given off.

3. Test the reaction of urine. Take 5 grains of hexamethylenamine. In 30–60 minutes collect the urine. Note the reaction. Acidify and distil 10–20 cc. Test the distillate for formaldehyde. It may not be necessary to distil the urine before testing. Make the test before distillation and, if in doubt, distil and test.

ACETALDEHYDE, ALDEHYDE OR ETHANAL

$CH_3\text{---}C\overset{\displaystyle O}{\underset{\displaystyle H}{\diagup\!\!\!\diagdown}}$ is not used in medicine, but some of its derivatives
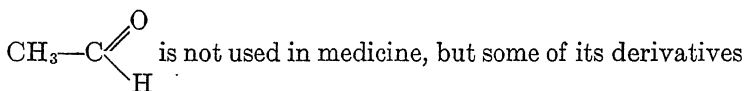
paraldehyde, chloral and chloral hydrate are important. From a purely chemical point of view, acetaldehyde is perhaps the most important aldehyde. It is a colorless liquid, B. P. 21°, sp. gr. 0.8, soluble in water, alcohol, and ether, dissolves phosphorus, sulphur, iodine. It occurs as a by-product in all sugar fermentations. The following method of preparation illustrates strikingly some of the characteristic reactions of aldehydes: (after Remsen):

Place 120 grams of granulated potassium bichromate in a 1 to 2 liter flask A.

(a) Place a stopper with two holes in the flask, and set on water bath.

(b) Insert a funnel tube in one opening and a condenser in the other. Elevate the condenser at an angle of 45°, so that it

acts as a reflux. Connect the free end of the condenser by means of rubber and a glass tube (E) with cylinders F and G, half-filled with ether. The glass tubes E and I should dip well into the ether.

Make a mixture of 100 cc. concentrated H_2SO_4 water 400 cc. and alcohol 120 cc. Cool the mixture to room temperature and pour it slowly into the flask.

If the liquid is added too rapidly to the bichromate mixture, the action may be too violent. Some alcohol may enter the condenser and flow back again into the flask. The aldehyde is soluble in the ether. Supply the condenser with water at about
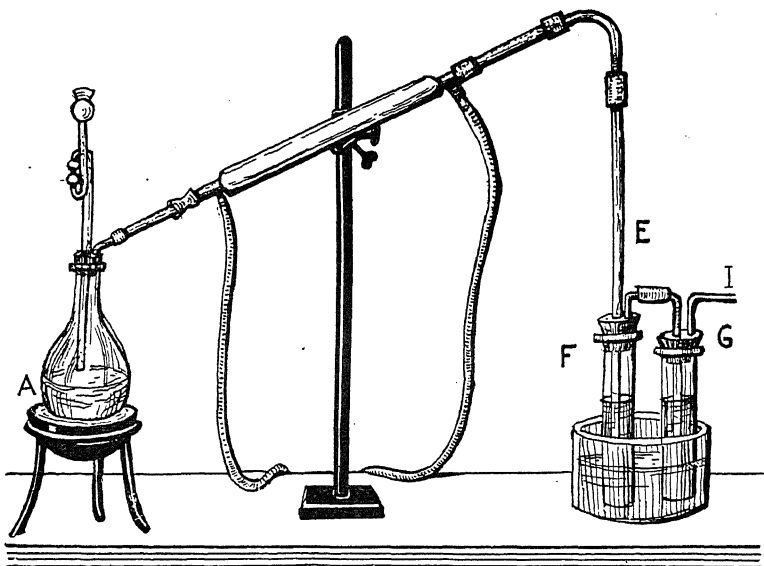
Fig. 1.

30°C. Heat is applied to finish the distillation. After the reaction is ended, the connections are broken and dry NH_3 gas is passed through the cold ethereal solution of the aldehyde.

Crystals of aldehyde ammonia are deposited. The ether and the crystals are poured on a filter and the crystals washed with ether. The pure crystals are then placed in a flask and sulphuric acid added when aldehyde is liberated. It may be distilled and condensed in a vessel surrounded by ice.

The reactions involved in the preparation of acetaldehyde are:

$$CH_3CH_2OH + O \rightarrow CH_3CHO + H_2O$$
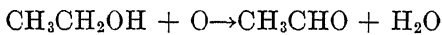
If one inhales fumes of acetaldehyde there is a feeling of suffocation with coughing. In animals its irritative action causes excitement followed by depression, and paralysis of respiration. A considerable portion of ingested aldehyde is oxidized in the body, traces escape in the breath and more in the urine. Kunkel describes a condition of aldehydeismus in people exposed to aldehyde fumes. In such cases there is thickening of the adventitia of the vessels and an increase of connective tissue between the lobes of the liver.

PARALDEHYDE

$(CH_3CHO)_3$. This is the polymer of acetaldehyde. It is detected only after being reconverted into acetaldehyde.

Graphic formula:
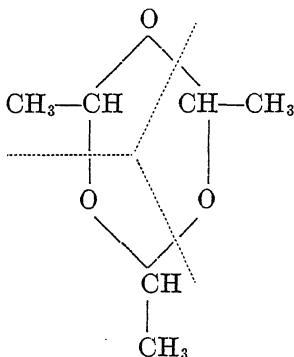
Paracetaldehyde, or paraldehyde

Paraldehyde is little used in therapeutics because of the persistent disagreeable taste. Formerly it was commonly used in medicine as a hypnotic. It is used now chiefly in delirium tremens—where it is often more efficacious than other sedatives. The dose is 0.5 gram but the patient soon becomes accustomed to it and if larger doses are given to get the effect, tremors, delirium, hallucinations and epileptiform convulsions may result.

CHLORAL AND CHLORALDEHYDE

Chlorine is an oxidizing agent. When it acts on alcohol, chloraldehyde is formed as follows:

1. $CH_3CH_2OH + Cl_2 \rightarrow CH_3CHO + 2HCl$
2. $CH_3COH + 6Cl \rightarrow CCl_3CHO + 3HCl$

There are many intermediate reactions in this, but the above are the essential steps. An important intermediate reaction is the union of alcohol and the aldehyde to form acetal;

$$
\begin{array}{ccc}
\mathrm{CH_3} & \mathrm{OH.C_2H_5} & \mathrm{CH_3} \\
| & & |\quad\diagup\mathrm{OC_2H_5} \\
\mathrm{C} = \mathrm{O} + & & \rightarrow\mathrm{C}\qquad\qquad + \mathrm{H_2O} \\
| & & |\quad\diagdown\mathrm{OC_2H_5} \\
\mathrm{H} & \mathrm{OH.C_2H_5} & \mathrm{H}
\end{array}
$$
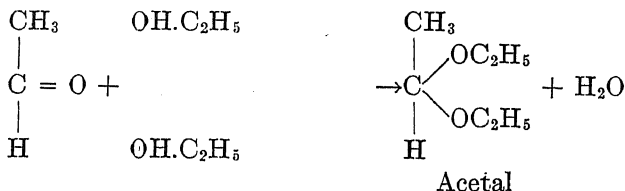
Acetal

Acetal is an uncertain hypnotic and produces unpleasant heart depression, and patients soon become habituated to it. By analogy one would think that water HOH would react with acetaldehyde to form an addition product, *e.g.*:

$$
\begin{array}{ccc}
\mathrm{CH_3} & & \mathrm{CH_3} \\
| & \mathrm{OHH} & |\quad\diagup\mathrm{OH} \\
\mathrm{C}{=}\mathrm{O} + & & = \mathrm{C}\qquad + \mathrm{H_2O} \\
| & \mathrm{OHH} & |\quad\diagdown\mathrm{OH} \\
\mathrm{H} & & \mathrm{H}
\end{array}
$$
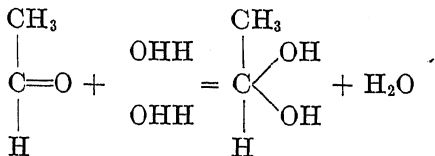
But there is a general law in organic chemistry that a single carbon atom cannot hold two OH groups. As a result, another molecule of water is eliminated and the aldehyde reformed. With chloraldehyde (chloral), however, the Cl in the molecule so modifies the action of the carbon atom that it does hold two OH groups in firm union. Chloral for this reason is the exception to the rule.

CHLORAL AND CHLORAL HYDRATE (Chloraldehyde)

Chloral is a colorless oily liquid with a pungent odor and acrid taste, while chloral hydrate is crystalline. Chloral itself is little used, the hydrate being very commonly used.

Chloral, $\mathrm{CCl_3CHO} + \mathrm{H_2O} = \mathrm{CCl_3CH(OH)_2}$, chloral hydrate.

Chloral hydrate like aldehydes is irritant to the skin and mucous membranes and is a very disagreeable drug to take. For these reasons if given in too concentrated a form it may cause vomiting. The burning or irritant action may be followed by some local anesthesia. When administered it should be well diluted with water and a flavoring agent like syrup of orange or citric acid. After too large a dose there may be hemorrhages in

the stomach and intestines, and sometimes in nose and lungs. By its continued use catarrh of the stomach and a skin rash frequently develop. With toxic doses the blood pressure and body temperature sinks, respiration is weakened, cyanosis, coma, and edema of the lungs result. All the symptoms of alcoholic intoxication may precede these symptoms.

The Fate of Chloral in the Body

Because chloral or chloral hydrate yield chloroform when heated with KOH, Liebrich explained their hypnotic action, by assuming that they yielded chloroform in the body. Chloral, however, is not decomposed to any extent in the body. The fate of chloral in the body is interesting since it is reduced rather than oxidized. It is well known that both oxidations and reductions occur in the body, but oxidations are much more frequent, and apparently more important. The fate of chloral seems to be as follows:

1. Chloral is reduced to the corresponding alcohol, trichlorethylalcohol.

$$CCl_3CHO \rightarrow CCl_3CH_2OH$$
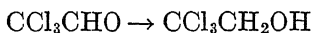
2. The alcohol combines with glycuronic acid and the combination is urochloralic acid, or $C_8H_{11}Cl_3O_7$. This substance reduces Fehling's solution, but does not ferment with yeast. It is also decomposed into the alcohol and glycuronic acid on boiling with dilute acids. The combination of trichlorethyl alcohol and glycuronic acid may be represented as follows:

Glycuronic acid   Urochloralic acid
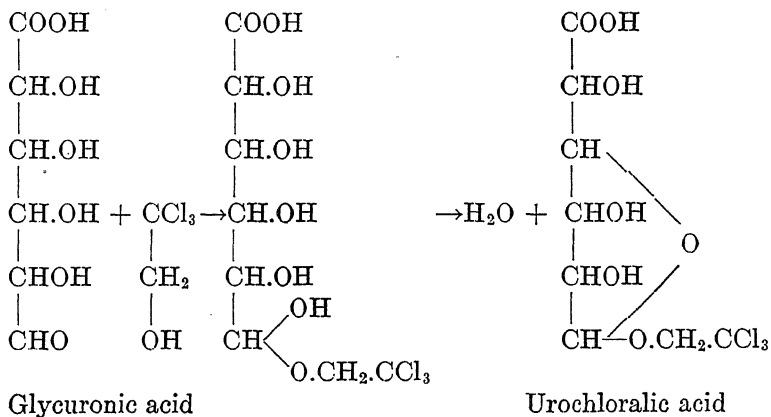
It should be noted in this representation that the glycuronic acid is formed before the union with the alcohol. As a matter of fact, such union of the alcohol with glucose may be necessary for the formation of glycuronic acid in the body (see p. 175, glycuronic acid).

1. Heated with KOH, chloral or its hydrate yields chloroform. Dissolve 0.5 grams chloral hydrate in 5 cc. of water, add a few drops of KOH and heat. Note the odor. $CCl_3CHO + KOH \rightarrow CHCl_3 + HCOOK$. All alkaline hydrates, carbonates, and borax cause this decomposition.

2. Like all aldehydes, chloral reduces Fehling's solution, and alkaline silver nitrate solutions.

3. In alcoholic solutions, with NaBr, or KBr, chloral forms chloral alcoholate

$$CCl_3CH \begin{cases} OC_2H_5 \\ OH \end{cases} \quad \text{an oily liquid}$$
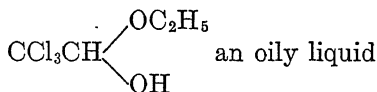
4. Chloral triturated with camphor, acetanilide, acetphenetidin, urethane, phenol, salol, or thymol, produces a liquid. Use equal parts of chloral and the others, to show this. Such combinations are incompatible in prescriptions (pharmaceutic or physical incompatibility).

5. It is also incompatible with antipyrine with which it forms $C_{13}H_{15}H_2O_3Cl_3$ (hypnal) and $C_{13}H_{13}Cl_3H_2O_2$ (chloral antipyrine). Hypnal resembles chloral hydrate in action while chloral antipyrine is inert.

6. A solution of chloral hydrate with a little resorcinol and a few drops of NaOH gives an intense red (rosolic acid), which is destroyed by HCl.

7. With ammonium sulphide, chloralhydrate gives an orange color, changing to brown. The color develops more quickly on warming.

8. Chloral is sometimes given as a poison ("knock-out drops"). In such cases, it is excreted in the urine. To obtain chloral from the urine, acidify with tartaric acid and distil. To obtain the whole of the chloral from the urine, it is necessary to distil in vacuum almost to dryness. Test the distillate for chloral.

To Test Urine Directly for Chloral

CAUTION: THIS IS DANGEROUS. To about $\frac{1}{3}$ of a test tube full of urine add one drop of anilin, then add 2 cc. of an alcoholic solution of NaOH. If chloral is present, it will be manifested by the disagreeable odor of phenyl isocyanide or carbylamine C_6H_5NC.

Chloroform also gives this reaction:

$$CHCl_3 + C_6H_5.NH_2 = C_6H_5.NC + 3HCl$$
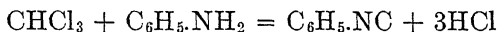
This is a very poisonous substance and must be handled with care. The products should be washed away through a sink pipe in a draught closet.

9. Pure chloral hydrate does not give the iodoform reaction.

10. **Nessler's Solution Test.**—Add a few drops of Nessler's solution to aqueous chloral hydrate and shake. A yellowish red precipitate forms changing to yellowish green. This is an aldehyde reaction.

11. Boil an aqueous solution of chloral hydrate with 0.3 gram solid sodium thiosulphate. A turbid brick red liquid results. KOH changes this to brownish red.

Chloralose is compound of chloral and grape sugar. It is made by heating together anhydrous chloral and glucose:

$$CCl_3CHO + C_6H_{12}O_6 = C_8H_{11}Cl_3O_6 + H_2O$$
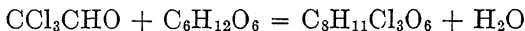
The introduction of the sugar into the molecule makes it act more like morphine than chloral, and it may produce restlessness, tremors and hemoglobinuria. Large doses by heightening the reflexes may produce strychnine-like convulsions. Why such a combination should so change the action of the original drug is beyond chemical explanation. All these compounds illustrate the reactivity of aldehydes.

Chemical Tests

1. Soluble—freely in hot water. Less readily in cold.
2. When hydrolyzed it yields glucose and chloral.

The compounds of bromine and iodine corresponding to chloral have no uses in medicine.

VI. KETONES

When primary alcohols are oxidized they yield aldehydes, while secondary alcohols yield ketones. Propyl alcohol (primary) $CH_3CH_2(CH_2OH)$ on oxidation yields CH_3CH_2CHO, propyl aldehyde. Isopropyl alcohol (secondary) $CH_3CH(OH)$-CH_3, yields $CH_3CO.CH_3$, acetone. Ketones have the general formula

$$\begin{matrix} R \\ \\ R \end{matrix}\!\!\diagdown\!\!\diagup CO$$
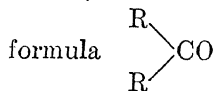
Ketones are also prepared by the distillation of the calcium salt of the corresponding acid. The reaction has been most carefully studied in the distillation of calcium acetate, and the ketone from this is called acetone. The reaction takes place according to the following equation:

$$\begin{matrix} CH_3{-}COO \\ \\ CH_3{-}COO \end{matrix}\!\!\diagdown\!\!\diagup Ca \rightarrow \begin{matrix} CH_3 \\ \\ CH_3 \end{matrix}\!\!\diagdown\!\!\diagup CO + CaCO_3$$
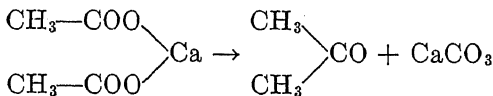
ACETONE

Acetone, $CH_3CO.CH_3$ is the most important ketone. It is of importance principally as a solvent, and in the preparation of chloroform, sulpho-methanum (sulphonal), etc. It has been used as an anesthetic, hypnotic and anthelmintic, but its use is now restricted to its solvent action, and the preparation of other drugs, especially the sulphone group of hypnotics.

It is a pathological constituent of urine, especially in diabetes and severe forms of cancer (carcinomatous acetonuria). It has also been found in the urine after poisoning with the following drugs (toxic acetonuria) phosphorus, carbon monoxide, atropine, curara, antipyrina, pyridine, male fern, chronic lead poisoning and in morphinism after discontinuance of the drug.

Secondary alcohols are more toxic than primary. Isopropyl alcohol in the case of rabbits is about five times as toxic as propyl. Two grains of isopropyl alcohol in a rabbit produces drowsiness and sleep. Acetone, however has feeble narcotic properties and is less toxic than ethyl alcohol. Archangelsky found that dogs show signs of narcosis when the blood contains 0.5 per cent. acetone. Smaller doses produce narcosis in rabbits, but the toxic action is not great. Urine almost always contains some acetone which is increased in diabetes and protracted fevers,

such as typhoid, tuberculosis and pneumonia. It has also been observed in the urine in various nervous and mental diseases.

Chemical Tests

1. Test solubility of acetone in water, alcohol, ether, chloroform and volatile oils. Note the odor.

2. Acetone is formed by the distillation of calcium acetate.

$$Ca(CH_3CO_2)_2 = CH_3COCH_3 + CaCO_3$$

3. Acetone occurs in the urine in diabetes. It yields iodoform when treated with iodine solution as does alcohol. See tests under alcohol.

4. **Legal's Test.**—To 1 drop of acetone in 5 cc. of water, add an equal volume of freshly prepared sodium nitro-prusside and a few drops of NaOH. A red color results which becomes darker on adding acetic acid. Creatinine gives this same red color but it disappears on adding acetic acid.

5. Acetone differs from aldehyde as follows:

(*a*) It does not polymerize.

(*b*) It does not reduce ammoniacal solutions of silver hydroxide.

(*c*) It is oxidized only by moderately powerful reagents and when oxidized yields acetic acid, carbon dioxide and water.

6. Acetone gives Lieben's iodoform test (page 23), even when NH_4OH is used instead of NaOH or KOH.

7. **Penzoldt's Test.**—Add acetone and a few drops of NaOH (5 per cent.) to a saturated aqueous solution of ortho-nitro-benzaldehyde. The mixture becomes yellow, then green on standing and after 15 minutes a blue precipitate of indigotin is formed. When shaken with chloroform indigotin goes into solution and colors the chloroform blue.

8. **Reynold's Test.**—Freshly precipitated mercuric oxide is dissolved by acetone. Add a little mercuric chloride, and an equal volume of alcoholic KOH to an acetone solution. Shake thoroughly and filter. To the filtrate add $(NH_4)_2S$ to form a layer. A black ring of HgS indicates that some mercuric oxide was dissolved.

CHLORETONE

Chloretone is acetone chloroform

$$\begin{matrix} CH_3 \\ \diagdown \\ \diagup \\ CH_3 \end{matrix} CO + CHCl_3 = \begin{matrix} CH_3 \\ \diagdown \\ \diagup \\ CH_3 \end{matrix} C \begin{matrix} OH \\ \diagup \\ \diagdown \\ CCl_3 \end{matrix}$$
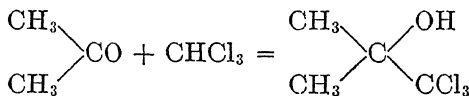
It is produced by the action of caustic alkalies on a mixture of acetone and chloroform. It is a peculiar camphoraceous crystalline body, sp. gr. 0.792 at 20°C. It is miscible with water, alcohol, ether, volatile and fixed oils. Calcium chloride sets it free from its aqueous solution. It reduces Fehling's solution.

It is more dangerous than chloral and is therefore little used except for laboratory animals. The mechanism of the action is unknown. Anesthetics or hypnotics when taken by mouth have the disadvantage that they cannot be removed if too much has been taken. In case of ether and chloroform, if it is seen that too much is being given, the drug can be removed and the excess in the body is soon exhaled.

Chloretone is less irritant to the stomach and it has been used to some extent as a substitute for chloral. It has also some local anesthetic properties, and has been used in the dressing of wounds, either in the form of dusting powder or in solution.

The fate of chloretone in the body is unknown. After the administration of large doses Houghton and Aldrich could not find it in any of the secretions or excretions and concluded that it is destroyed in the body.

VII. ORGANIC ACIDS

Organic acids are either the second products of the oxidation of alcohols, or the third products of the oxidation of hydrocarbons:

I	II	III	IV
C_2H_6	C_2H_5OH	CH_3CHO	CH_3COOH
ethane	alcohol	aldehyde	acid

The characteristic acid group is carboxyl—COOH. The basicity of the acid depends upon the number of the carboxyl groups in the acid.

When salts are formed, substitution of the carboxyl hydrogen takes place:

$$CH_3COOH + NaOH = CH_3COONa + H_2O$$
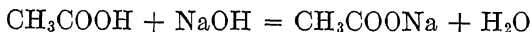
The introduction of the COOH group into the hydrocarbon or alcohol changes the toxicity of the members and of the methane series but slightly. With the dibasic acid the proximity of the

COOH groups in the molecule seems to have some influence. Thus in oxalic $\begin{matrix} \text{COOH} \\ \text{COOH} \end{matrix}$ where the carboxyls are closer than in malonic $\text{CH}_2\big\langle\begin{matrix} \text{COOH} \\ \text{COOH} \end{matrix}$ the toxicity is greater.

In the aromatic series, the introduction of a carboxyl lessens the toxicity. Benzoic acid C_6H_5COOH is less toxic than benzol. Amino benzoic acid, $C_6H_4\big\langle\begin{matrix} \text{COOH} \\ \text{NH}_2 \end{matrix}$ is less toxic than aniline, $C_6H_5NH_2$. Also, salicylic acid, $C_6H_4\big\langle\begin{matrix} \text{OH} \\ \text{COOH} \end{matrix}$ is less toxic than phenol.

Acids of the paraffin series or their salts that are absorbed, are oxidized to carbonates in the body and increase the alkalinity of the blood. Aromatic acids are excreted chiefly in combination with glycuronic, amino acetic, or sulphuric acids.

ORGANIC ACIDS OF METHANE SERIES

Methyl alcohol, when oxidized, gives formaldehyde, and if oxidation proceeds far enough, formic acid:

$$CH_3OH + O \rightarrow HC\big\langle\begin{matrix} O \\ H \end{matrix} + H_2O$$

Formaldehyde

$$HC\big\langle\begin{matrix} O \\ H \end{matrix} + O \rightarrow HCOOH$$
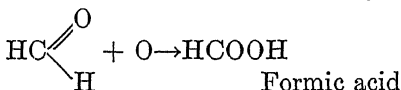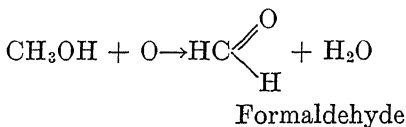
Formic acid

Formic acid as such is not important in medicine. It occurs in nettles and in the sting of insects and is formed in the body when formaldehyde or any of its preparations are taken. The rate of formation of acid from aldehyde is so slow in comparison with the rate of oxidation that it is oxidized to CO_2 and H_2O about as rapidly as it is formed. Only under special conditions may it be found in the blood or urine. Dakin finds that formic acid is a constant constituent of the urine during fasting and the

quantity is considerably increased after carbohydrate and fat ingestion and to a lesser extent also after protein ingestion. All three classes of food substances yield formic acid as an end product of metabolism but it is so readily oxidized that it is eliminated in only small amounts in the urine.

It is the strongest acid of the series and much more toxic than other members except butyric which also has some narcotic properties. In presence of metallic rhodium it is spontaneously decomposed into hydrogen and carbon dioxide. This mechanism may be of value in the explanation of fermentation by assuming that yeast produces an organic catalyst that acts similarly.

It has been employed internally in rheumatism, and locally by allowing bees to sting the involved part. The local hyperemia so caused is beneficial.

In the presence of alkali, or when introduced into the body, formic aldehyde shows the phenomenon known as the Cannizzaro reaction, *i.e.* there is both an oxidation and reduction of the aldehyde;

$$2HCHO + H_2O \rightarrow CH_3OH + HCOOH$$
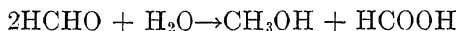
ACETIC ACID

Acetic acid is formed from ethyl alcohol in the same manner that formic acid is prepared from methyl alcohol.

$$C_2H_5OH + O = CH_3C\underset{H}{\overset{O}{\diagup}} + H_2O$$

$$CH_3C\underset{H}{\overset{O}{\diagup}} + O = CH_3COOH$$
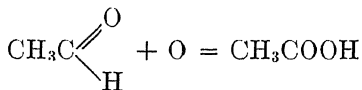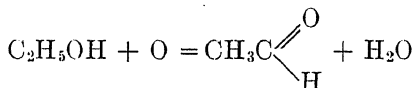
It has a wide use in medicine and as a food. Vinegar is impure acetic acid. In therapeutics the acetates are used as diuretics and refrigerants. Acetic acid is used as a solvent and preservative in pharmacy; aceta are solutions of drugs in acetic acid.

Acetic acid is oxidized in the body to CO_2 and H_2O. The CO_2 combines with the bases of the body and renders the urine alkaline. Nearly all organic acids of methane series are oxidized in this way and are excreted as carbonates. They lessen the H

ion concentration of the blood and act as diuretics, both because of their alkalinity and their salt action.

However the capacity of the animal body to oxidize acetic acid is limited and normal human urine contains on the average between 50 and 300 mgm. per day.

Amino-acetic acid or glycocoll CH_2NH_2COOH occurs in the body as a constituent of proteins and the bile acids, and in the urine of horses as hippuric acid. When benzoates are taken as medicines, they are excreted combined with glycocoll as hippuric acid;

$$C_6H_5COOH + H_2NCH_2COOH = C_6H_5CO.NH.CH_2COOH + H_2O$$
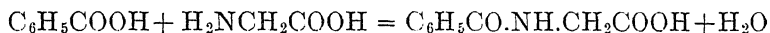
In the same way salicylic acid combines with glycocoll to form salicyluric acid

$$C_6H_4\Big\langle {OH \atop CO.NH.CH_2.COOH}$$

Recent work by Hanzlik throws some doubt on the occurrence of this reaction in the body. Note that salicyluric acid is in no way related to uric acid as the name might suggest.

CARBONIC ACIDS

This acid is described both in organic and inorganic chemistry; $CO\Big\langle {OH \atop OH}.$ It is not known in the free state, but its salts are extremely important in medicine. It is thought to exist in solutions of carbon dioxide and water, and in the blood.

It forms amides and salts like a dibasic acid.

$$CO\Big\langle {OH \atop OH} \qquad CO\Big\langle {NH_2 \atop OH} \qquad CO\Big\langle {NH_2 \atop OC_2H_5} \qquad CO\Big\langle {NH_2 \atop NH_2}$$
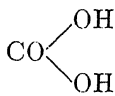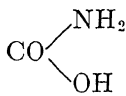
Carbonic acid   carbamic acid   urethane   urea
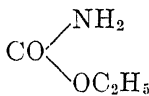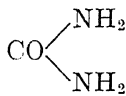
$$CO\Big\langle {NH_2 \atop ONH_4} \qquad\qquad CO\Big\langle {ONa \atop ONa}$$
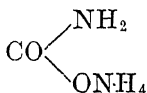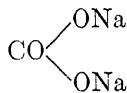
ammonium carbamate   sodium carbonate, etc.

The salts of carbonic acid are much used in therapeutics in effervescent cathartics, as antacids, in baking powders, many beverages, such as soda water, potash water, champagne, and other sparkling wines. Effervescent cathartics are essentially a carbonate or bicarbonate mixed with an organic acid of such a nature that the salt formed is but little absorbed from the gastro-intestinal tract, such as the citrates, tartrates, malates, etc. The CO_2 liberated masks the taste of many medicines and has a stimulating action on the gastro-intestinal tract. Absorption is hastened by it. It is excreted, much of it by eructation, some is absorbed and given off by the lungs. It is the normal stimulus of the respiratory center, but has slight action on the organism after absorption. This substance is slightly irritating to mucous membranes and by its action on the stomach may increase appetite. On prolonged application it has an anesthetic action. Because of this action carbonic acid or effervescent drinks are used to allay vomiting. Carbon dioxide snow is used especially for local anesthesia, this being due more to freezing than to specific action. The hydrogen ion concentration of the blood can not be altered appreciably by the acid or carbonated drinks, but can be changed by the soluble carbonates.

The amount of carbon dioxide in the air should not exceed .03 per cent. but 3 per cent. will produce no immediate toxic symptoms. It is only when CO_2 reaches 5 per cent. that it produces poisonous symptoms. It is not nearly so toxic as methylene and many other gases. The toxic effects produced in crowded rooms, formerly thought to be due to CO_2, are mainly due to the heat and moisture, always present in such cases.

UREA

Urea $= CO\!\!\begin{array}{l}\diagup NH_2 \\ \diagdown NH_2\end{array}$ is the diamide of carbonic acid:

$$CO\!\!\begin{array}{l}\diagup OH \\ \diagdown OH\end{array}$$
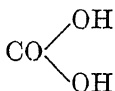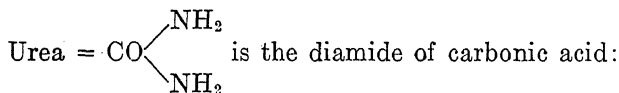
It is of interest as the basis of veronal, which is diethylmalonyl urea. A compound of the hydrochloride of quinine and urea, $C_{20}H_{24}O_2N_2HCl$. $CO(NH_2)_2 HCl$, is used as a local anesthetic.

The urine on an average diet contains about 2 per cent. urea, which acts as a diuretic. According to Fosse, also Bamberger and Landsiedl, it occurs in very small amounts in higher plants and has also been reported in bacteria. Plants can use urea as a source of nitrogen, and microörganisms can convert it into ammonium carbonate.

$$CO\begin{cases}NH_2\\NH_2\end{cases} + 2H_2O \rightleftarrows (NH_4)_2CO_3$$
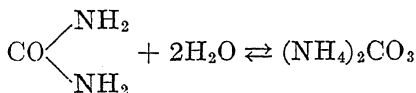
Besides being the main end product of protein digestion urea is of interest in relation to Wöhler's synthesis of ammonium cyanate into urea, which was the first organic substance artificially prepared:

$$NH_4CNO \rightarrow CO\begin{cases}NH_2\\NH_2\end{cases}$$
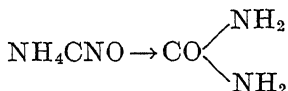
OXALIC ACID

Oxalic acid, $\begin{matrix}COOH\\|\\COOH\end{matrix}$ is of importance in medicine only as a

toxic agent. It is toxic because it removes calcium, which is necessary for life, and is, therefore, a general protoplasm poison. Also, because it precipitates calcium, it prevents the clotting of blood, and prevents rennet from clotting milk.

Its relation to cellulose and the sugars is seen from the fact that sugars, starches, and cellulose yield oxalic acid when boiled with nitric acid. Its presence in the urine in some instances may arise from incomplete oxidation of carbohydrates. Its relation to CN is seen from the following formula:

$$\begin{matrix}CN\\|\\CN\end{matrix} + 4H_2O = \begin{matrix}COOH\\|\\COOH\end{matrix} + 2NH_3$$

$$2NH_3 + (COOH)_2 = (COONH_4)_2 \text{ ammonium oxalate}$$
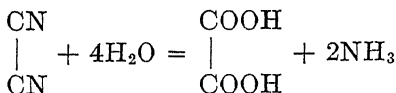
Oxalic acid is related to formic acid. When sodium formate is heated rapidly, sodium oxalate is produced:

$$\begin{matrix}NaCOOH\\\\NaCOOH\end{matrix} = \begin{matrix}NaOOC\\|\\NaOOC\end{matrix} + H_2$$
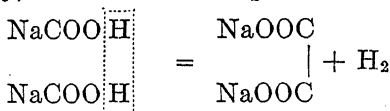
Under proper conditions especially when heated in glycerine, this reaction may be reversed, and oxalic acid carefully heated will yield formic acid.

$$\begin{matrix} COOH \\ | \\ COOH \end{matrix} \rightarrow HCOOH + CO_2$$
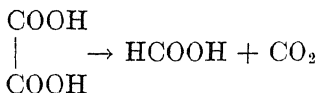
Soluble calcium salts precipitate oxalates as calcium salts. These salts are, therefore, antidotal to oxalates. Whether or not any oxalic acid can be oxidized in the body, is a disputed question. Marfori claims that 30 per cent. of the amount taken reappears in the urine while Faust found 100 per cent. Hildebrandt, found that 60 per cent. of oxalic acid injected subcutaneously in rabbits was oxidized. Dakin found 90 per cent. oxidized under the same conditions. It appears in the urine as "envelope" crystals. These may be sufficient to block the tubules and cause nephritis. Glycosuria and indicanuria occur frequently, after large doses of oxalates. Tomatoes, spinach, rhubarb, sorrel, and other plants contain considerable oxalate, and most of this when eaten appears in the urine. In some cases oxalate poisoning has been caused by these plants.

MALONIC ACID

Malonic acid, $CH_2\begin{cases} COOH \\ COOH \end{cases}$ is the next higher homologue of oxalic acid. The use of the cyanides in building up compounds is illustrated in the formation of malonic acid, which is formed from monochloracetic acid:

$$\begin{matrix} CH_2Cl \\ | \\ COOH \end{matrix} + KCN + H_2O \rightarrow \begin{matrix} CN \\ | \\ CH_2 \\ | \\ COOH \end{matrix} \rightarrow \begin{matrix} COOH \\ | \\ CH_2 \\ | \\ COOH \end{matrix} + KCl$$
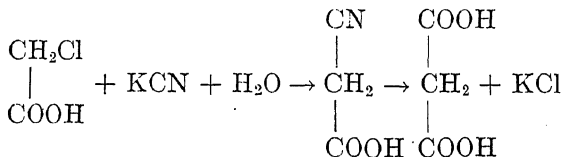
Malonic acid is a crystalline compound, which melts at 132°C. It is found in nature in the juice of beets, where it occurs as the calcium salt. It is a constituent of veronal. Barbituric acid

or malonyl urea is obtained from alloxantin by heating it with concentrated sulphuric acid and from dibrombarbituric acid by the action of sodium amalgam. Veronal (q.v.) is diethyl malonyl urea or diethyl barbituric acid.

SUCCINIC ACID

Oxalic, malonic and succinic acid form an homologous series of dibasic acids:

$$
\begin{array}{ccc}
\begin{array}{c} COOH \\ | \\ COOH \end{array} &
CH_2 \Big\langle \begin{array}{c} COOH \\ COOH \end{array} &
\begin{array}{c} CH_2COOH \\ | \\ CH_2COOH \end{array} \\
\text{oxalic} & \text{malonic} & \text{succinic}
\end{array}
$$
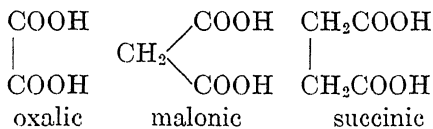
None of these are used to any extent in medicine. As the COOH groups become more widely separated in the molecule the toxicity decreases; hence malonic acid is less toxic than oxalic. This is still further exemplified in citric and tartaric acids.

Succinic acid occurs in amber, fossil wood, in many plants, asparagus, etc., in brain, muscle and in the urine after the ingestion of plants containing it. It may be prepared from its elements by forming acetylene from carbon and hydrogen. This is reduced to ethylene. If ethylene be passed into bromine, ethylene dibromide is formed:

$$
\begin{array}{c} CH_2 \\ | \\ CH_2 \end{array} + Br_2 = \begin{array}{c} CH_2Br \\ | \\ CH_2Br \end{array}
$$
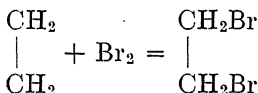
This when treated with an alcoholic solution of KCN forms

$$
\begin{array}{c} CH_2CN \\ CH_2CN \end{array}
$$

which is hydrolyzed to $\rightarrow CH_2COOH.CH_2COOH$.

TARTARIC ACID

Tartaric acid may occur in levo, dextro, meso, and racemic forms. It is dihydroxy succinic acid:

$$
\begin{array}{cc}
\begin{array}{c} CH_2COOH \\ | \\ CH_2COOH \end{array} &
\begin{array}{c} CHOH.COOH \\ | \\ CHOH.COOH \end{array} \\
\begin{array}{c} \text{succinic} \\ \text{acid} \end{array} &
\begin{array}{c} \text{tartaric} \\ \text{acid} \end{array}
\end{array}
$$
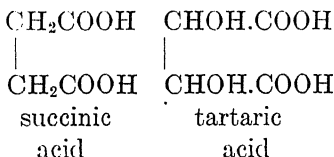
It was on these acids that Pasteur made his important dis-

coveries on the polarization of light by organic substance. He found that certain crystals dissolved in water turned the polarized ray to the left. Others turned it to the right; and a mixture of the two was racemic or inactive (external compensation). On studying the composition of the organic substances, he found that the active crystals are mirror images of each other. It has been found that only those with an asymmetric carbon are optically active. No single base of an organic substance is known that is optically active without the presence of an asymmetric carbon atom. However a substance may contain two asymmetric C-atoms and be inactive. This occurs in the meso form of tartaric acid, cf. formula III. This is internal compensation. The importance of this physico-chemical property to living matter can hardly be estimated. The mould, penicillium glaucum, ferments dextro, but not levo tartaric acid. Yeast will ferment l. fructose, l. glucose, l. mannose, or l. galactose. Dextro epinephrine is only about $\frac{1}{12}$ as toxic as l. epinephrine; d. hyoscyamine is but feebly active in comparison with l. hyoscyamine. It is probable that time will greatly emphasize the relationship of optical properties and life processes.

The levorotatory form is represented in formula (I), the dextro in (II), and meso tartaric in (III).

$$
\begin{array}{ccc}
\text{(I)} & \text{(II)} & \text{(III)} \\
\text{COOH} & \text{COOH} & \text{COOH} \\
| & | & | \\
\text{HO—C—H} & \text{H—C—OH} & \text{HO—C—H} \\
| & | & | \\
\text{H—C—OH} & \text{HO—C—H} & \text{HO—C—H} \\
| & | & | \\
\text{COOH} & \text{COOH} & \text{COOH}
\end{array}
$$
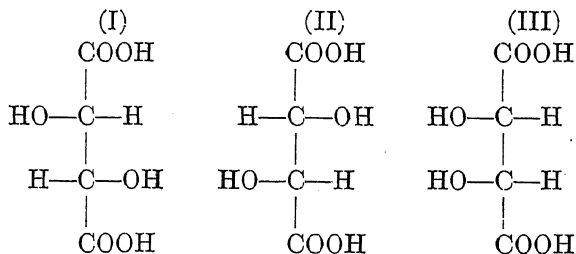
The central C atoms in (I) and (II) are asymmetric (each valence has a different element or radical in combination), so that when both forms are in the same solution, the influence of one on polarized light neutralizes the other.

Tartaric acid is used in medicine as an expectorant and emetic in tartar emetic, which is antimonyl potassium tartrate.

$$
1. \quad 2 \left\langle \begin{array}{l} \text{CHOH} \quad \text{COOHK} \\ \text{CHOH} \quad \text{COO(SbO)} \end{array} \right\rangle \text{H}_2\text{O}
$$
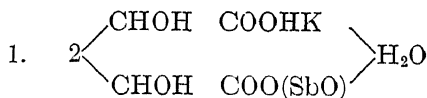
2. Rochelle Salt, or sodium potassium tartrate, $C_4H_4O_6K\,Na + 4H_2O$, is used as a cathartic and antacid.

3. The acid salt of tartaric acid is used in domestic economy as cream of tartar or baking powder. The essentials of a baking powder are: something that will liberate CO_2 slowly and efficiently, and will not leave a harmful or toxic residue in the food. Cream of tartar fulfills these conditions. The reaction in this case is:

$$
\begin{array}{ccc}
\text{CHOH.COOK} & & \text{CHOH—COOK} \\
| & + \text{NaHCO}_3 = & | & + \text{H}_2\text{O} + \text{CO}_2 \\
\text{CHOH.COOH} & & \text{CHOH—COONa} \\
\text{Cream of tartar} & & \text{sodium potassium tartrate}
\end{array}
$$

CITRIC ACID

Citric Acid,
$$
\begin{array}{l}
\text{CH}_2\text{—COOH} \\
| \quad\diagup\text{OH} \\
\text{C}\diagdown \\
| \quad\diagdown\text{COOH} \\
\text{CH}_2\text{—COOH}
\end{array}
$$
occurs in the juice of many
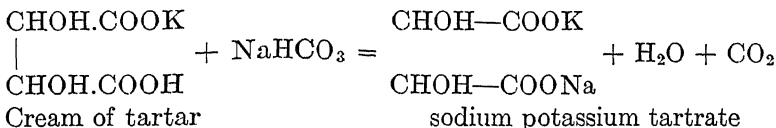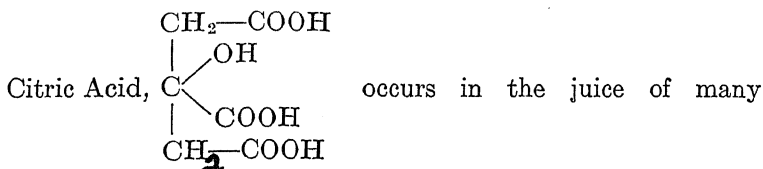
plants, especially in lemon juice, where it may reach 5 per cent. and in gooseberries, 1 per cent. It is also found in raspberries, currants, and other acid fruits, and is said to be found in the milk of animals, probably being derived from the food. It is formed in the fermentation of glucose by citromycetes pfefferianus. In medicine its use is as a substitute for lemon juice; in the syrup of citric acid as a vehicle and refrigerant. Magnesium citrate is a much used cathartic in iron and ammonium citrate as a soluble form of iron in citrated caffeine, etc.

Citrophen or citrophenin is a combination of citric acid and phenacetin:

$$
\begin{array}{l}
\text{CH}_2.\text{CONHC}_6\text{H}_4\text{OC}_2\text{H}_5 \\
| \\
\text{COH.CONHC}_6\text{H}_4\text{OC}_2\text{H}_5 \\
| \\
\text{CH}_2\text{CONHC}_6\text{H}_4\text{OC}_2\text{H}_5.
\end{array}
$$
It is used as an analgesic and antipyretic.
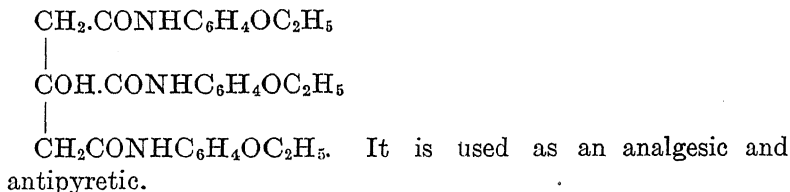
The reactions of acetic acid, acetone, and citric acid are inter-

esting, and the relationship also shows how the cyanides may be disintoxicated by the body.   Calcium acetate when distilled gives acetone:

$$\begin{matrix} CH_3.COO \\ \\ CH_3.COO \end{matrix} \Big\rangle Ca = \begin{matrix} CH_3 \\ \\ CH_3 \end{matrix} \Big\rangle CO + CaCO_3$$
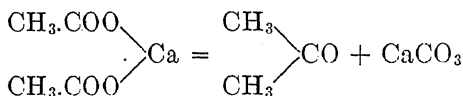
If chlorine is conducted through cold acetone, dichloracetone is formed:

$$\begin{matrix} CH_2Cl \\ | \\ C=O \\ | \\ CH_2Cl \end{matrix} + 2KCN \rightarrow \begin{matrix} CH_2CN \\ | \\ C=O \\ | \\ CH_2CN \end{matrix} + 2KCl$$

Dichloracetone   Acetonedicyanide
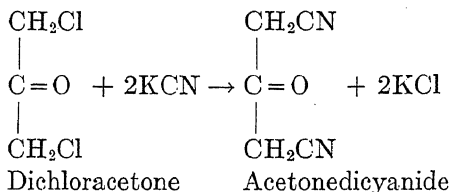
When this is hydrolyzed it gives acetone dicarboxylic acid; and this gives citric acid as follows:

$$\begin{matrix} CH_2COOH \\ | \\ CO \\ | \\ CH_2COOH \end{matrix} + HCN = \begin{matrix} CH_2COOH \\ | \quad OH \\ C \\ | \quad CN \\ CH_2COOH \end{matrix} + 2H_2O \rightarrow \begin{matrix} CH_2COOH \\ | \quad OH \\ C \\ | \quad COOH \\ CH_2COOH \end{matrix} + NH_3$$

Acetone dicar-   Cyanhydride   Citric acid
boxylic acid   of citric acid
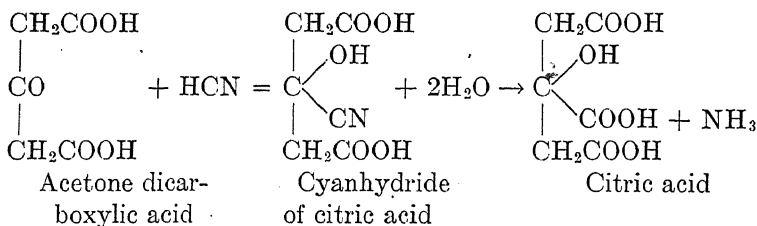
LACTIC ACID

Lactic acid, from (lac = milk) is but little used in medicine. It is somewhat used as a local application to tuberculosis ulcers of the nose and throat, especially on the larynx.

$$\text{Lactic acid} \begin{matrix} CH_3 \\ | \\ CHOH \\ | \\ COOH \end{matrix} \text{ is of interest because of its relation to acetic}$$
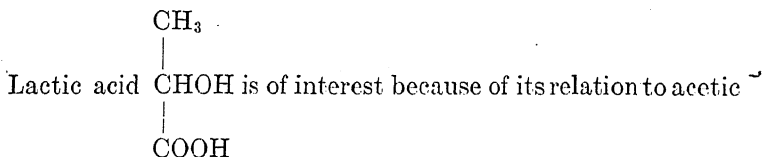
and formic acid and to glucose and amino acids derived from protein. It is formed in the stomach in all fermentations and dyspepsias when it may reach 0.4 per cent. There is some doubt whether or not lactic acid exists in the normal blood. It is present, however, in all cases where

there is asphyxiation or reduction of tissue respiration and in such cases appears in the urine. It occurs especially after poisoning with phosphorus, arsenic, hydrazines, chloroform, etc., *i.e.*, after those poisons which act on the liver causing hyperglycemia, reduction of glycogen, and fatty degeneration. It may also occur in the course of diabetes and wasting diseases, and is always present in cases of acidosis. Lactic acid since it contains an asymmetric C atom exists in dextro, levo, and racemic or inactive forms. It was first discovered by Scheele in 1780, who isolated it from sour milk. In the form of sour milk, it was advocated by Metschnikoff but without any sufficient reason as a means of prolonging life. Since milk is an important vitamin containing food, it per se would be of great benefit in deficiency diseases and some of these benefits may have been unduly credited to lactic acid. In the destruction of lactic acid by bacteria, propionic, acetic and formic acids may be formed:

$$
\begin{array}{cccc}
CH_3 & CH_3 & CH_3 & H \\
| & | & | & | \qquad = CO_2.H_2O \\
CHOH & CH_2 & COOH & COOH \\
| & | \\
COOH & COOH \\
\text{Lactic} & \text{propionic} & \text{acetic} & \text{formic}
\end{array}
$$
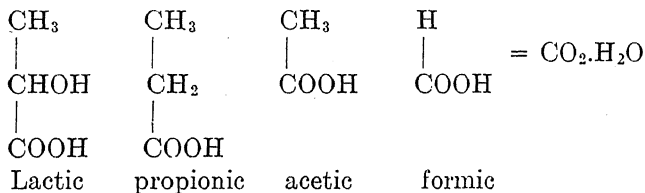
Zinc lactate $Zn(C_3H_5O_3)_2.3H_2O$ is the most characteristic salt of lactic acid. The acid may be identified by the analysis of this salt.

HYDROCYANIC ACID

Hydrocyanic acid is usually considered with the paraffin acids, but it is not a derivative of the paraffins. It is of direct interest to the paraffins because it forms addition products with aldehydes and ketones. These can be hydrolyzed, enabling the formation of a product richer in carbon than the initial *e.g.*:

$$
\begin{array}{ll}
CH_3I + KCN & = CH_3CN + KI \\
CH_3CN + 2H_2O & = CH_3COOHNH_3
\end{array}
$$

The relation of HCN to formic acid is shown by the following:
$$HCN + H_2O \rightarrow HCOONH_4 \quad \text{(ammonium formate)}$$

It is, therefore, the nitril of formic acid. Hydrocyanic acid 2 per cent., dilute hydrocyanic, is used in medicine as an antemetic and in cough mixtures, as a depressant of the respiratory centre. On account of the readiness with which it decomposes, it is not so

much used as formerly. It also exists in wild cherry, in amygdalin, in KCN, $Hg(CN)_2$ and other compounds used more or less.

Because of its toxic action this drug is falling into disuse It is of considerable importance in toxicology. It is absorbed even from the skin. It is toxic to all ferments and tissues. It first stimulates then paralyzes the central nervous system. The peripheral muscles and nerves are weakened and eventually paralyzed. The tissues cannot use oxygen and soon die from asphyxia. In such cases lactic acid may be found in the blood and urine. The oxidative processes of the blood are also checked and the color of the blood is bright red due to oxyhemoglobin as is to the fact that the tissues from internal asphyxia cannot take oxygen from the blood. Whether or not such a compound as cyanhemoglobin is formed is still disputed. It is probably formed and readily decomposed, though it is harder to reduce than oxyhemoglobin.

Hydrocyanic acid, if it does not kill is changed to sulphocyanides in the tissues. This seems to be a simple chemical process which occurs without the action of living protoplasm. The sulphocyanate test for hydrocyanic test is based on this fact. It is as follows:

To a dilute solution of hydrocyanic acid, or a distillate suspected of containing it, add a few drops of a solution of potassium hydroxide, and twice as much yellow ammonium sulphide. Evaporate to dryness on a water bath; dissolve in a little water and acidify with dilute hydrochloric acid. Filter to remove sulphur. If the solution contained hydrocyanic acid the filtrate will give a blood red color on the addition of a drop of dilute ferric chloride, this is due to the formation of ferric sulphocyanate.

Hydrocyanic acid occurs in many plants, in the form of glucosides—cyanogenetic glucosides. It is present principally in the seed, buds, leaves and bark. The cyanide is held to be a direct product of photosynthesis, and may be of fundamental importance in the metabolism of the plant and perhaps in the evolution of life processes. Gautier thinks that prussic acid and its compounds may be formed in the plant by the reduction of nitrates by formaldehyde. This theory agrees with the distribution of both nitrates and cyanides in the plant. The amount of cyanide in plants varies greatly and may amount to as much as 0.3 per cent. In many cases free hydrocyanic will be liberated

from such plants on chewing—owing to digestion of the glucoside —and can be detected in this way.

To isolate hydrocyanic acid from a plant or tissue: digest the finely pulverized substance mixed with water in an incubator or on a water bath for two hours at a temperature of 40°C. If the temperature is raised much above this, it will kill the ferment and prevent the setting free of HCN. Acidify the digest with tartaric acid and distil with steam. Test the distillate by:

1. **Prussian Blue Test.**—Add a trace of KOH, then a few drops of freshly prepared ferrous sulphate solution and a drop of dilute ferric chloride solution. Shake well and warm gently. Finally acidify with dilute hydrochloric acid. A blue color is formed at once if the quantity of HCN is considerable, if only a minute amount is present a bluish green color only develops.

2. Hydrocyanic acid gives a white precipitate with $AgNO_3$.

3. **Vortmann's Nitro-prusside Test.**—To a dilute solution of hydrocyanic acid add a few drops of potassium nitrate solution, then a few drops of ferric chloride and enough dilute sulphuric acid to give a yellow color. Heat to boiling and add enough ammonium hydroxide to remove excess of iron, filter, and add a few drops of very dilute ammonium sulphide. A violet color passing through blue green and yellow, indicates hydrocyanic acid. It is due to the conversion of the cyanide into potassium nitro-prusside—$K_2Fe(NO)(CN)_5$ which changes color when ammonium sulphide is added.

Picric Acid Test.—When a solution of hydrocyanic acid is made alkaline with KOH and heated in a water bath at 50°–60°C. with a few drops of picric acid, it gives a blood red color due to the formation of potassium isopurpurate—$C_8H_4N_5O_6K$. Sulphides present in decomposing organic matter will also give this test and sugars under similar conditions will give a red color due to the formation of picramic acid—which is 2 amino 3, 4, di-nitro phenol $C_6H_2(NH_2).(NO_2)_2.OH$. This last is the basis of Benedict's method for the estimation of blood sugar.
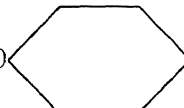
Isopurpuric acid does not exist in the free state, but only as the potassium salt. Nietzki and Petri (Ber d. deutsch. Chem. Gesellschaft 1900–33–1788)—think isopurpuric acid ($C_8H_3O_6N_5$) is dicyano-picraminic acid = 5 oxy. 6 amino—2, 4 di nitro isophthalic nitrile: see page 98.

Purpuric acid, the formula of which is not definitely known, is of biological interest in that its ammonium salt,

$C_8H_4(NH_4)N_5O_6 + H_2O$ is the dye stuff murexide. The murexide test is given by uric acid caffeine, xanthine, theobromine and many nuclein bases (see p. 288).

GENERAL PHARMACOLOGY OF THE ACIDS

The introduction of COOH into the Marsh Gas series gives rise to acids with relatively slight toxicity. The anesthetic action of the alkyl radicals is lessened by combination with carboxyl. The introduction of carboxyl into the aromatic series lessens the toxicity of the benzyl group. In addition to the carboxyl group the acyl groups exert an action. Acetyl salicylic acid is more effective as an antipyretic and analgesic than is salicylic acid. Acetyl atoxyl is said to be less toxic than atoxyl.

The replacement of the hydrogen of the amino group in para-

mino phenol with an acetyl group, $HO\langle\underline{\quad}\rangle NH.COCH_3$

lessens the toxicity, and gives a compound with greater antineuralgic properties.

Lactyl phenetidine (lactophenin)

$$C_2H_5\langle\underline{\quad}\rangle NH—CO—CH—CH_3$$
$$\underset{OH}{|}$$
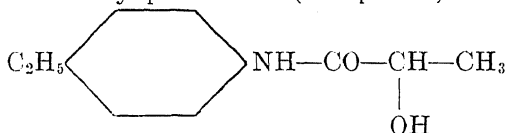
is more soluble, and has a less antipyretic action than phenacetin. Ecogonine-methyl ester has no anesthetic action but its benzoyl derivative, cocaine is noted for its local anesthetic effect. Most artificial cocaines contain the benzoyl group. The toxicity of aconitine is closely related to the benzoyl and acetyl groups present in the alkaloid. The mechanism of the action of these and many other similar compounds is little understood, but the total action in each case seems to be the algebraic sum of the actions of the component chemical groups of the drug. In addition to these there is a molecular action and a hydrogen ion action. For the effects of the hydrogen ion, see acidosis, p. 350; see also amino acids, p. 304.

VIII. IODOFORM AND PHYSIOLOGICAL SUBSTITUTES

Iodoform, or triiodomethane, *was the first solid antiseptic known*. It is prepared by the action of iodine upon alcohol or acetone, in the presence of an alkali or an alkaline carbonate. Its formation is also used to test for the presence of alcohol or acetone. A solution of I in KI is added to the solution of alcohol, or acetone, and warmed, then dilute NaOH or KOH is added, drop by drop until the color has disappeared. Iodoform is formed:

$$CH_3COCH_3 + 3KIO = CH_3COCI_3 + 3KOH$$
$$CH_3COCI_3 + KOH = CH_3COOK + CHI_3$$
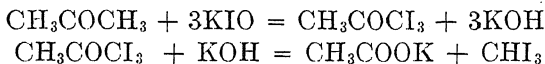
The potassium hypoiodite KIO is formed when dilute KOH is added to the I in KI solution: $2KOH + 2I \rightarrow KIO + KI + H_2O$. The hypoiodites are easily decomposed into iodides, and iodates: $3 KIO = KIO_3 + 2KI$. Both the iodate and iodide are usually formed in the solution with the iodoform, even when KI has not been added. Strong alkalies cause the formation of the iodate; and, therefore, if a too strong alkali is added, it interferes with the reaction. For this reason, sodium carbonate or potassium carbonate instead of the hydrate is sometimes recommended in making the iodoform test. From alcohol, iodoform is prepared, possibly according to the following reaction:

$$C_2H_5OH + I_8 + 6KHCO_3 = CHI_3 + 5KI + KCOOH + 6CO_2 + 5H_2O$$
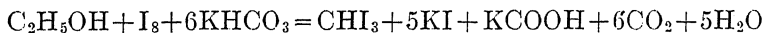
Ethyl iodide, acetic ether, and other compounds are probably also produced. The result appears to be greatly influenced by the temperature, and the relative amounts of the materials used. Iodine is an oxidizing agent and the probable mechanism is:

$$C_2H_5OH + O = CH_3C{\overset{O}{\underset{H}{\diagdown}}} + H_2O$$

$$CH_3C{\overset{O}{\underset{H}{\diagdown}}} + I_6 = CI_3C{\overset{O}{\underset{H}{\diagdown}}} + 3HI$$

$$CI_3C{\overset{O}{\underset{H}{\diagdown}}} + KOH = CHI_3 + KCOOH$$
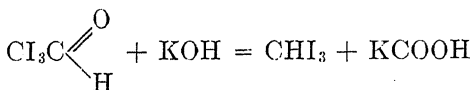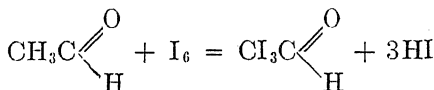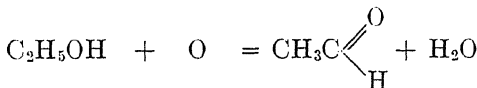
Iodoform melts at about 115°C. It is nearly insoluble in water, but soluble in alcohol, glycerine, carbon bisulphide, ether

and in fats. In medicine it is sometimes used in the form of an ointment.

It is volatile at ordinary temperatures and distils readily in steam. When it is suspected in organic matter, and its separation is desired, acidify with tartaric acid and distil with steam. Extract the distillate with ether and evaporate the ether in a suitable dish. Iodoform remains as yellow hexagonal plates with a characteristic odor.

Tests: Lustgarten's.—In a test tube warm a little iodoform solution in alcohol with a few drops of sodium phenolate—made by dissolving 2 parts of phenol, 4 parts of sodium hydroxide and 7 of water. A red precipitate is formed which settles to the bottom. Pour off the supernatant fluid and dissolve the precipitate in dilute alcohol—a carmine red color results.

Phenylisocyanide Test.—Add a few drops of aniline to a little iodoform solution in alcohol, then a few drops of alcoholic KOH solution. When heated gently, phenylisocyanide—C_6H_5NC is produced. This is recognized by its very characteristic and repulsive odor. For reaction see page 43.

Iodoform is sometimes used as a disinfecting dusting powder, and any action it has is due to the liberation of iodine. It has two serious disadvantages:

1. Its disagreeable and persistent odor.

2. In cases of abraded surfaces, sufficient may be absorbed to produce toxic symptoms. For these reasons its use is becoming restricted.

Various other iodine compounds have been devised, with the idea of securing the iodine effect, without the disadvantages of iodoform. The following are the most common:

ARISTOL, OR DITHYMOL-DI-IODIDE.

The stearoptene, thymol, from oil of thyme has the formula:
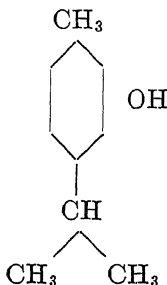
It is a solid crystalline body, which is used in medicine, especially in the treatment of hook-worm disease. It has also been much used in biological chemistry as a preservative for urine and other fluids. Since it combines with iodine–also an antiseptic—it was thought that a valuable iodine compound could be obtained without the disadvantages of iodoform. Eichkoff in 1890 prepared aristol or thymol iodide by the action of iodine on thymol in alkaline solution.

$$C_6H_2 \Big\langle \begin{matrix} C_3H_7 \\ CH_3 \\ OI \end{matrix}$$

$$C_6H_2 \Big\langle \begin{matrix} OI \\ CH_3 \\ C_3H_7 \end{matrix}$$
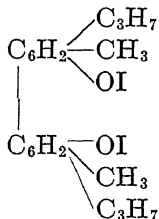
This is a chocolate colored powder and contains about 45 per cent. iodine. It has been used as a dusting powder especially in soft ulcers, eczema, psoriasis, lupus, burns, infections of ear, nose and throat and in many other cases where the odor of iodoform has been a drawback. Its action is similar to iodoform, and its only advantage is that it is odorless.

Europhen-or-di-iso-butyl orthocresol iodide.

This is analogous to thymol iodide. It has the formula:

$$C_6H_2 \Big\langle \begin{matrix} C_4H_9 \\ CH_3 \\ OI \end{matrix}$$

$$C_6H_2 \Big\langle \begin{matrix} OI \\ CH_3 \\ C_4H_9 \end{matrix}$$
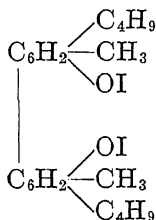
and is a condensation product of two molecules of isobutyl-ortho cresol with one atom of iodine. The action is similar to thymol iodide. It contains about 28 per cent. iodine.

Iodol or tetraiodo pyrrol.

$$\begin{matrix} I.C & — & C.I \\ \| & & \| \\ I.C & & C.I \end{matrix}$$
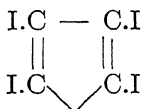
was one of the first iodoform substitutes. It is prepared by the action of iodine on alkaline solutions of pyrrol or indirectly by the action of KI on tetrachlor-pyrrol.

$$C_4H_4NH + 8Cl = C_4Cl_4NH + 4HCl$$
$$\text{pyrrol} \qquad \text{tetra-chlor-pyrrol}$$
$$C_4Cl_4.NH + 4KI = C_4I_4.NH + 4KCl$$
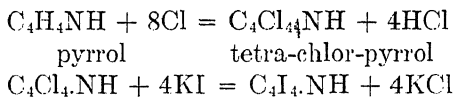
Iodol is a tasteless and odorless powder with an action similar to iodoform.

Besides the above iodine containing bodies, from which iodine is liberated readily in the body, others have been prepared, but since these do not liberate iodine in the body, they cannot be classified as true iodoform substitutes.

In the iodoform substitutes the iodine is not attached directly to the benzene ring but replaces the H of the hydroxyl group. In Loretin, 1 oxy, 2-iodo—4 sulphonic acid,
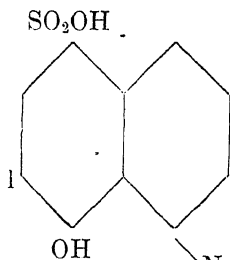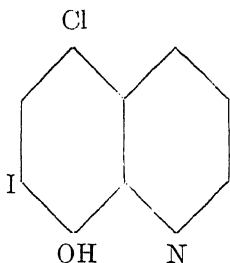
and vioform 1, oxy, 2-iodo, 4 chlor quinoline

and nosophen or tetraiodophenol phthalein $C_{20}H_{10}I_{14}O_4$ and

Losophan—or tri-iodo di-metacresol—$C_6HI_3 \Big\langle \begin{array}{l} OH \\ CH_3 \end{array}$

and sozoiodol (iodo para phenol sulphonic acid)

$$C_6H_2I_2 \diagup \begin{matrix} OH \\ SO_2OH \end{matrix}$$
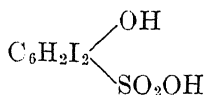
the I is attached to the ring.

Such compounds are practically undecomposed by the body, and of little value as antiseptics so far as the iodine content is concerned. They are therefore not real substitutes for iodoform.

All phenols have a high antiseptic value, and the introduction of iodine increases this to some extent. The increase is not sufficient to warrant approval.

Besides the above iodoform substitutes, organic combinations of iodine have been prepared for administration internally to take the place of potassium iodide. Iodides in the form of potassium or sodium are sometimes too rapidly absorbed, cause irritation of stomach, skin eruptions and other untoward manifestations. Many attempts have been made to avoid these complications by combining the iodine with organic substances that will be slowly decomposed in the body and slowly absorbed. The combinations are usually with protein matter, and the composition in most cases is not fixed or definite as in the iodoform substitutes.

THYREOGLOBULIN is the normal iodine-containing body of the thyroid gland. The active ingredient of this has recently been isolated by E. I. Kendall and has the formula:

or thyro-oxy-indole
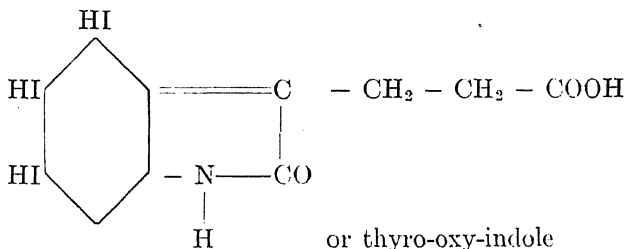
IODO-SPONGIN is the iodine compound of the sponge.

IODOALBIN is a compound of iodine and blood albumin, containing approximately 21.5 per cent. of iodine. It passes through the stomach unchanged, but is decomposed in the intestine.

IODOPIN is iodized sesame oil. As is well known, unsaturated

oils may absorb or add iodine—the iodine number. Two preparations of iodopin are on the market—one 10 per cent. and one 25 per cent. The action is the same as that of potassium iodide, but it is claimed that iodism is less likely to develop.

Iodocasein is a compound of iodine with milk casein, containing about 18 per cent. of iodine, in organic combination. Many other such potassium iodide substitutes have been prepared, but the principle is the same as the above.

The supposed or claimed advantage of these organic preparations is that iodism is less likely to develop. By iodism is meant the untoward symptoms that develop after the prolonged use of iodides, the most common being catarrh of the respiratory passages and adnexa, bronchitis, salivation, skin eruptions, eczema, bullæ, pemphigus, purpura, fetid breath, nausea and general malaise. A dermatitis resembling ivy poisoning is sometimes seen after iodoform has been used.

The fatal dose of iodoform or its substitutes is not definitely known. Barois (Arch. de Med. et de Pharm. Militare, 1890) records the death of a woman on the 9th day after the injection of 3 grams of iodoform in ether. Gaillard (Bull. de Chirurg., 1889) records a comatose condition and apparent death (but from which recovery took place) after the injection of about 6 grams iodoform into an abscess. v. Bonsdorff (Jour. Am. Med. Assoc., 67, 1916, 1052) reports death due to the use of about 40 cc. of 10 per cent. iodoform solution, 10 cc. at a time being injected into the pleural cavity in a case of tuberculosis in an alcoholic. The death in this case was probably due to other causes. Much larger doses than any here recorded have been injected without apparent injury.

The symptoms of poisoning in addition to iodism are diuresis, somnolence, hallucinations, delirium, lassitude, diminished reflexes, convulsions, paralysis. As in many cases of poisoning, sodium carbonate in 1 gram doses may be beneficial, because of its effect on the acidosis which develops.

The Fate of Iodoform in the Body

Iodoform and its substitutes are readily decomposed in the alkaline fluids of the body, and the iodine is excreted as iodides. Some decomposition takes place when it is used on wounds as

a dusting powder. The iodides formed after the administration of iodoform have been found in the saliva, perspiration, bronchial secretions, urine and other fluids, just as after the administration of potassium iodide. Iodo albuminates are also formed as after the use of iodides, and the final excretion of the total iodine as sodium or potassium iodide, may be long delayed.

Some iodide undergoes decomposition in the body and free iodine is said to have been found in the stomach. If this were absorbed however it must circulate as an albuminous compound until converted into the inorganic form in which it is excreted. Free iodine has not been demonstrated out of the acid medium of the stomach yet many theories which assume its presence, have been devised to explain skin eruptions, and the inflammatory reactions of the mucous membranes.

BROMINE COMPOUNDS

Combinations of bromine similar to iodine have been prepared amongst which are bromopin, analogous to iodipin. Sabromine $Ca(C_{22}H_{41}O_2Br_2)_2$, the dibrombehenate of calcium, has a feeble bromide action, because it is stored in the fatty tissues and liberated slowly, as valerobromide:

$$\begin{array}{l} CH_3 \\ \rangle CH.CH.BrCOONa \\ CH_3 \end{array}$$

which is formed by the action of bromine on valerianic acid; and adalin which is bromdiethyl—acetyl urea:

$$\begin{array}{l} C_2H_5 \\ \rangle CBrCONHCO.NH_2 \\ C_2H_5 \end{array}$$

As might be surmised from the ethyl groups of this formula such combinations of bromides are nerve depressants. The bromides are hypnotics, and are used in medicine only to depress the central nervous system. They are used for this purpose in chorea, epilepsy, and have also been used in seasickness and in whooping cough. Since bromides are used to a considerable extent, bromism often develops. This in the main is similar to

iodism, but the skin eruptions and depression are more pronounced. Acne is often very troublesome.

Bromides accumulate in the body; that is, they are not excreted as rapidly as absorbed. This is partly explained by the fact that the body cannot well distinguish between the bromine and the chlorine ion, consequently chlorine is excreted and bromine retained. HBr, is sometimes formed in the stomach instead of HCl.

It has been questioned by some whether the depressant effect of the bromides is due to the presence of the bromine ion or the absence of the chlorine ion. In favor of the view that it is due to lessened chloride, it has been found that the depressing action of the bromides is more pronounced when the chlorides of the diet are diminished and Loeb has found that fish are depressed by the administration of bromide, but remain normal if chloride also is added. However, large doses of bromides depress animals before the chlorides are much diminished so that while poverty of chlorides may aid the action of bromides they are not the cause of it. Bromides are excreted, in the same manner as the iodides.

IX. BENZENE OR BENZOL

Benzene, C_6H_6, is derived from coal tar. It is the mother substance of a long series of products, many of which are important in medicine. Because many of them are odoriferous, the series is known as the aromatic series. The formula generally given to the compound is that of Kekule:

$$
\begin{array}{ccc}
 & CH & \\
CH & & CH \\
CH & & CH \\
 & CH & \\
\end{array}
$$
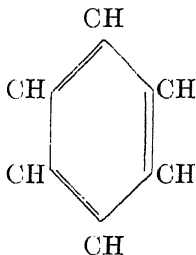
The reasons for assigning this formula to it are:

1. All the hydrogen atoms react the same, hence they must be similarly linked.

2. It acts like a saturated compound—yet if it were an open chain structure, it could be represented only as a highly unsaturated compound.

3. Under certain conditions it unites with 6 atoms of bromine to form $C_6H_6Br_6$. If it were an unsaturated compound related to hexane, it should unite with eight atoms, since hexane when saturated has the formula $C_6H_{14}Br_6$. Hence it seems to be a closed ring.

4. In favor of this is the fact that when gaseous benzene and hydrogen are passed through a heated tube containing finely divided nickel, 6 atoms of hydrogen are absorbed and hexamethylene is formed. This corresponds with the formula:
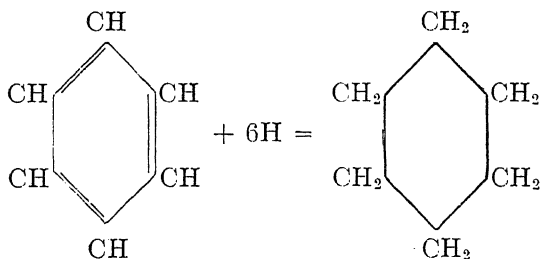
That all the hydrogen atoms in benzene are the same, is supported by the following facts:

1. There is but one mono substitution product of chlorine, bromine, NH_2 etc.

2. The theory calls for 3 possible di-substitution products and these are known, and only these, e.g.:
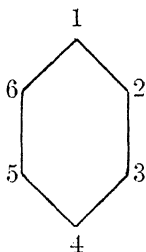
(1.2 and (1.6) di-substitution products are the same. Also (1.3) and (1.5) (1.4) and (2.5) and (3.6) are the same.

3. Three tri-substitution products only are found, while more would be expected if the H atoms were different.
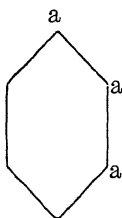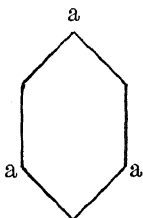
adjacent   symmetric   asymmetric
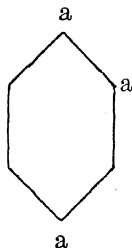
These are all that can be found.

It should be remembered that the existence of the benzene ring is still theoretical yet all the facts so far can best be explained on the basis of this theory.

Benzene is a colorless, highly refractive liquid, B. P. 80.5°C., Sp. gr. 0.88 at 20°. It is highly inflammable. In commerce it is not pure, being usually mixed with other hydro-carbons such as toluene. It is insoluble in water; is a good solvent for fats, resins, alkaloids, iodine, and other substances, and is broken up only with difficulty. Under certain conditions it will yield substitution products. With HNO_3 it gives nitrobenzene. $C_6H_6 + HNO_3 = C_6H_5NO_2 + H_2O$. When heated with sulphuric acid, it gives benzene sulphonic acid. In the body it is but slightly acted on, passing through for the most part unchanged. A slight amount may be oxidized to phenol which is excreted combined with sulphuric acid. Benzene has been used to a considerable extent of late in the treatment of leukemias as it causes a reduction of the number of the leucocytes, the dose being from 0.5 to 1 cc., four times a day. Frequent examination of the blood is necessary and too great doses or too prolonged use of it is decidedly harmful, as it may cause an aplastic anemia. By this is meant that, while it reduces the number of leucocytes, it also acts on the bonemarrow in a harmful way so that the normal production of red cells is lessened or stopped.

While benzene is relatively inactive chemically, the fact that it is volatile and will dissolve lipoids confers on it a pharmacologic activity which is due entirely to its physical or solvent action.

ιis action is manifested on the motor side of the nervous system,
d is stimulating. Members of the methane series act mainly
the sensory side and are depressant.

X. PHENOLS

1. Phenols (Fr. Phenol, Greek Phaino,—shine. Latin, oleum,
.) Hydroxyl derivatives of the methane series are known as
ɔohols. Hydroxyl derivatives of the benzene series are called
enols. Only when the OH is attached directly to a carbon
ɔm of the ring does the term phenol apply.

2. Since all the H atoms of benzene are the same, only one
ɔnhydroxy phenol is possible, and only one is known. Phenol
ɔbtained from coal tar, or is made synthetically. It is found in
ιall quantities in combination in urine, and is derived from
otein.

Phenol is formed from benzene by the action of oxygen in the
esence of a catalyzer like platinum black or aluminum chloride.
ιall amounts of it are also formed in the human body from
ministered benzene.

Phenol occurs in colorless deliquescent prisms which melt at
°C. and turn to pink or brown on standing. It boils at 183°C.
d is volatile in steam. One gram of phenol dissolves in 15 cc.
water at 25°C. It is very soluble in alcohol, glycerine, chloro-
ːm, ether, carbon disulphide or in fixed or volatile oils. A
ιter solution is faintly acid to litmus. When heated phenol
ɣstals melt, forming a highly refractive liquid.

Its solubility is peculiar. When 10 per cent. of water is
ded to phenol it liquefies. This is known as phenol liquefra-
m, and may be regarded as a solution of water in phenol. If
ɔre water be added the solution is destroyed and a clear solution
not obtained until 15 cc. of water is added for each gram of
.enol. This may be considered as a solution of phenol in water.

Phenol gives a violet coloration, phenolic reaction, with ferric
lts, and a pale yellow precipitate (of tri-bromphenol
ːH$_2$Br$_3$OH) with bromine water.

It is a strong germicide, a general protoplasm poison, and is
creted from the body mainly as phenyl sulphuric acid or
njugated sulphate.

It is used in medicine mainly for its antiseptic action, and forms the basis of many synthetic drugs whose actions are antiseptic and antipyretic. As pointed out under iodoform substitutes, iodine when attached to the benzene ring is not decomposed in the body. All phenols are antiseptic but the addition of iodine increases the antiseptic action. This is the basis for the large number of iodine compounds on the market.

Properties of Phenols

The phenols have acid properties, but they are weaker than carbonic acid hence they are not soluble in sodium carbonate and will not decompose carbonates. Sodium phenolate is not formed by sodium carbonate but by the use of NaOH. Phenols which contain strongly negative substitute groups may be sufficiently acid to decompose carbonates. Picric acid for example, which is trinitro phenol, is strongly enough acid to do this.

$$C_6H_2 \Big\langle {(NO_2)_3 \atop OH}$$
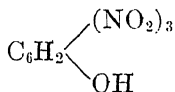
Phenols have alcoholic properties and form ethers, not directly as with ordinary alcohols, but by use of alkyl iodides, and sodium phenolate:

Phenyl-methyl-ether
(anisol)
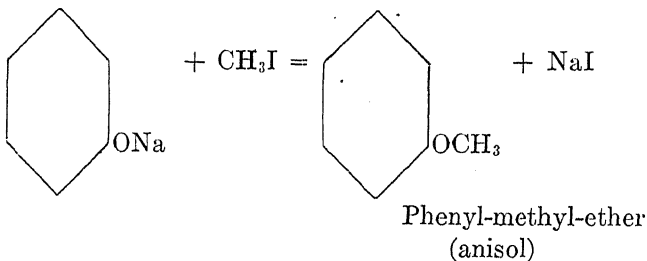
Ethers have the general formula ${R \atop R'}\Big\rangle O$. In this formula, (phenyl) $C_6H_5 = R$ and (methyl) $CH_3 = R'$ The product is a mixed ether.

The introduction of the OH group into benzene greatly increases its reactivity, and accordingly increases its antiseptic toxic properties. The tendency of the aromatic group as a whole

is to stimulate the motor side of the central nervous system while the paraffin series are depressant. In compounds with a paraffin side chain the depressant action usually predominates. The local action of phenols is always anesthetic, this explains the anodyne action of oil of cloves, eugenol, benzyl alcohol, etc., when applied to tooth cavities or injected hypodermically. Increase in the number of OH groups in phenols as in the paraffin series, lessens the physiological activity.

In case of poisoning by carbolic acid a part is oxidized in the body to the dihydroxy benzenes, pyrocatechol and hydroquinone. The dark color of the urine is due to further oxidation of the hydroquinone with the formation of quinone products. Normal urine contains considerable free sulphate; after carbolic acid there is little if any free sulphate, all of it being combined with the phenol. If such urine is boiled with a mineral acid the ethereal sulphate is decomposed and the sulphate can then be precipitated with barium chloride, while the sulphates in the body combine in this way with phenol. In cases of phenol poisoning, the injection of sulphates helps but little.

Carbolic acid, in cases of poisoning can be separated from the tissues by distillation with steam. Long continued distillation is necessary to remove the last traces. In case of a man dying 15 minutes after taking 15 cc. liquid carbolic acid (Ber. d. Deut. Chem. Gesell., 16., 1337 1883), Bischoff found

> 0.171 gram in stomach and intestine
> 0.028 gram in blood
> 0.637 gram in liver
> 0.200 gram in kidney
> 0.314 gram in brain.

This gives one an idea of how quickly poisons spread through the body.

Resorcinol, (1.3) or meta dihydroxyphenol,   is
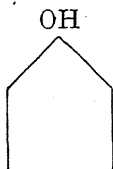
used mainly for the preparation of eosin, fluorescene, and azo dyes. It occurs in certain resins, especially galbanum and asafœtida. Heated with sodium, it yields the blue indicator known as lacmoid, which turns red with acids. Many other meta and para compounds yield resorcinol when fused with KOH. It crystallizes from water in colorless plates or prisms which melt at 118°C. Formerly resorcinol was much used in some of the skin diseases and has been injected into the bladder in cystitis and infections of the genitourinary tract, but it is irritant and likely to be painful if used in this way. At present it is not much used in medicine.

Quinol or **hydroquinone** or **para dihydroxy benzene** (1.4) is named because it can be obtained from quinone by reduction with sulphur dioxide and water.

| Quinone | | Hydroquinone |
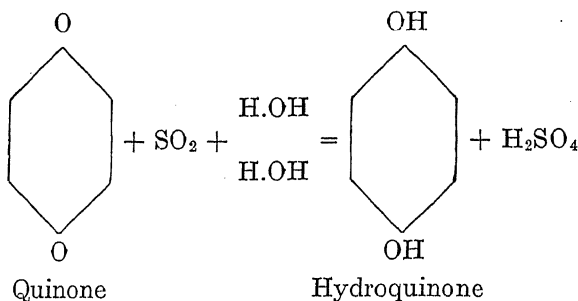
It was first obtained by the dry distillation of quinic acid:

$$C_6H_7(OH)_4COOH + O = C_6H_4(OH)_2 + CO_2 + 3H_2O$$
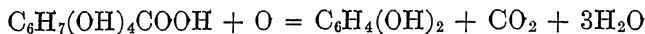
It occurs in nature in combination as a glucoside arbutin, and uncombined in some leaves and flowers (vaccinum vitis idœa). The form is colorless and crystalline and melts at 170°C. This substance has been used as an antipyretic but has been superseded by the modern antipyretics.

DIHYDROXY PHENOLS OR DIHYDROXY BENZENES

Three di-hydroxy phenols are theoretically possible, and all are known and can be prepared from plants. They are, catechol (1.2), resorcinol (1.3) and hydro-quinone (1.4).

Catechol, pyrocatechol or pyrocatechin or 1.2 hydroxy benzene occurs in beech-tar.
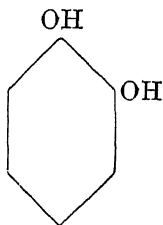
As the name indicates, (pyros-fire), it is derived from the destructive distillation of catechu, which contains protocatechuic acid:—
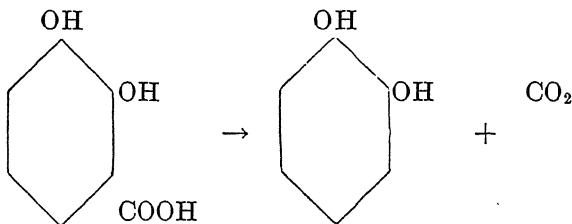
It crystallizes in colorless prisms from benzene, and melts at 104°C. It can also be prepared by fusing phenol sulphonic acid with KOH:
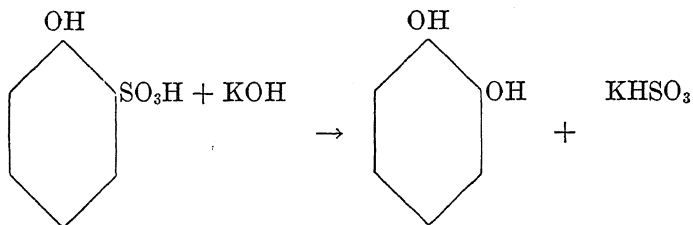
It occurs in small amounts combined with sulphuric acid in the urine of horses and human beings. It is also found in many tannins—the pyrocatechol tannins, especially those of pine and oak barks (not in oak galls), acacia, cutch, and gambir.

Pyrocatechol has met with little use in medicine. It was formerly used as an antipyretic, but it is toxic and forms methemoglobin readily. This is the parent substance from which synthetic adrenalin or epinephrine is derived, and itself produces

an appreciable rise of blood-pressure. Epinephrine is derived from catechol according to the formula given under epinephrine (p. 236).

TRIHYDROXY BENZENES OR TRIHYDRIC PHENOLS

I **Pyrogallol** or **pyrogallic acid,** 1.2.3, is so-called because it is formed from gallic acid $C_6H_2(OH)_3COOH$ (1.2.3.5) by heating.

gallic acid   pyrogallol

It is also formed by fusing hemotoxylin with KOH. Its dimethyl ether is found in beechwood creosote. Pyrogallol is the best known member of the trihydric phenols. It crystallizes in colorless plates which melt at 132°C. In excess of caustic alkali it absorbs oxygen readily and is employed in gas analysis for this purpose. It is used in certain skin diseases and in hair dyes.

II **Phloroglucinol,** 1.3.5, trihydroxy benzene, was first obtained from the glucoside phlorizin. It is also found in the glucosides, quercitin and hesperidin, and can be produced by fusing catechu, kino and other resins with KOH. It can be formed from resorcinol, which illustrates a frequent reaction that takes place on fusion with alkalies, namely, the replacement of hydrogen by hydroxyl:

Resorcinol   →   phloroglucinol.

Phloroglucinol is a white crystalline body that melts at 219°C. and tastes sweet. It is not used in medicine but is used in chemistry as a reagent with HCl to detect galactose, pentose, or glycuronic acid. These give a red color when heated with an equal volume of HCl specific gravity 1.09 and a little phloroglucinol is added (Tollen's reaction).

Gallic acid and tannic acid are phenols.
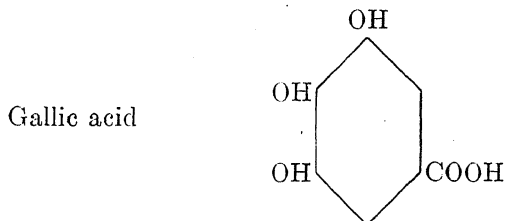
Gallic acid

on heating gives pyrogallol—see formula p. 94.
Tannic acid is digallic acid.
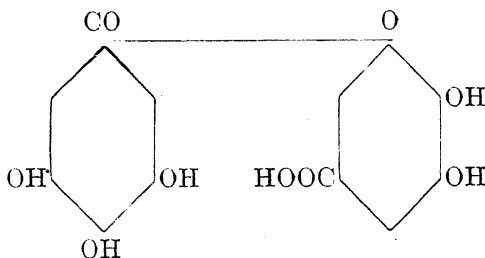
The tannins are sometimes divided into the pyrogallol and the catechol varieties, according to the color they give with ferric salts. The pyrogallol group gives a dark blue, and the catechol group gives a greenish color (see tannins).

CRESOLS

Cresols (cresote + ol) are methyl phenols. There are three cresols; ortho, meta, and para.
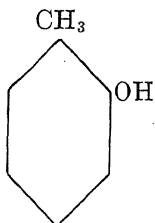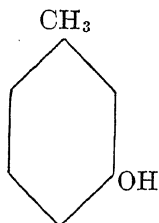
Ortho   *Meta*   *Para*

They occur in the distillate from coal tar and the tars from pine and beechwood. Like phenols, they react with ferric chloride to give colored solutions, and with bromine to give precipitates. They are readily nitrated.

Creosote from beechwood tar consists chiefly of a mixture of phenols, cresols, and guaiacols.

Guaiacol, so called because it was first obtained
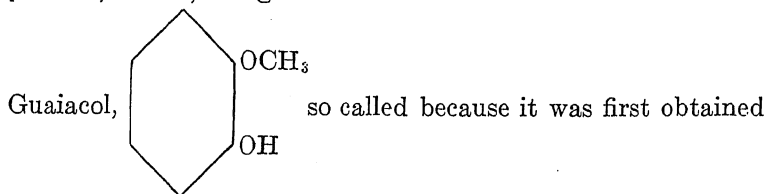
from guaiac resin, is the mono-methyl-ether of pyrocatechin. It possesses both the properties of an ether and a phenol, gives a methyl green color with iron salts and is converted into anisol or phenyl methyl ether on reduction with Zn.
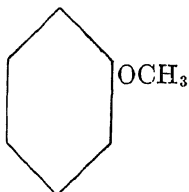
Anisol
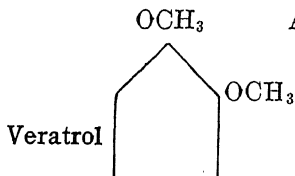
Veratrol is the dimethyl ether of pyrocatechin

Creosote (Gr. Kreas, flesh; Soter, preserver) is a mixture of phenols and cresols and guaiacols, obtained during the distillation of wood tar.

Creosotum, owing to the presence of phenols, has much the same action as phenol itself. Due to its anesthetic properties, creosote on cotton is sometimes inserted in a cavity to allay the pain of toothache. In addition, it possesses caustic and antiseptic properties. Many derivatives, based on the salol principle (q.v.) have been introduced, as intestinal antiseptics.

Creosote carbonate is one of these. It is a mixture of the carbonates of the various constituents of creosote, chiefly guaiacol and creosol. The formation of this ester greatly lessens the toxicity and caustic action of the original mixture, which is said to be less toxic and more powerfully antiseptic than phenol. It is a tasteless, odorless powder, well borne by the stomach.

Picric acid or tri-nitro-phenol is the most important nitrophenol derivative. The introduction of the nitro group into phenols increases the antiseptic and toxic action.

It is a powerful blood poison, renal irritant and respiratory and cardiac depressant. The introduction of the nitro groups also increases the acidity of the phenols. Phenol will not decompose sodium carbonate but picric acid will. Sodium phenolate is formed in the reaction, while only by the action of NaOH is it formed from phenol. The prolonged consumption of small quantities of picrate colors first the conjunctiva of the eyes, but later the entire skin may become yellow. This may be mistaken for jaundice. Picric acid is changed to picramic acid in the body, and this colors the urine red. Some is excreted unchanged in the urine and feces. It produces anuria, strangury, vomiting and may cause convulsions, like phenol. The red color of picramic acid has been utilized by Benedict and others as a method for the quantitative determination of glucose, and the reaction in the body is probably with glucose. The picramic acid is not so toxic as picric.

Tests for Picric Acid

I. The material or solution containing it in yellow aqueous, alcoholic or ethereal solutions have the same color. It is easily extracted with ether; and is somewhat soluble in water. The tests are made in water solution.

II. It dyes a thread of cotton, wool or silk yellow.

III. A solution of picric acid warmed to 60°C. with a few drops of KCN gives a red color due to the formation of isopurpuric acid. This acid does not exist in the free state but is present in this test as the K salt. The formulas assigned to isopurpuric acid are
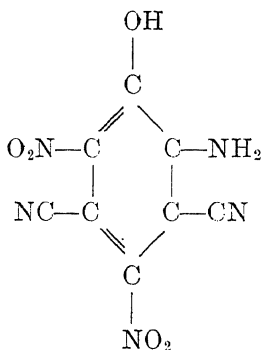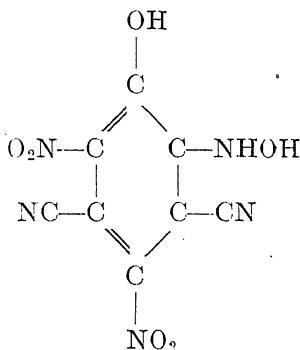
Nietzki-Petri   Borsche

IV. When picric acid is made alkaline with a solution of sodium carbonate and a trace of glucose added (1 cc. 0.1 per cent.) and heated on a water bath or over a free flame a red color due to picramic acid is developed. This has the formula—
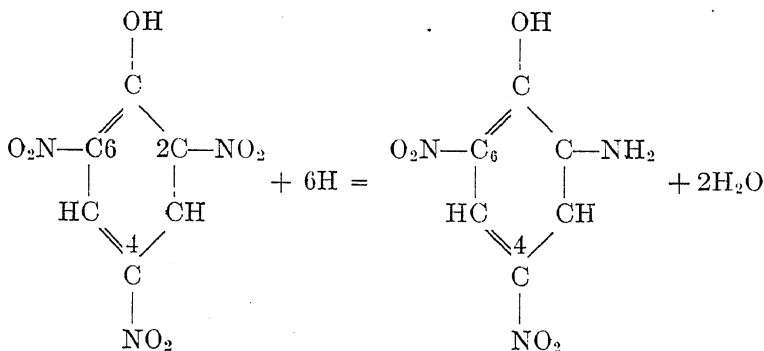
Picric acid   Picraminic acid or picramic acid.

This color is very similar to that of isopurpuric acid.

Reactions of the Phenols

1. Practically all phenols give a color reaction with Fe_2Cl_6 varying from greenish to violet. This reaction is known as the

phenolic reaction. For this reason, phenols are incompatible with iron salts. (Hydro quinone does not give a color with iron, which oxidizes it to quinone.)

2. All phenols give Liebermann's reaction: when a phenol is treated with sulphuric acid and a nitroso compound or a nitrite is added, it yields colored solutions. When the solution is treated with an excess of alkali, it assumes an intense blue or green color.

3. Pyrocatechol, pyrogallol, and phloroglucinol are precipitated with lead acetate. Resorcinol and hydroquinone are not. (a) They all reduce Fehling's solution on warming.

4. Nearly all phenols reduce ammoniacal solutions of silver nitrate and salts of mercury and gold to their respective metals.

5. Generally, phenols react with an aqueous solution of NaOH to form soluble salts, but they are insoluble in Na_2CO_3.

6. With bromine water, most phenols yield a precipitate of brominated phenol. The most important reactions are those with alkalies, ferric chloride and bromine water, and Liebermann's reaction. The fact that phenol gives C_6H_5ONa, sodium phenolate with NaOH, but is too weak to decompose sodium carbonate, distinguishes phenols from acids.

When taken into the body, the phenols are combined and excreted with sulphuric acid, glycuronic acid, etc. Yet phenol, when heated in a test tube with sulphuric acid, is not changed to any extent, because it is less basic than alcohol and does not form salts so easily.

7. All monhydric phenols give Millon's test. When heated with Millon's reagent (A solution of mercuric nitrate containing free HNO_3) a red color is produced.

Like the alcohols, phenols contain an hydroxyl group, and reagents which act on the hydroxyl will act on a phenol:

$$C_6H_5OH + CH_3COCl = CH_3CO.O_6C_5H + HCl$$
$$\text{acetyl chloride}$$
$$C_6H_5OH + PCl_5 = C_6H_5Cl + POCl_3 + HCl$$
$$C_6H_5OH + Na = C_6H_5ONa + H$$
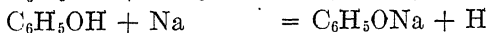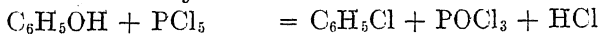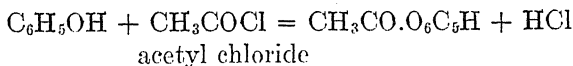
Phenols also form ethereal salts or esters which are decomposed only in alkaline solutions. The irritating action on the stomach of one or both components of such salt can be avoided in this way

and the antiseptic effect retained.   This is an important reaction in medicine; the Nencki salol principle is based on this fact.   The principle is this: To get the antiseptic effect of the phenols, or derivatives in the intestine or genito-urinary tract, they cannot be used as such because they are caustic and irritating to the stomach.   In the form of their ethereal salts they pass through the stomach unchanged but in the neutral reaction of the intestine, these salts are slowly decomposed into their components. The physiological action of the components is therefore obtained and the irritation of the stomach avoided.   Since Nencki was the first who used salol with this idea in mind, the principle when used with any combination is known as Nencki's salol principle:

$$C_6H_5(OC.C_6H_4OH) + H_2O = C_6H_5OH + C_6H_4OHCOOH$$
Phenol salicylate (salol)   Phenol   Salicylic acid.
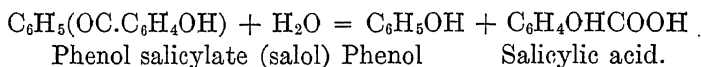
The phenols correspond to tertiary alcohols since they yield neither aldehydes nor acids on oxidation.   When, they have paraffin side chains, these side chains may be oxidized and yield the same alcohol aldehydes and acids as when they are free: *e.g.*, when oxidized with chromyl chloride CrO_2Cl_2:

Toluene   Benzyl alcohol   Benzaldehyde   Benzoic acid.
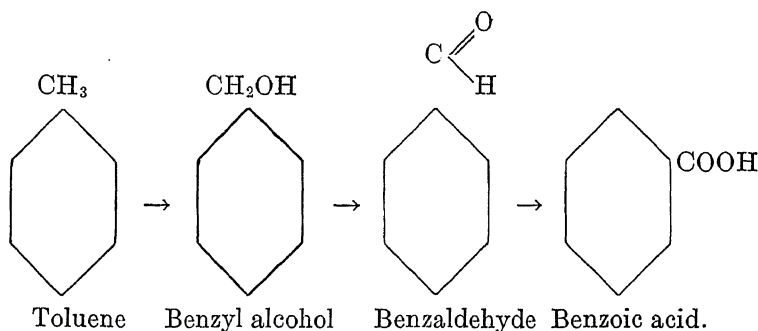
Toluene can be regarded either as methyl benzene or phenyl methane—

$$H-\underset{|}{\overset{H}{\underset{|}{C}}}-C_6H_5$$
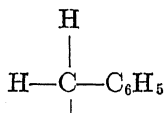
It is a colorless liquid which boils at 110°C. It is used as a laboratory antiseptic especially to prevent the growth of bacteria when the action of ferments is to be determined. It has relatively little action on ferments. It is of direct interest in medicine only as a source of other drugs, such as benzyl alcohol, benzaldehyde and benzoic acid. Toluene can be oxidized in the body to benzoic acid and is excreted combined with glycocoll as hippuric acid (q.v.).

Friedel and Craft's Reaction for Toluene Synthesis.—When benzene is treated with methyl chloride in the presence of aluminum chloride, which acts as a catalyzer, toluene is formed according to the following reaction:
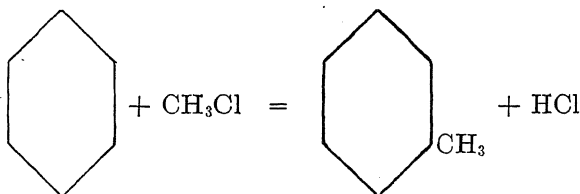
Toluene is also formed by the dry distillation of balsam of tolu or by distilling toluic acid with lime

$$C_6H_4(CH_3)COOH = C_6H_5CH_3 + CO_2.$$
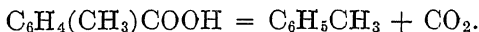
XI. AROMATIC ALCOHOLS, AND PHENOL ALCOHOLS

When a benzene compound contains an hydroxyl group in a side chain it is known as an aromatic alcohol. There may also be mixed compounds in which both phenol and alcoholic groups are present, *e. g.*:

1. Benzyl alcohol or phenyl carbinol

$C_6H_5CH_2OH$ or
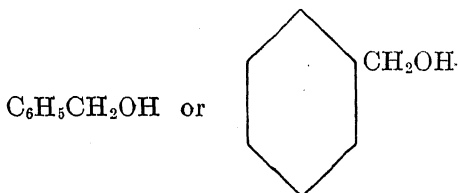
is a type of the aromatic alcohols; while

2. Saligenin or salicyl alcohol

$C_6H_4OHCH_2OH$ or
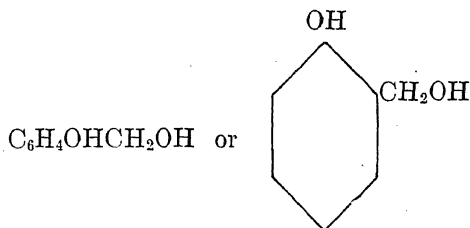
is both a phenol and an aromatic alcohol.

Benzyl alcohol has recently come into vogue as a local anesthetic, and benzyl benzoate has been advised in a variety of internal conditions thought to be due to a spasmodic condition of smooth muscle. It undoubtedly has some local action, but it will take some time to evaluate it as a therapeutic agent. It has the general properties of alcohols.

Saligenin.—Saligenin is found in willow bark in the glucoside salicin which is a combination of saligenin and glucose (p. 193). It can be prepared synthetically by the action of formaldehyde on phenol—
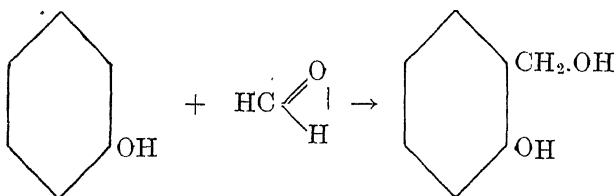
Saligenin is oxidized in the body to salicylic acid. Like all phenols it has anesthetic properties.

Cinnamyl alcohol, $C_6H_5CH:CH.CH_2OH$, is another phenol alcohol, but it differs from benzyl alcohol in that the side chain is unsaturated. It is a crystalline substance with the odor of hyacinths, and is present as an ester in the resin storax. It can also be prepared by heating benzaldehyde and sodium acetate together, in presence of a dehydrating agent,

$$C_6H_5—CH\overline{|O + H_2|}CH——COONa$$
benzaldehyde   sodium acetate
$$= C_6H_5—CH = CH——COONa$$
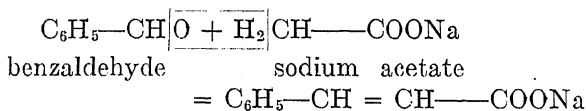
It is not used as a medicine, but the aldehyde is added to perfumes to give the odor of cinnamon. Other aromatic aldehydes used in perfumes are:

Citral or geranial . . . which gives the odor of lemon—

$$(CH_3)_2C:CH.CH_2.CH_2.C(CH_3):CH.CHO$$

Vanillin . . . which gives the odor of vanilla—

$$C_6H_3 \begin{cases} CHO & 1 \\ OCH_3 & 3 \\ OH & 4 \end{cases}$$
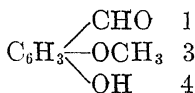
Piperonal . . . which is related to vanillin and coumarin—
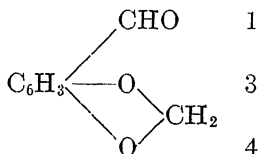
It possesses the odor of heliotrope to a remarkable degree. In commerce it is known as heliotropin.

ALDEHYDES OF THE AROMATIC SERIES

Benzaldehyde is found in bitter almonds as the glucoside amygdalin:

$$C_{20}H_{27}NO_{11} + 2H_2O = 6C_6H_{12}O_6 + HCN + C_6H_5CHO$$

amygdalin   glucose   benzaldehyde
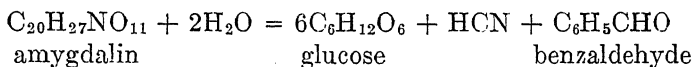
Benzaldehyde also occurs in ester combination with benzoic and cinnamic acid in balsam of tolu, peru, and in storax.

Salicylic aldehyde—

Saligenin + O =   Salicylic aldehyde
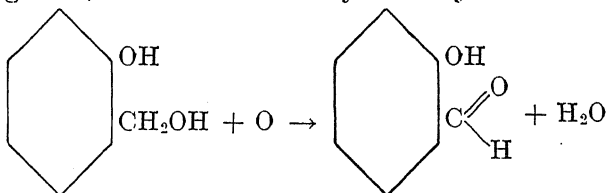
The free aldehyde occurs in the essential oil of spiroea ulmaria and in the blossoms of meadow sweet and other volatile oils.

It is a fragrant colorless liquid B.P. 196° C., which is readily oxidized to salicylic acid.
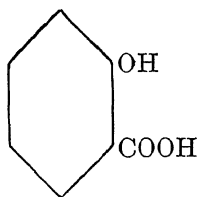
In the body each of these aldehydes is oxidized to the corresponding acid.

KETONES OF THE AROMATIC SERIES

The only aromatic ketone used to any extent in medicine is aceto phenone, or hypnone or phenyl methyl ketone, $C_6H_5CO.CH_3$. It has fairly strong hypnotic properties, due to the methyl group, but the action is more powerful and possesses no advantages over the well known hypnotics of the aliphatic series.

Phenyl ethyl ketone, $C_6H_5CO.C_2H_5$, has a more powerful action than acetophenone but less than the aliphatic series. It also is oxidized in the body to benzoic acid.

Benzo phenone, $C_6H_5:CO.C_6H_5$, has slight hypnotic properties, but much less than that of the aliphatic ketones.

When fused with KOH it breaks down into benzoic acid and benzene and we should expect this reaction to take place to some extent in the body.

XII. ACIDS AND RELATED COMPOUNDS

Benzoic Acid.—Benzoic acid, C_6H_5COOH, is readily prepared by oxidation of benzaldehyde. It is found in gum benzoin and in all balsams. Crystallization takes place from hot water in glistening flat plates or needles which melt at 120°–121°C. It reacts readily with alkali hydrates and carbonates to form benzoates. Benzoic acid or the benzoates have very little toxicity. They are not much used in medicine at the present time, having been superseded by the salicylates.

When taken into the body, benzoic acid combines with glycocoll (amino acetic acid) to form hippuric acid, and is excreted as

such $C_6H_5COOH + H_2N.CH_2COOH = C_6H_5CO.HN.CH_2COOH$ (hippuric acid).

Salicylic acid is the most important hydroxy benzoic acid in materia medica. It occurs as the methyl ester in the oil of wintergreen (oleum gaultheria) and in the oil of birch (oleum betulæ).

There are some of the free acids in these oils, and also in the buds of spiræa ulmaria. It can be prepared by the action of CO_2 on sodium phenate at 200°C.

$$2C_6H_5ONa + CO_2 = C_6H_4{<}^{OH}_{COOH} + C_6H_5OH$$
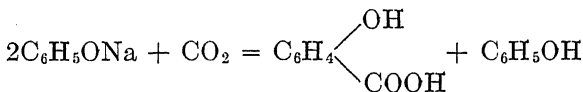
Salicylic acid is a strong antiseptic and has been used in the preservation of food, wines, beer, etc.
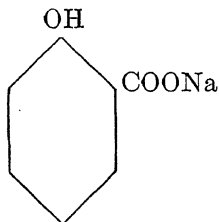
Sodium salicylate is a frequent remedy in the treatment of acute rheumatism. Its derivatives, salol, and aspirin, are used for the same purpose.

It was formerly believed that the synthetic salicylic acid possessed toxic properties and should not be used in medicine. Recent investigation has shown, however, that the natural and synthetic salicylates are identical in therapeutic action. The earlier toxic action was due to impurities.

When the carboxyl (COOH) group is introduced into the phenol-nucleus, the action of the phenol is greatly modified, and the toxicity lessened. The extent of the change, however, depends on the relation of the OH and COOH in the ring. If they are in the ortho (1:2) position, as in ordinary salicylic acid, the antiseptic power is about the same as phenol and the antipyretic action is greatly increased. The 1:3 and 1:4 oxybenzoic

acids are neither antiseptic nor antipyretic in action. Also the introduction of a methyl group in place of the hydroxyl hydrogen

As in ortho-methoxy benzoic acid

OCH_3

$COOH$
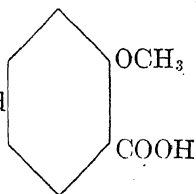
greatly lessens the antiseptic and antipyretic action, just as methoxy quinine is less antipyretic than quinine.

On the other hand, the introduction of the acetyl group, CH_3CO, as in aspirin, does not cause much change in action, and in some respects improves the salicylate as a therapeutic agent.

Aspirin is acetyl salicylic acid and is prepared by the action of acetyl chloride on salicylic acid at high temperatures.

OH

$COOH$

$+ CH_3CO.Cl =$

$OOCCH_3$

$COOH + HCl$
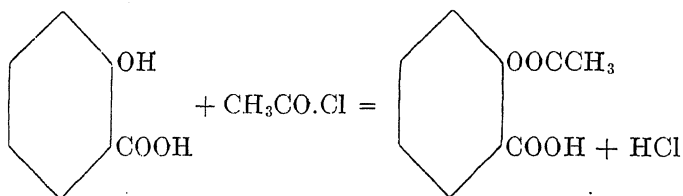
The stomach tolerates it better than sodium salicylate.

Salol is phenyl salicylate. It is formed by the action of a dehydrating agent like $POCl_3$ on a mixture of phenol and salicylic acid.

OH

$COO\boxed{HHO}$

$\rightarrow$

OH

$COOC_6H_5 + H_2O$

salicylic acid   phenol   salol

It is also formed by heating salicylic acid at 200–220°C.

$$2C_6H_4\!\!<^{OH}_{COOH} = C_6H_4\!\!<^{OH}_{COOC_6H_5} + H_2O + CO_2$$

Salol is used as an intestinal antiseptic, the action being due mainly to the slow liberation of phenol, in the natural alkalinity of the intestine. The principle of giving salol to obtain the action of phenol and salicylic acid in the intestine without their irritating action on the stomach was first used by Nencki and is known as Nencki's salol principle (q.v.), p. 100.

Mesotan or the monomethyl ester of salicylic acid is used to a considerable extent in medicine. It is prepared by the action of chlor methyl ether on sodium salicylate:

Sodium salicylate + Chlormethyl →   Mesotan
ether

When used locally in acute rheumatism it may produce dermatitis, probably by the irritative action of its hydrolytic products. It readily undergoes hydrolysis as follows:

Mesotan   →   salicylic   formal-   methyl
                       acid   dehyde   alcohol

Nothing definite can be stated about the form in which the salicylates are excreted. It was formerly taught that salicylic acid combines with amino acetic acid and is excreted as salicyluric acid (cf. benzoic acid). Recent work does not substantiate

this statement. In the earlier work it is thought that the product isolated as salicyluric from the urine was salicylic acid, mixed with some impurities.

Cinnamic acid or phenyl acrylic acid, $C_6H_5CH:CHCOOH$, is of interest because many balsams contain it, and it is the most important phenyl derivative containing an unsaturated side chain. Leucocytosis in experimental animals is caused by the use of it, and for this reason it was used for a time in tuberculosis with the idea of increasing phagocytosis. The clinical results have not shown any benefit.

It may be prepared by the condensation of benzaldehyde and acetic acid or sodium acetate on

$$C_6H_5 \; C \underset{\diagdown H \; + \; \text{acetic acid}}{\overset{\diagup \boxed{OH_2} \; CH.COOH}{}} = C_6H_5CH.CH.COOH + H_2O$$

benzaldehyde. $\qquad\qquad\qquad\qquad\qquad$ cinnamic acid
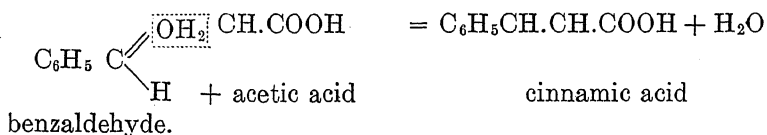
Balsams are resins or oleoresins that contain cinnamic or benzoic acids, or both these acids. The acid or its preparations has very few, if any, uses in medicine.

Phenyl quinoline carbonic acid (atophan) or acidum phenyl cinchoninicum or phenyl quinoline carboxylic acid = 2 phenyl quinoline 4 carboxylic acid, $C_{16}H_{11}O_2N$,
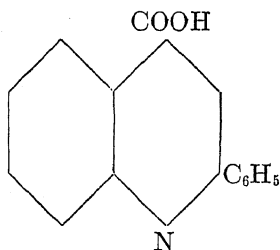
melts at 210 c. with partial decomposition. It is insoluble in cold water, slightly soluble in cold alcohol, hot alcohol and ether. A saturated solution in dilute HCl gives reddish brown crystals with platinic chloride. It is soluble in ammonia from which it is precipitated by $AgNO_3$ or lead acetate. It is used chiefly in gout to increase the uric acid elimination. It does not relieve the pain and inflammation of an acute attack to the same degree as the wine of colchicum, or the alkaloid colchicine.

The ethyl ester of atophan

$$COOC_2H_5$$
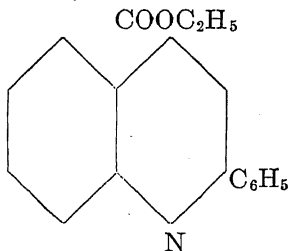
is known as acitrin.

Novatophan is the methyl derivative of acitrin and is the trade name for ethyl, 6 methyl phenyl quinolin, 4 carboxylate—
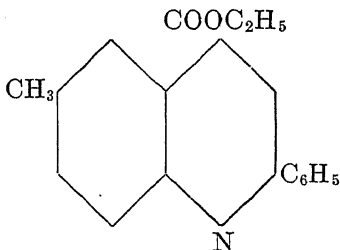
Its properties and uses are the same as phenyl cinchoninic acid.

XIII. ANILINE AND TOLUENE DERIVATIVES

Aniline is the basis of the modern antipyretics.

When concentrated HNO_3 acts upon benzene, nitrobenzene is formed:

$$C_6H_6 + HNO_3 = C_6H_5.NO_2 + H_2O$$
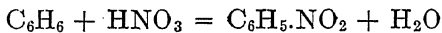
Nitrobenzene is a pleasant smelling colorless oily liquid with the odor of bitter almonds, often used to scent soaps, but mainly in the manufacture of aniline. It soon darkens on exposure to air. Its boiling point is 208°C. It has a strong poisonous action. There are on record cases in which from 10–20 drops has caused death. It changes the blood to a chocolate color but no methemoglobin has been found, but a special absorption band between C and D (Fihlene's nitrobenzene band) appears. Nitrobenzene also causes paralyses of the central nervous system. It is excreted as glycuronic acid in the urine. Its use in medicine is

ited. When introduced into the body some of it is reduced to
·a-amino phenol.

$$\text{OH} - \bigcirc - \text{NH}_2$$
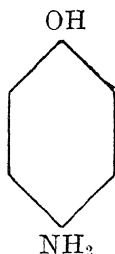
his compound is of interest because all of the aniline com-
inds or antipyretics are supposed to cause a reduction of
iperature due to the formation of this substance in the body.
Jitrobenzene on reduction with nascent hydrogen gives aniline.
s is the characteristic test (see tests for aniline, p. 112):

$$\bigcirc \!-\! NO_2 + 6\dot{H} = \bigcirc \!-\! NH_2 + 2H_2O$$
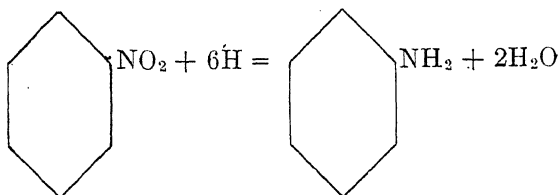
niline is moderately toxic in its action and produces hemo-
)inuria, and an abundance of urobilin. The typical symp-
is of aniline poisoning are vertigo, asthenia, gastritis,
opia, and sometimes exfoliative dermatitis. Since the para-
no-phenol is less toxic, attempts have been made to use this
stance as the starting point of synthetic antipyretics, rather
n aniline. Phenacetin is the result of such research.
.cetphenetidinum or phenacetin:

$\bigcirc$	$OC_2H_5 - \bigcirc$	$OC_2H_5 - \bigcirc$
NH_2	NH_2	$NHCOCH_3$
Aniline	Phenetidin	Acetphenetidin
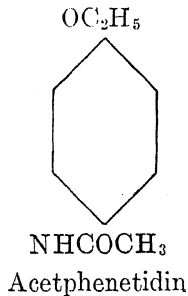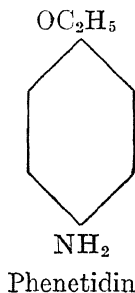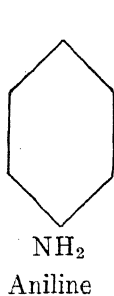
The following reactions occur in the preparation of phenacetin

I.

OH + HNO_3 = OH + H_2O

NO$_2$

Phenol   Para-nitro-phenol
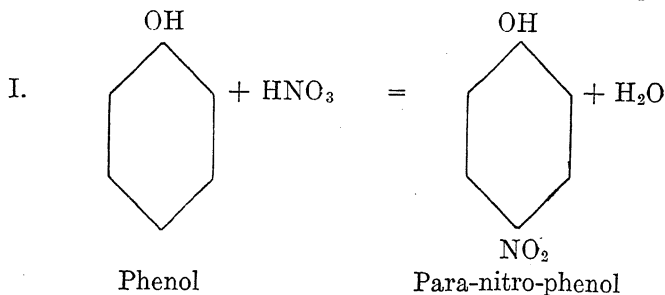
There is also some ortho nitrophenol formed which can be separated from the para by distillation with steam:

II.

OH + NaOH = ONa + H_2O

NO$_2$ NO$_2$

III.

ONa + C_2H_5I = OC_2H_5 + NaI

NO$_2$ NO$_2$
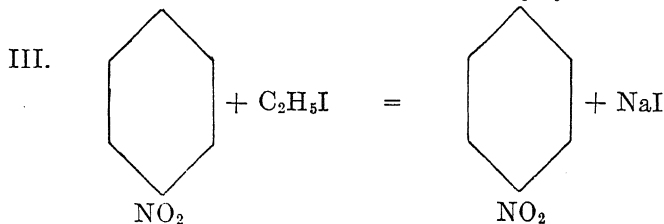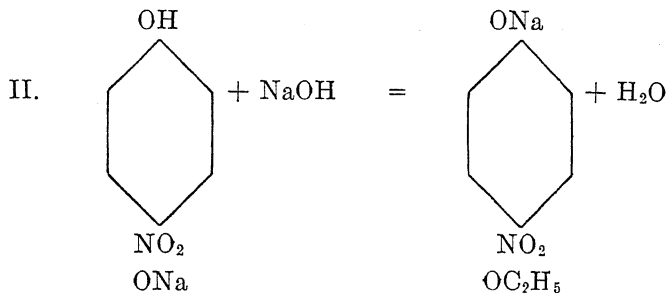
This is reduced with hydrogen to phenetidin.

IV.

OC_2H_5 + CH_3COOH = OC_2H_5 + H_2O

NH$_2$ NHCOCH$_3$
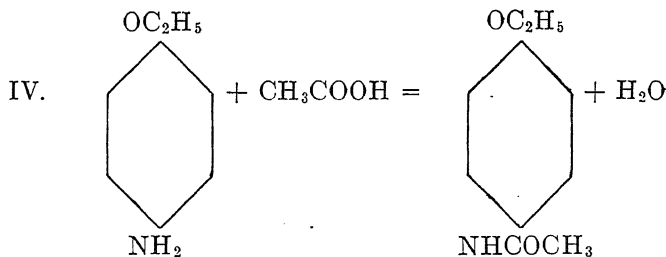
Phenetidin   Paraacetphenetidin or phenacetin.

If aniline be taken internally, it is excreted in combination with glycuronic acid as glycuronate, which will reduce Fehling's solution. Some aniline may be formed free in the urine. Aniline is a weak base and some of it will distil from acid solution. It gives the following tests:

I. **Hypochlorite Test.**—To an aqueous solution of aniline add a few drops of a filtered solution of bleaching powder or sodium hypochlorite drop by drop. A purple-violet color changing to red is produced if aniline be present.

II. **Chromic Acid Test.**—To a solution of aniline in a porcelain dish add a few drops of concentrated sulphuric acid and a few drops of a solution of potassium dichromate. A blue color results.

III. **Bromine Water Test.**—Bromine water with aniline gives a flesh colored precipitate. The test is sensitive to 1 in 50,000.

IV. **Phenyl Isocyanide Test.**—Aniline contains the NH_2 group and will give the phenyl isocyanide test.

A few drops of aniline solution with chloroform and KOH, when heated, gives the repulsive odor of phenyl isocyanide. Acetanilide will also give this test. When acetanilide is boiled with KOH or alcoholic KOH it is decomposed into aniline and potassium acetate. It will then give the tests for aniline.

V. Ether or chloroform will extract acetanilide from acid aqueous solution. Acetanilide will give the indo-phenol test.

Boil acetanilide with concentrated HCl and evaporate almost to dryness. Cool and add 5 cc. saturated aqueous carbolic acid solution, then a few drops of hypochlorite solution. A violet-red color is produced. Carefully add a layer of ammonium hydrate; this will take on an indigo-blue color.

Other drugs (phenacetin) give this blue color, which is characteristic of acetanilide only when preceded by the violet-red color. See indo–phenol reactions (Richter's Organic Chem., 1911, vol. II, p. 173).

ACETANILIDE

Acetanilide (antifebrine) is formed when aniline is treated with acetyl chloride or acetic anhydride.

I.

$$+ CH_3COCl \rightarrow + HCl$$

NH_2 $NH.COCH_3$
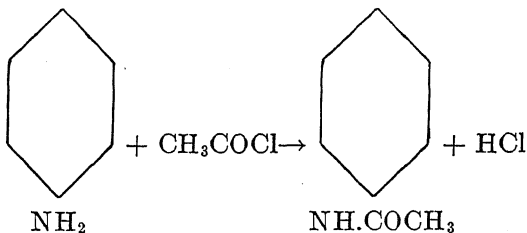
II. The usual method of preparation is by boiling a mixture of aniline and acetic acid for some hours:

$$C_6H_5NH_2 + CH_3COOH = C_6H_5NH.CO.CH_3 + H_2O$$
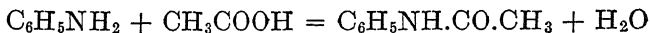
Acetanilide is a colorless crystalline substance which melts at 116°C. It is hydrolyzed to its components rather readily. This happens in the body, where aniline is converted into para-amino phenol, which in greater part is excreted combined with sulphuric and glycuronic acids. Some of it is excreted as oxy-carbanile,
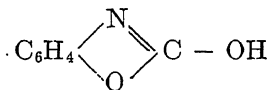
These changes reduce the toxicity of aniline. The antipyretic action is thought to be due to the paramino-phenol.

Antipyrine or phenyl dimethylpyrazolon is an antipyretic of importance. It is not an aniline derivative, but is more closely related to phenyl hydrazine.

Hydrazine, $HN_2.NH_2$, is a strong base and extremely toxic.

Phenyl hydrazine, $C_6H_5NH.NH_2$, is a compound of great practical importance and is easily prepared by the reduction of diazo-benzene chloride (benzene diazonium chloride) as follows:

$$C_6H_5.NH_2 + HCl + HNO_2 = C_6H_5N:N.Cl + 2H_2O$$
Diazo benzene chloride
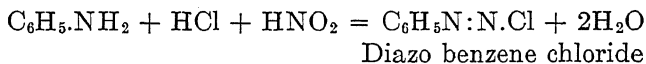
When this is reduced with HCl and stannous chloride

$$C_6H_5N:N.Cl + 4H = C_6H_5NH.NH_2HCl$$
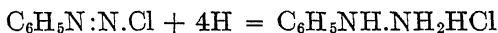
phenyl hydrazine, HCl, is produced which, when treated with NaOH, the HCl is removed as NaCl. The technic of carrying

out any of these reactions can be obtained from any book on methods in organic chemistry.

Phenyl hydrazine is a most important reagent for the identification of aldehydes and ketones with which it readily combines to form hydrazones and osazones. With beta-diketones and β-ketone esters, it forms ring compounds containing nitrogen, the so-called pyrazoles and pyrazolones.

Phenyl methyl pyrazolone is formed when phenylhydrazine is heated with aceto-acetic ether, as follows:

$$CH_3-CO \atop H_2C-CO-OC_2H_5 \quad + \quad {H_2N \atop HN-C_6H_5} \rightarrow {CH_3-C=N \atop H_2C-CO}{>}N-C_6H_5 \\ + H_2O + C_2H_5OH$$

Aceto-acetic ester   Phenyl   Phenyl methyl
                            hydrazine   pyrazolon
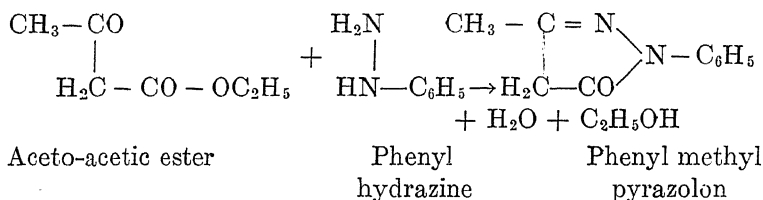
The name pyrazole comes from pyrrole, a feeble basic body found in coal tar and in the dry distillation of bones (pyros, fire; oleum, oil). By the introduction of N into this ring, it becomes pyrazole.

$$\begin{array}{c} CH \quad\quad CH \\ CH \quad\quad CH \\ N \end{array}$$

Pyrrole

$$\begin{array}{c} CH \quad\quad CH \\ N \quad\quad CH \\ NH \end{array}$$
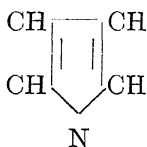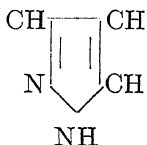
Pyrazole

Pyrazolon is:

$$\begin{array}{c} CH \quad\quad CH_2 \\ N \quad\quad C=O \end{array}$$
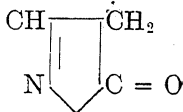
1. Phenyl 2.3 dimethyl pyrazolon, or antipyrine, is:

$$CH_3C\underline{\hspace{1.5cm}}CH$$
$$CH_3N\underset{\displaystyle C_6H_5N}{\diagdown\diagup}C = O$$
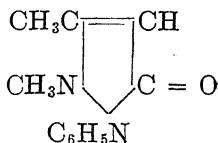
The pyrazolons or ketohydro pyrazoles are the pyrazole derivatives known for the longest time and are produced by the elimination of alcohol from the hydrazones of β-ketonic esters.

Phenyl hydrazone aceto-acetic ester, 1.3 Phenyl methyl pyrazolon β-ketonic esters, are esters in which the ketone group $C = O$ is the β position with reference to the COOH group. For example, in aceto-acetic ester:

$$CH_3.CO\ CH_2\ COOC_2H_5$$
$$(\beta)\ \ (a)$$
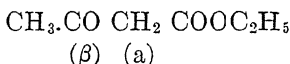
The CO is in the β, position, and this reacts with phenyl hydrazine to form phenylhydrazone aceto acetic ester:

$$CH_3.C - CH_2 - COOC_2H_5. \qquad CH_3.C = CH_2$$

$$\underset{O}{\overset{\diagdown\diagdown}{}} \qquad\qquad = \qquad \underset{NC_6H_5}{\overset{\displaystyle N\ \ \ \ C = O}{\diagdown\diagup}}$$

$$\underset{H_2\ \ \ \ \ \ \ H}{N\underline{\hspace{1cm}}N - C_6H_5}$$
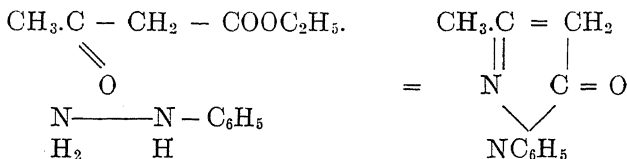
This, on loss of alcohol and water, gives, 1:3 phenyl methyl pyrazolon. Aceto-acetic ester reacts under some conditions as if the constitution were

$$CH_3.C(OH):CH.COOC_2H_5$$
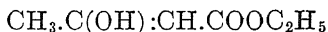
This last form is known as the "enol" form (alcoholic), the other as the "keto" form. By using the enol form, the formation of phenyl dimethyl pyrazolon or antipyrine can be more simply explained.

I.

$$\begin{array}{ll} CH_3 & CH_3 \\ | & | \\ C\ OH\ \ \ \ \overset{H}{\diagdown}N.HNC_6H_5 & C - NH.HNC_6H_5H_2O \\ || \qquad \diagup & = \qquad || \\ CH\ \ \ \ \ \ H & CH \\ | & | \\ COOC_2H_5 & COOC_2H_5 \\ \text{aceto acetic ester} & \text{aceto-acetic} \\ \text{"enol" form} \qquad + & \text{hydrazone} \\ \qquad\qquad \text{phenyl hydrazine} & \end{array}$$
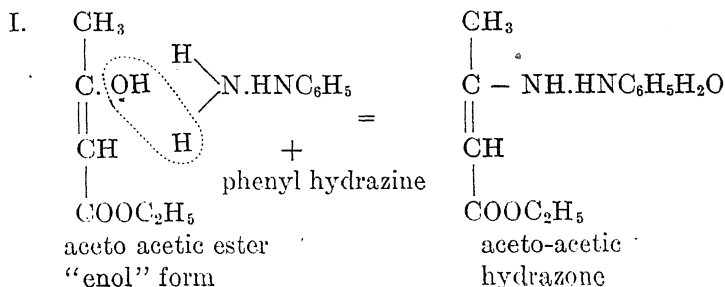
II. On heating, this loses alcohol and gives:

$$\begin{array}{l} CH_3 \\ \| \\ C——NH \\ | \quad\quad | \\ CH \quad\quad | \\ | \quad\quad | \\ CO——NC_6H_5 \end{array}$$ or 1 phenyl.3 methyl pyrazolon.
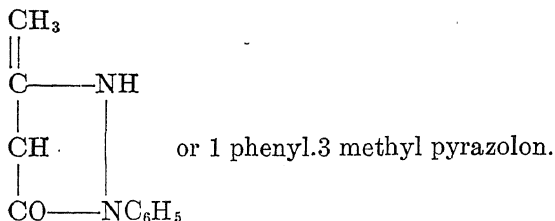
When this is treated with methyl iodide antipyrine is formed:

$$\begin{array}{cc} CH_3C===CH & CH_3C===CH \\ | \quad\quad | & | \quad\quad | \\ HN \quad CO + CH_3I \;=\; CH_3N \quad CO + HI \\ \searrow\swarrow & \searrow\swarrow \\ NC_6H_5 & NC_6H_5 \end{array}$$
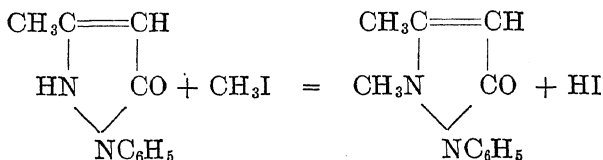
phenyl methyl pyrazolon   phenyl dimethyl pyrazolon

Antipyrine is classed as an artificial alkaloid and like alkaloids it unites with acids, hence when prepared in this way it is combined with HI. The free antipyrine is separated just as strychnine is extracted from strychnine sulphate—by making alkaline with NaOH and extracting with ether, from which it is crystallized.

The structural formula for antipyrine is proved by the synthesis from methyl phenyl hydrazine and aceto-acetic ester.

(I) $$\begin{array}{ll} CH_3 \quad\quad CH_3 \\ | \quad\quad\quad | \\ C.\boxed{OH \quad H} N-NHC_6H_5 \\ \| \\ CH \quad\quad + \\ | \\ COOC_2H_5 \end{array}$$ (II) $$\begin{array}{l} CH_3 \\ | \quad\quad\quad /CH_3 \\ C——N-NC_6H_5 \\ \| \quad\quad\quad H \\ CH \\ | \\ CO\; OC_2H_5 \end{array} \rightarrow$$

=

Aceto-acetic ester (enol)

(III) $$\begin{array}{c} CH_3.C===CH \\ | \quad\quad | \\ CH_3.N \quad C=O \\ \searrow\swarrow \\ NC_6H_5 \end{array}$$
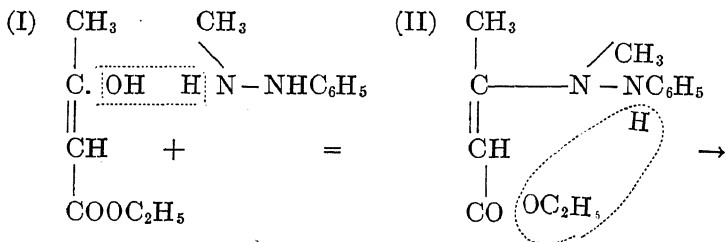
Antipyrine was discovered in a search for artificial quinine. It has none of the quinine action on the malarial organism and is injurious to the hemoglobin, lessening its oxygen carrying power. It is very useful in the treatment of neuralgic pains, and like phenacetin is superior to morphine in this condition. It is eliminated largely unchanged in the urine though some glycuronate is formed.

Pyramidon is said by many to be superior in most respects to antipyrine.

PYRAMIDON

Pyramidon-dimethylaminoantipyrine is obtained by the following reactions: a solution of antipyrine hydrochloride is acted on by nitrous acid, the result being nitroso antipyrine.

$$
\begin{array}{ccc}
\mathrm{CH_3} & & \mathrm{CH_3} \\
| & & | \\
\mathrm{C{-}{-}N.CH_3} & & \mathrm{C{-}{-}N.CH_3} \\
|| \quad\quad | & = + \mathrm{HNO_2} = & || \quad\quad | \quad + \mathrm{H_2O} \\
\mathrm{CH} \quad\quad | & & \mathrm{NO{-}C} \quad\quad | \\
| & & | \\
\mathrm{CO{-}N.C_6H_5} & & \mathrm{CO{-}N.C_6H_5}
\end{array}
$$
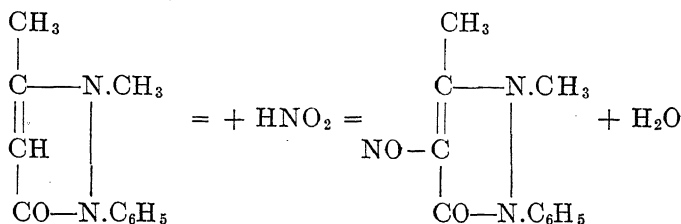
When this is reduced, amino antipyrine results:

$$
\begin{array}{c}
\mathrm{CH_3} \\
| \\
\mathrm{C{-}{-}N.CH_3} \\
|| \quad\quad | \\
\mathrm{NH_2{-}C} \quad\quad | \\
| \\
\mathrm{CO{-}N.C_6H_5}
\end{array}
$$
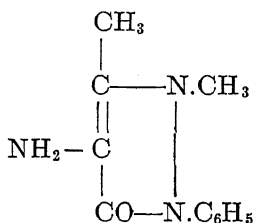
This is isolated by means of its benzylidene derivative, and when it is methylated by treatment with methyl iodide it gives pyramidon.

$$
\begin{array}{c}
\mathrm{CH_3} \\
| \\
\mathrm{C{-}{-}N.CH_3} \\
|| \quad\quad | \\
\mathrm{(CH_3)_2N.C} \quad\quad | \\
| \\
\mathrm{CO{-}N.C_6H_5}
\end{array}
$$

deep green color due to the formation of iso-nitroso antipyrine on the addition of 1 cc. dilute sulphuric acid. If the solution be concentrated, green crystals of nitroso-antipyrine form.

4. Fuming nitric acid added to antipyrine gives a green color. Heated with excess of nitric acid, it gives a red color.

5. Add a few drops of sodium or potassium nitrite, then sulphuric acid, a green to blue color appears. If much antipyrine be present nitroso antipyrine $C_{11}H_{11}(NO)(ON_2)$ will separate out in crystals.

Salicylic Acid Tests

1. It melts at 156°–159°C.

2. One gram dissolves in 460 cc. of water, or 42 cc. of chloroform, or 3 cc. of ether.

3. Its saturated water solution is colored intensely bluish violet with ferric chloride solution.

4. An aqueous solution warmed with Millon's reagent gives a deep red color (monohydroxy phenol test).

5. Bromine water precipitates salicylic acid as tribrom phenyl hypobromite – a white crystalline precipitate (see phenol, p. 89).

$$C_6H_4 \begin{cases} OH \\ COOH \end{cases} + 4Br_2 = CO_2 + 4HBr + Br$$

PHENACETIN: ACETPHENETIDiNE

1. Acetphenetidine melts at 133°–135°C.

2. It is soluble in 1310 cc. of water, 15 cc. of alcohol or 90 cc. of ether.

3. Boil several minutes with 3 cc. conc. HCl. Dilute with 10 cc. water, filter and cool. A few drops of chromic acid or chlorine water will produce a green color.

4. Boil with 3 cc. conc. HCl. Dilute to 10 cc., cool and filter, and add 2 cc. 5 per cent. phenol, and a little calcium hypochlorite solution. A carmine red color develops which changes to blue on addition of ammonium hydroxide.

SACCHARIN

Saccharin is the ortho sulphonated derivative of benzoic acid, and can be prepared from toluene. The following formulas indicate the essential reactions:

$$C_6H_5CH_3 + H_2SO_4 = C_6H_4\!<\genfrac{}{}{0pt}{}{CH_3}{SO_3H} + PCl_5 =$$

$$C_6H_4\!<\genfrac{}{}{0pt}{}{CH_3}{SO_2Cl} + NH_3 =$$

$$C_6H_4\!<\genfrac{}{}{0pt}{}{CH_3}{SO_2NH_2} = C_6H_4\!<\genfrac{}{}{0pt}{}{COOH}{SO_2NH} = C_6H_4\!<\genfrac{}{}{0pt}{}{CO}{SO_2}\!>NH + H_2O$$

Benzosulphinidum or
saccharin

This substance is not oxidized by the body, and has no food value. It is used for its sweetening properties only and for hiding disagreeable tastes. It is 300 to 500 times sweeter than cane sugar, and has been used in the past as an adulterant of food products.

It is a white, crystalline powder, acid in reaction with a faint aromatic odor. One grain dissolves in 290 cc. water or 31 cc. alcohol, or about 25 cc. boiling water. It is very soluble in chloroform or ether. It dissolves readily in alkalies. It liberates CO_2 from carbonates which forms a salt by replacement of the imide hydrogen (compare with phenol).

0.2 Gram in 10 cc. of sulphuric acid, when kept at 48°–50°C. for 10 minutes, gives not more than a trace of color. It will not reduce Fehling's solution. With ferric chloride it gives no phenolic reaction, or precipitate—absence of phenols and benzoic acid. It is excreted in the urine unchanged.

deep green color due to the formation of iso-nitroso antipyrine on the addition of 1 cc. dilute sulphuric acid. If the solution be concentrated, green crystals of nitroso-antipyrine form.

4. Fuming nitric acid added to antipyrine gives a green color. Heated with excess of nitric acid, it gives a red color.

5. Add a few drops of sodium or potassium nitrite, then sulphuric acid, a green to blue color appears. If much antipyrine be present nitroso antipyrine $C_{11}H_{11}(NO)(ON_2)$ will separate out in crystals.
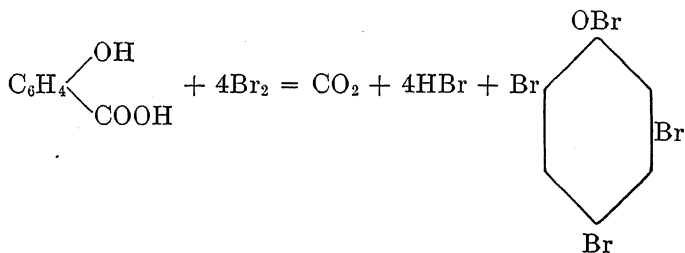
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5. Bromine water precipitates salicylic acid as tribrom phenyl hypobromite – a white crystalline precipitate (see phenol, p. 89).

PHENACETIN: ACETPHENETIDINE

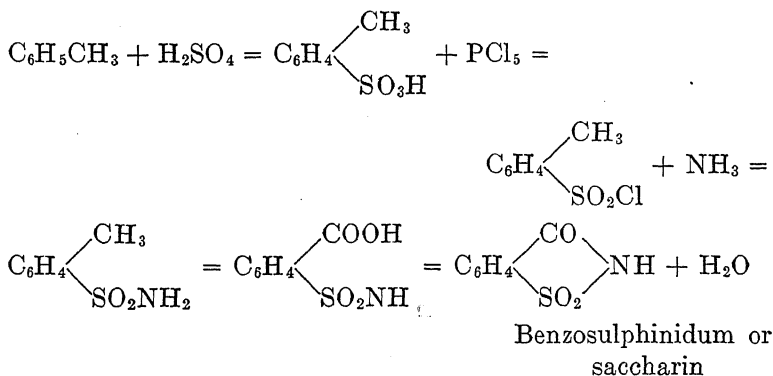1. Acetphenetidine melts at 133°–135°C.

2. It is soluble in 1310 cc. of water, 15 cc. of alcohol or 90 cc. of ether.

3. Boil several minutes with 3 cc. conc. HCl. Dilute with 10 cc. water, filter and cool. A few drops of chromic acid or chlorine water will produce a green color.

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SACCHARIN

Saccharin is the ortho sulphonated derivative of benzoic acid, and can be prepared from toluene. The following formulas indicate the essential reactions:

$$C_6H_5CH_3 + H_2SO_4 = C_6H_4 \begin{cases} CH_3 \\ SO_3H \end{cases} + PCl_5 =$$

$$C_6H_4 \begin{cases} CH_3 \\ SO_2Cl \end{cases} + NH_3 =$$

$$C_6H_4 \begin{cases} CH_3 \\ SO_2NH_2 \end{cases} = C_6H_4 \begin{cases} COOH \\ SO_2NH \end{cases} = C_6H_4 \begin{cases} CO \\ SO_2 \end{cases} NH + H_2O$$

Benzosulphinidum or
saccharin

This substance is not oxidized by the body, and has no food value. It is used for its sweetening properties only and for hiding disagreeable tastes. It is 300 to 500 times sweeter than cane sugar, and has been used in the past as an adulterant of food products.

It is a white, crystalline powder, acid in reaction with a faint aromatic odor. One grain dissolves in 290 cc. water or 31 cc. alcohol, or about 25 cc. boiling water. It is very soluble in chloroform or ether. It dissolves readily in alkalies. It liberates CO_2 from carbonates which forms a salt by replacement of the imide hydrogen (compare with phenol).

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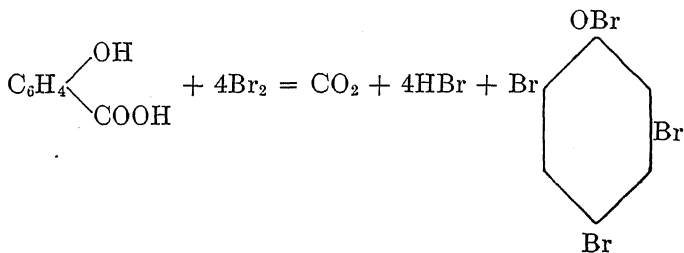
THYMOL IODIDE

Thymol iodide, or aristol, is a compound obtained by the condensation of two molecules of thymol and the introduction of two atoms of iodine into the phenolic groups:
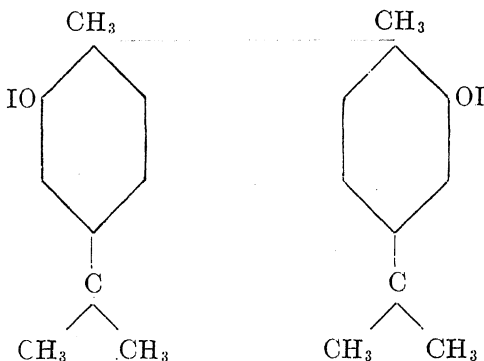
This is a reddish yellow bulky powder containing 45 per cent. of its weight of iodine. It has a slight aromatic odor, and has been used to replace iodoform as a dusting powder, but is much inferior to it as an antiseptic. It is insoluble both in water and glycerol, and is slightly soluble in alcohol, but is soluble in ether, chloroform, or collodion. The antiseptic action of all these iodine-containing organic compounds is due to the liberation of free iodine. The pure product contains no free iodine since it does not color starch paste. The amount of iodine in the product and the amount of thymol iodide can be determined therefore by determining the iodine content as follows:

Dry over sulphuric acid in a desiccator.

Mix 0.25 gram with 0.3 gram anhydrous sodium carbonate in a crucible. Cover the mixture with another gram of anhydrous sodium carbonate. Gradually raise the temperature to that of dull redness, and hold at this temperature until the whole is carbonized completely. This converts the iodide into sodium iodide. Cool and extract with hot distilled water. Filter and wash until the filtrate shows no test with silver nitrate (all the

iodide has been dissolved). Evaporate the filtrate and washings to 150 cc. on a water bath, and add an aqueous solution of $KMnO_4$ (1:20) until the hot liquid remains permanently pink. This converts the I into KIO_3. Add enough alcohol slowly to remove the pink color which is a disturbing factor, make to 200 cc. Mix well, filter through a dry filter, reject the first 50 cc. and take the next 100 cc. = $\frac{1}{2}$ the whole, for determination. Add 1 gram of pure KI and acidify distinctly with H_2SO_4. Titrate the liberated iodine with tenth-normal sodium thiosulphate, adding starch solution near the end, as an indicator. Each cc. of tenth-normal sodium thiosulphate corresponds to 0.002115 gm. of thymol I. In the reaction the acid added converts the KIO_3 into the bi-iodate $KH(IO_3)_2$ and this liberates iodine from the added potassium iodide according to the formula:

$$KH(IO_3)_2 + 10KI + 11HCl = 12I + 11KCl + 6H_2O$$

$$12)389.94 \qquad 12)1523.04$$
$$10)32.495 \qquad 10)126.92$$

$$3.2495 \text{ gm.} \qquad 12.692 \text{ gm. in 1000 mils } \frac{N}{10} \text{ V.S.}$$
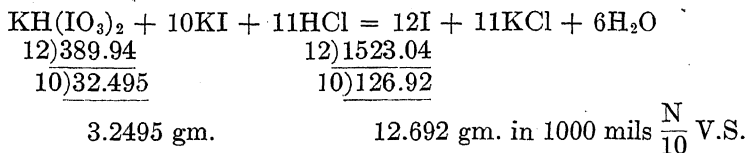
Since in this reaction 12 atoms of iodine are titrated but only 2 atoms of this or $\frac{1}{6}$ comes from the thymol, the I. factor for the thymol is $\frac{1}{6}$ of 12.692 or in tenth-normal solution $\frac{1}{6}$ of 0.012692 = 0.002116 gm. iodine per cc. thiosulphate.

PHENOLPHTHALEIN

This phenol derivative has always been important in chemistry as an indicator. It has recently been used in medicine as a mild cathartic either by itself or mixed with other substances, as agar. Kidney function has been determined by its use, but for this purpose its derivative phenolsulphonephthalein is more commonly used.

Formation of phenolphthalein:

When toluene is treated with bromine at ordinary temperatures in the absence of direct sunlight, bromine may be substituted for H in the ring, a mixture of ortho, meta and para brom toluene being obtained:
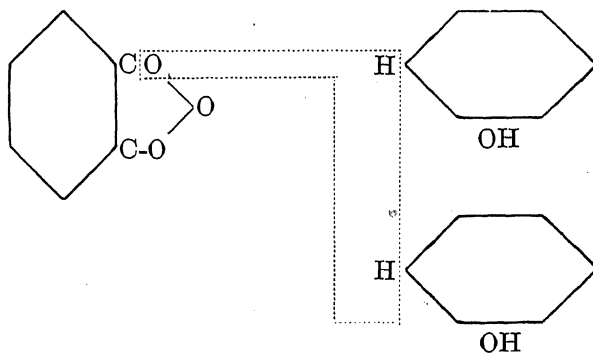
or
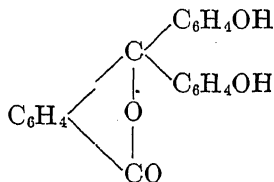
While phenolphthalein is insoluble in water it is dissolved by the bile in the intestine and develops a mild irritant action. It is used in medicine almost solely for its cathartic effect. In this respect it resembles the senna group of cathartics, but has the advantage of being tasteless, and can be made readily into tablets.
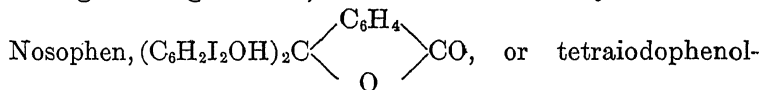
Nosophen, $(C_6H_2I_2OH)_2C\overset{C_6H_4}{\underset{O}{\diagup\diagdown}}CO$, or tetraiodophenol-phthalein, is a powerful antiseptic. It is an iodine compound in which the iodine is attached directly to the ring; consequently, it is but little if any broken down by the body. When taken internally it is not absorbed but passes through the system unchanged, a small amount being absorbed and excreted by the kidneys unchanged. If the urine is alkaline it has a pink color. This absorption and excretion may be shown by taking 0.15 gram phenolphthalein in a capsule, collecting the urine every hour for three hours and making it alkaline with sodium hydroxide. It has been used as a dusting powder. Since it contains two hydroxyl groups, it can form salts with the heavy metals such as bismuth, iron, mercury, and zinc.
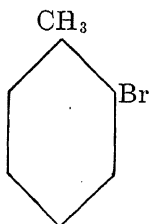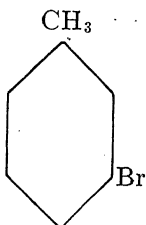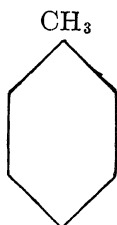
ortho   meta   para

If ortho brom toluene is treated with methyl bromide and sodium, xylene is formed:

$$+ CH_3Br + 2Na =$$

$$+ 2NaBr$$
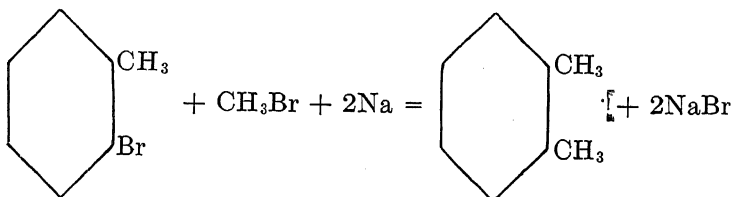
O. xylene on oxidation gives phthalic acid:

$$+ 4O =$$

$$+ 2H_2O$$
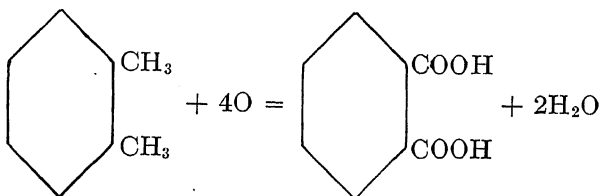
Phthalic acid

When phthalic acid loses water, phthalic anhydride results:

$$=$$
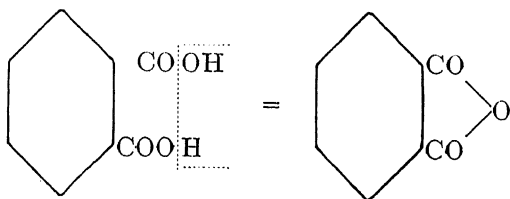
This combines with two molecules of phenol to form phenolphthalein:

Phenolsulphonephthalein:

$$\begin{array}{ccc} & C_6H_4 & C_6H_4OH \\ & \diagup\diagdown & \\ SO_2 & C & \\ & \diagdown\diagup\diagdown & \\ & O & C_6H_4OH \end{array}$$
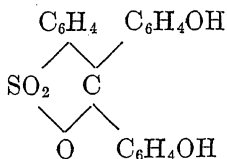
is a product of the interaction of phenol and sulphobenzoic acid anhydride:

$$\begin{array}{cc} & C_6H_4 \\ & \diagup\diagdown \\ SO_2 & CO_2 \\ & \diagdown\diagup \\ & O \end{array}$$
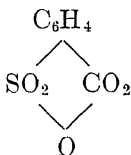
This phthalein is a bright red crystalline powder slightly soluble in water and alcohol with a yellow color, but soluble in dilute alkalies, in which it gives a purer red than phenolphthalein. It is used in medicine to test the kidney function. When 6 mgm. are injected intramuscularly or intravenously, 60–80 per cent. of it is excreted by the normal kidneys within two hours. The amount excreted is determined by making the urine alkaline and comparing the color with a known concentration of the drug treated in the same way.

Determination of Kidney Function

Give the patient about 300 cc. water to insure diuresis. In twenty minutes the bladder should be emptied, and 6 milligrams of the phthalein injected into a large muscle. The phthalein for injection can be procured on the market in solution ready for use. The time of injection is noted, and the urine collected at the end of one hour and ten minutes and again one hour after the first collection. Keep the samples separate, and determine the amount of phthalein excreted immediately or, if this cannot be done, preserve by the addition of phosphoric acid until the determination can be made as follows:

Make both samples sufficiently alkaline with 20 per cent. NaOH to bring out the maximal color. Dilute to 1000 cc. with water

and filter. Compare the color with that produced by 6 milligrams of the phthalein in a liter of water or normal urine treated in the same way. A colorimeter may be used, but sufficiently accurate results may be obtained by diluting the standard in a graduated cylinder until the colors are matched.

In normal cases 40 to 60 per cent. of the drug should be eliminated in the first hour and 20 to 25 per cent. more in the second hour, making a total of 60 to 85 per cent.

XIV. NAPHTHALENES (Tar Camphor)

Naphthalene occurs in coal tar in larger quantities than any other hydrocarbon and it is rather easily isolated. It is also formed when the vapors of many organic compounds are passed through red hot tubes. The luminosity of coal gas is largely dependent on its naphthalene content. Distillation takes place between 170° and 230°. The pure product melts at 79° and boils at 218°. It crystallizes in large lustrous plates and has a characteristic odor. Clothing may be protected from moths by naphthalene which is used in the form of moth balls. On oxidation, naphthalene and its derivatives may yield phthalic acid (p. 124), which is used in the preparation phenolphthalein.

Naphthalene · Phthalic acid · Nitronapthalene

Nitrophthalic acid · Amino napthalene · Phthalic acid
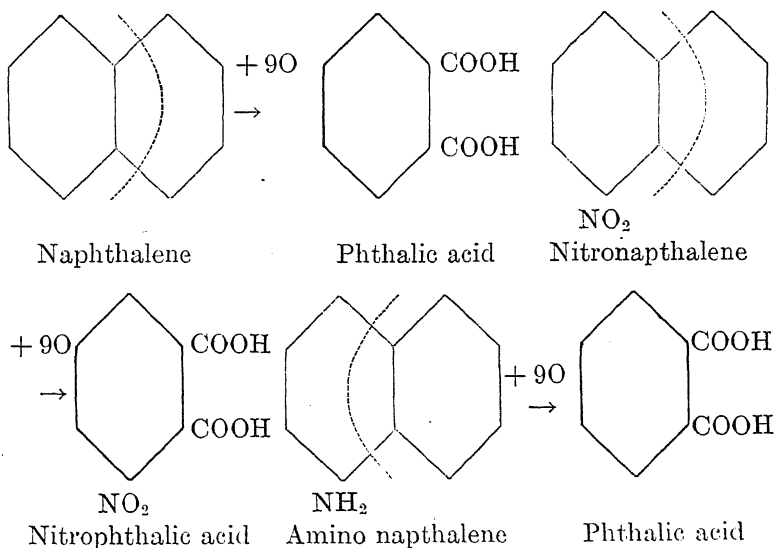
Napthalene compounds, while extensively used in the manufacture of dyes, are but little used in medicine; some are employed principally as antiseptics and preservatives.

The products most used are the α and β napthols:
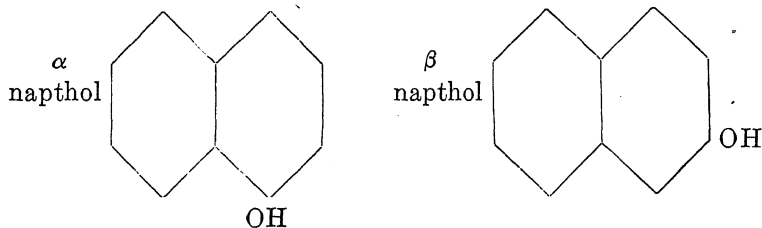
These give the reactions of the phenols. The α napthol is far more toxic than the β napthol, and is not employed in medicine. β napthol is used mainly in dermatology, and as an intestinal antiseptic. It has been used in the treatment of hookworm, and as a food preservative. Its use as a hookworm remedy is much less important since thymol and oil of chenopodium have been used.

Beta-napthol combines with benzoic acid to form benzonapthol and with salicylic acid to form β napthol salicylate. Betol is a proprietary β napthol salicylate.

The napthols are eliminated from the body, combined with glycuronic and sulphuric acids. Most phenols are excreted in this way.

ANTHRACENES

The anthracenes are a very important group of drugs. Many of the most used cathartics owe their action to anthracene derivatives.

Anthracene is a derivative of coal tar, and can also be prepared synthetically. The dye alizarin, or "Turkey red," is prepared from it. Crystallization is in colorless plates which melt at 213° and boil at 351°C.

Its synthesis from ortho brom benzyl bromide and sodium is shown by the reaction:
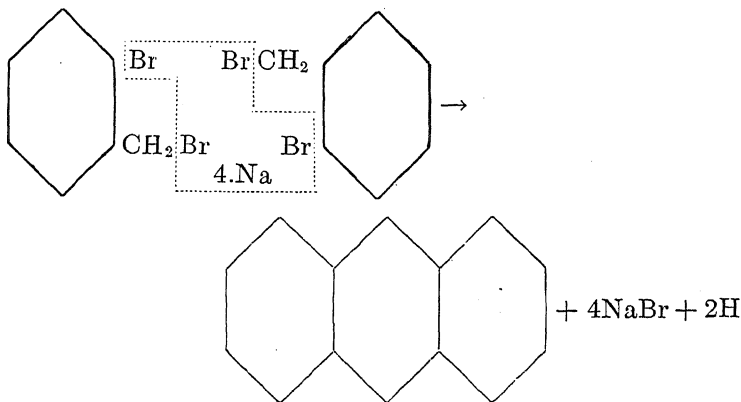
Anthracene may also be prepared by the method of Anschütz, from benzene, aluminum chloride, and tetrabrom ethane.

$$C_6H_6 + \begin{array}{c} BrCH.Br \\ | \\ BrCH.Br \end{array} + C_6H_6 \quad \rightarrow \quad C_6H_4 \begin{array}{c} CH \\ | \\ CH \end{array} C_6H_4$$
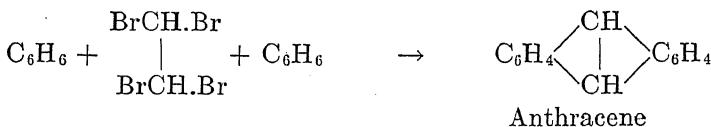
Anthracene

This synthesis proves the structure of anthracene to be two benzene nuclei, united by the groups CH—CH linked to the 2 ortho atoms of the benzene nuclei.

Nitric acid converts anthracene into anthraquinone.
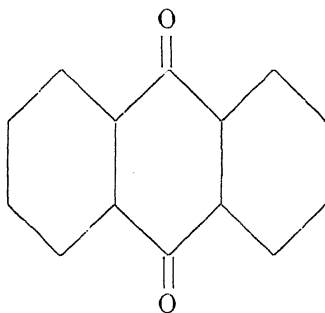
Anthraquinone

The active principles of senna, rhubarb, cascara, aloes, etc., consist of the anthracene derivatives, emodin, cathartin, chrysophanic acid, and their compounds.
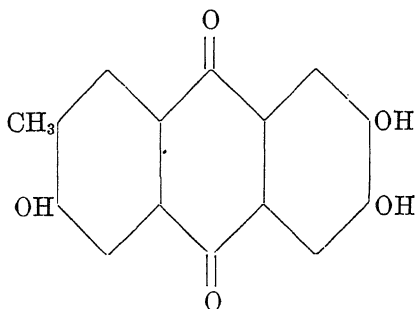
Emodin or trioxymethyl anthra-
quinone
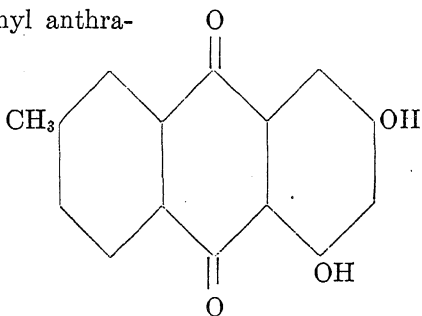
Chrysophanic acid or dioxymethyl
anthraquinone

These substances occur in the glucosides of rhubarb. The
digitalis glucosides also are anthracene derivatives.

QUINONES

The quinones are a peculiar class of substances that have no
analogues in the aliphatic series. Benzo quinone was the first
number, and was prepared from quinic acid. There is some
doubt about the formula—two forms being given:

1.   and   2.
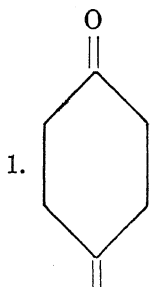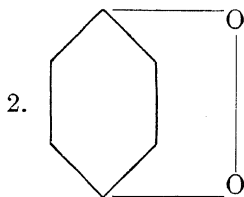
bromine atoms, and behaves like a diketone and unites with two molecules of hydroxylamine with a loss of two molecules of water to form quinone dioxime:

$$O + 2\,NH_2OH \rightarrow \qquad + 2\,H_2O$$
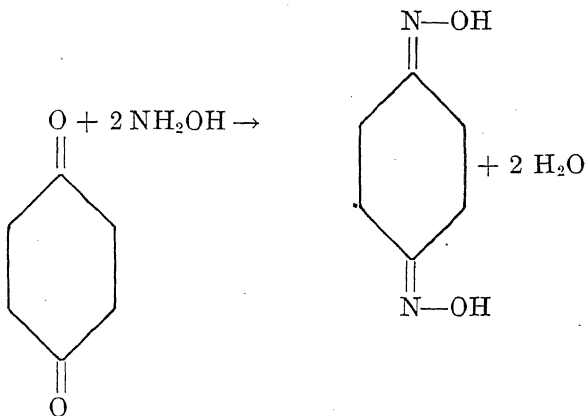
Quinone in the body is reduced to hydroquinone (quinol) which in turn unites with sulphuric and to some extent glycuronic acid.

Vieth (quoted by May) has investigated the purgative action of the synthetic anthra quinones, and his results indicate that the position of the OH groups has some relation to the activity, and that the presence of the methyl group has little influence. The structure of the molecule is indicated as follows:
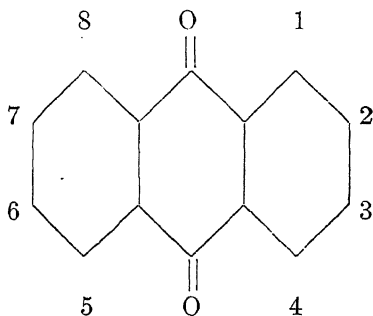
The purgative action of the products arranged in terms of the strongest, or anthrapurpurin as 1 is shown in the following table:

This purgative action also gives some indication of the length of time the substance remains in the intestine—chrysophanic acid because of its rapid absorption exerts little cathartic action.

	Substance	Strength of action
Anthrapurpurin.........	1–2–7 trihydroxy-anthraquinone	1
Flavopurpurin..........	1–2–6 trihydroxy-anthraquinone	$\frac{1}{2}$
Anthragallol............	1–2–3 trihydroxy-anthraquinone	$\frac{1}{3}$
Purpuroxanthin.........	1–3 dihydroxy-anthraquinone	$\frac{1}{6}$
Alizarine-Bordeaux......	1–2–3–4 tetrahydroxy-anthraquinone	$\frac{1}{10}$
Purpurin..............	1–2–4 trihydroxy-anthraquinone	$\frac{1}{20}$

Anthra purpurin diacetate has been sold as a purgative, but it is absorbed to a considerable degree and irritates the kidney. Anthraquinone acts more like a diketone than a true quinone. It is readily reduced in the body, and readily forms an oxime with hydroxylamine (see quinone). Emodin is partly absorbed and is then excreted in the urine, which turns red on the addition of an alkali. Sufficient may be excreted in the milk to purge an infant. In passing through the intestine all these drugs may produce griping, and since they do not cause evacuation until they enter the large intestine they are thought to act only on this part of the tract.

An important derivative of anthracene is acridine:
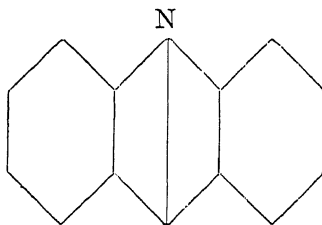
and phenyl acridine:
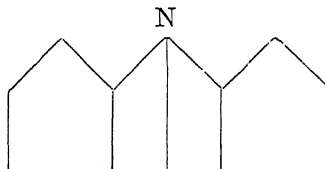
These are the basis of a few technically important dye stuffs, which are amino derivatives of these compounds. These acridine dyes are among the list of industrial poisons to which the attention of physicians practicing in industrial communities has been called by the Bureau of Labor in Bulletin, May, 1920.

XV. HETERO CYCLIC COMPOUNDS

This is a group of nitrogen bases which are of interest chiefly as being the important nuclei of akaloids. These are pyridine, quinoline, isoquinoline, and related bodies. They are found to some extent in the light oil of coal tar, in which they are the basic constituents.

Pyridine has the formula.
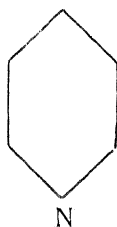
It may be regarded as an ammonia derivative in which the valences of the nitrogen are occupied by a ring. The alkaloids have a similar structure. The nitrogen of pyridine, being unsaturated, can add acids as does ammonia, e.g.:

H   Cl   Pyridine hydrochloride.
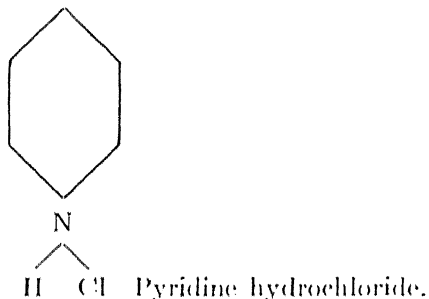
Pyridine can be obtained from coal tar, bone oil, and can be prepared from penta methylene diamine by heating:

$$CH_2 \begin{cases} CH_2-CH_2-NH \\ \quad\quad + \boxed{H} \\ CH_2-CH_2-\boxed{NH_2} \end{cases} \rightarrow \quad \text{(piperidine ring)} \quad + NH_3$$

NH
Piperidine

$$+\ 3H_2O$$

N
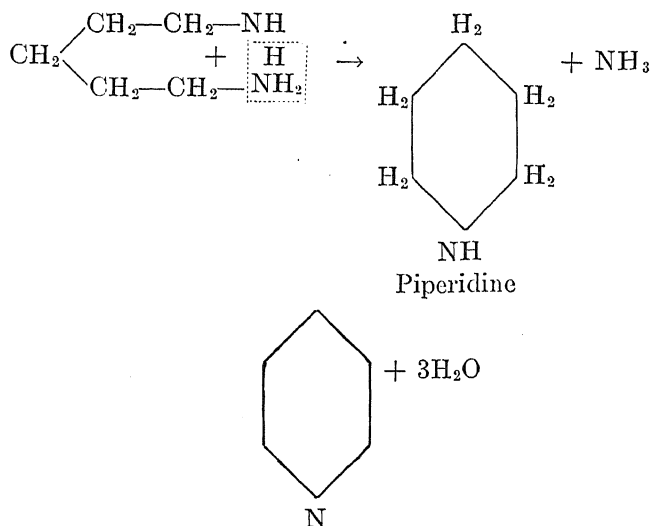
Piperidine + 3. oxygen→ Pyridine + water

There are other ways of preparing pyridine, as by the condensation of aceto-acetic ether as described under antipyrine formation.

XVI. CARBOHYDRATES

The greatest part of plants consists of compounds of carbon, hydrogen, and oxygen, called carbohydrates. In most of these compounds the hydrogen and oxygen are in the same proportion as in water. They are classified as follows:

1. **Monosaccharides,** the glucose group, or monoses, simple sugars, including glucose, fructose, galactose, pentose, etc. These will not yield simpler sugars on hydrolysis, but break into smaller molecules. Water and CO_2 are the ultimate products, whether oxidation occurs in the body or in the test tube.

2. **Disaccharides,** the cane sugar group (bioses, saccharbioses), include cane sugar, maltose, lactose, etc. On hydrolysis these break up into simpler sugars, or monosaccharides. The hydrolytic products are the same in the body as in the test tube.

3. **Polysaccharides,** the cellulose group (or amyloses amyloids), which include starches, glycogens, gums, pectins, celluloses, etc. They are not sugars, but can be hydrolyzed into sugars.

The carbohydrates are of importance primarily as food, and secondarily as medicines.

The main carbohydrates used in medicine are: acacia, tragacanth, starch, flaxseed, cane sugar, fructose, and glucose.

DIFFERENCE BETWEEN STARCHES, GUMS, CELLULOSES AND SUGARS

1. The products of digestion are different.   Starch breaks down during digestion as follows:

Starch $(C_6H_{10}O_5)x$

Maltose ⟍ Amylodextrin

Maltose   Erythrodextrin

Maltose   Achrodextrin

Maltose   Maltose

Glucose   Glucose

CO_2 H_2O CO_2 H_2O
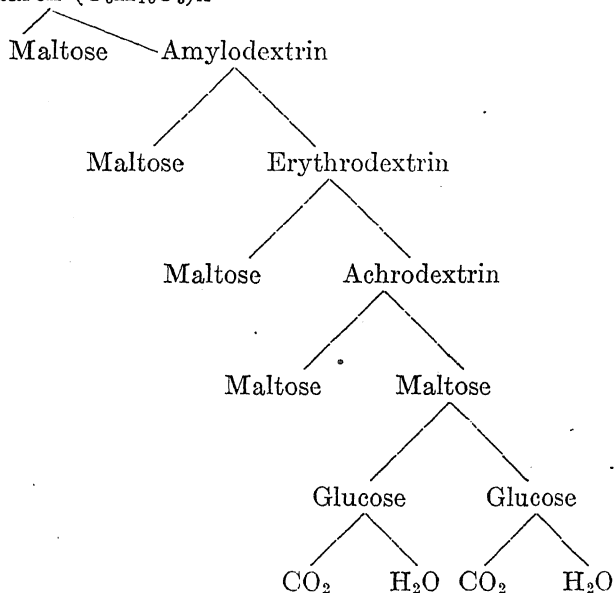
There are probably many intermediate products between these such as other dextrins, alcohol, etc., and probably other sugars formed, but the final products are, in all cases, carbon dioxide and water.   Often some sugars and dextrins are found in cooking and this is why cooked food is sweeter than uncooked.

General Tests

1. Examine the various gums, sugars, and celluloses, and make notes of the physical differences.

2. Test the solubility in water and alcohol (see under mucilages).

3. **Molisch's Reaction.** Treat the carbohydrate in solution with a few drops of 15 per cent. alcoholic solution of alpha napthol. Then add slowly, sliding down the side of the tube, enough H_2SO_4 to form a layer at the bottom of the tube. A reddish violet band appears at the line of contact. This reaction reveals the presence of a carbohydrate even when in combination with protein. The test is due to the formation of furfurol (furfural or furfurane aldehyde).

It has the formula $C_4H_3O.COH =$

HCO

O
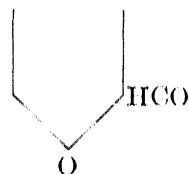
Furfurol

On oxidation it yields pyromucic acid $=$

COOH

O
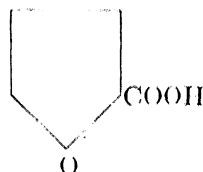
Mucic acid (*q.v.*) also yields pyromucic acid on destructive distillation. Furfural results from the oxidation of pentoses and pentosanes (sawdust, gums, bran, etc.) The name comes from furfur = bran. It is contained in beer, brandy, fusel oil, etc., and was formerly thought to modify the intoxication by fusel oil, but it is not so considered now. It is a colorless oil, has a pleasant odor and gives the aldehyde reactions.

(*a*) To show the presence of furfural: Place about 3 grams of bran, gum arabic, or any of the above mentioned substances in a distilling flask. Add 100 cc. 12 per cent. HCl. Distil over 10 30 cc. Let it drop on a filter paper moistened with aniline acetate or a mixture of 5 drops colorless aniline and 8 drops of acetic acid. Note the color; add a few drops of this to a few cc. of the distillate.

(*b*) Treat the distillate with a few drops of 15 per cent. alcoholic solution of a napthol. Compare with Molisch's test.

STARCHES $(C_6H_{10}O_5)x$

Starches yield maltose and hexose sugars only on hydrolysis. The vegetable gums and mucilages in addition to hexoses give an abundance of pentoses.

Galactose is often found among the gum hexoses, consequently when oxidized with nitric acid gums yield mucic acid $(COOH (CHOH)_4COOH)$.

Starches, dextrins, dextose, levulose, cane sugar, or maltose do not yield mucic acid on oxidation.

Tests for Starch

1. Add a few drops of iodine solution to a little thin starch paste. The resultant blue color is due to $C_6H_{10}O_5I$. When heated, the color disappears, to reappear on cooling. The color can be destroyed by adding anything that has a stronger affinity for the (I) than has starch, e.g., Ag salts, alkaline hydrates, and sodium thiosulphate (see decolorized tincture of iodine).

2. Test starch solution with Fehling's solution. No reduction.

3. Boil a solution of starch with a few drops of dilute H_2SO_4. Neutralize, or make slightly alkaline with KOH or NaOH, and again try Fehling's test. This time there is a reduction. Explain.

NOTE.—Fehling's solution is reduced by anything containing aldehyde or ketone groups. The reducing sugars are either aldoses or ketoses. The statement is sometimes made that the reduction is due to the aldehyde and ketone groups, and in the case of these simple sugars this may be correct, but the fact that chloroform, adrenalin and other drugs reduce Fehling's solution renders the explanation questionable. Fehling's solution on standing also reduces itself because of the tartrate it contains, and tartrates contain no aldehyde or ketone groups. A. P. Mathews thinks that the alkali of the Fehling breaks the sugar into fragments and these fragments are reducing bodies.

4. Dry starch treated with I in KI solution gives a brown color.

5. Starch paste when hydrolyzed by saliva or acids fails to give the iodine reaction.

SUGARS

Sugars are predigested foods. The bioses are hydrolyzed into monoses before absorption. The characteristic sugar group is an aldehyde or ketone group with one or more

$$\begin{array}{ccc} \text{OH} & \text{O} & \text{OH O H} \\ | & \diagup\!\diagup & |\ \ ||\ \ | \\ -\text{C}-\text{C} & \text{or} & -\text{C}-\text{C}-\text{C}-\text{H} \\ | & \diagdown & |\ \ |\ \ | \\ \text{H} & \text{H} & \text{H H H} \end{array}$$
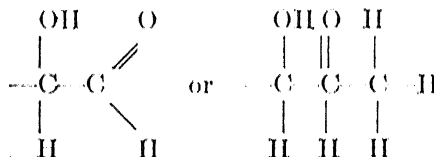
hydroxyl groups. Invariably one hydroxyl group is in the alpha position with reference to the aldehyde or ketone group.

Tests for Sugars

1. All sugars give Molisch's reaction. This is a general test for carbohydrates. See p. 136.

2. With iodine, starches give a blue color; gums, a port wine color; sugars, no reaction, and celluloses, no reaction.

3. With Fehling's solution, starches, gums, and celluloses give no reduction until they are hydrolyzed. Cane sugar does not reduce it until inverted, while all other common sugars reduce Fehling's solution directly.

Apply Fehling's test to a solution of cane sugar. Hydrolyze as under acacia, and again test. Explain and write reaction.

4. **Fermentation.** Pentoses do not ferment with yeast as all other common simple sugars do. Maltose ferments directly, cane sugar and lactose only after hydrolysis. To a 2 per cent. solution of each of these sugars add a small particle of yeast and keep at a temperature of 40°C. Results?

The Uses of Sugars. They are used as flavoring and sweetening agents in medicines, and in strong solutions as preservatives. Molasses is used in domestic medicine as a laxative. Lactose is used in the preparation of infant foods and as an excipient or vehicle in pharmacy. Levulose is sometimes given to diabetics who cannot utilize glucose, but the advisability of this is questionable since it is perhaps as difficult to oxidize in the body as dextrose and other sugars. In cases of glycosuria it is often necessary to distinguish between pentosuria, levulosuria, lactosuria and glucosuria. To determine this, differences of rotation, fermenta-

tion, the melting point of the osazone and other tests must be made.

CELLULOSE

Cellulose is a mixture of complex carbohydrates. Next to water, it is the most abundant substance in plants where it constitutes the greater part of the cell wall. Because it is not a pure chemical, it is often called crude fiber. Celluloses are not digestible except by strong reagents and the higher animals digest but little cellulose, although some of the lower animals do. This indigestibility renders cellulose valuable in the treatment of chronic constipation. In such cases cellulose acts by stimulating the bowel mechanically. Apparently some indigestible volume is needed to elicit the normal function of the intestine. This is one of the reasons why fruits and vegetables are so highly recommended in cases of chronic constipation.

The celluloses include vegetable fibers, cotton, linen, hemp, filter paper, etc. They are insoluble in water, alcohol and ether. While they are indigestible, strong H_2SO_4 converts them into dextrin and glucose. Treated with HNO_3, cellulose yields guncotton, cellulose hexanitrate, which is highly explosive. If the HNO_3 is allowed to act a short time only, the tetra and penta nitrates are formed. These are not explosive, and dissolve readily in a mixture of alcohol and ether with the formation of collodion (see collodion and flexible collodion.)

Tests for Cellulose

1. Examine guncotton. Test its solubility in water and alcohol.

2. Dip a piece of filter paper in a mixture of 4 volumes of H_2SO_4 and one of water and immediately wash it off with water. Let dry and apply the iodine test. Compare the test with the original paper.

3. **Crude Fiber.**—The term fiber is applied to those carbohydrate products in drugs or in food which are insoluble in dilute acids and alkalies. Inasmuch as they are not pure cellulose, they are often designated as crude fiber.

To determine the amount of crude fiber in a food or drug: Weigh out 2 grams of the dry material. Extract with ether until

all lipoids are extracted. Boil the residue with 200 cc. of
per cent. H_2SO_4 for 30 minutes, using a reflux conde
Filter through asbestos, wash with boiling water. Transfe
asbestos, etc., to the flask again and repeat boiling with 1.2
cent. NaOH 200 cc. Boil for 30 minutes, filter through a G
crucible and wash free from alkali with hot water. Di
110°C. until the weight is constant. Incinerate and v
again. The loss in weight is considered to be crude fiber.

HEMICELLULOSE

Hemi, pseudo, reserve cellulose, or paragalactane subst:
are not well defined and seem to be mixtures of mannans, xy
arabans, galactans, or complexes which when treated witl
dilute HCl or H_2SO_4 may yield galactose, rhaminose, man
fructose, arabinose, or xylose, whereas ordinary cellulose
not, except when treated with strong acids. The seeds of r
plants, especially nut shells and stony seeds, cocoanut rind
young plant tissues, contain the reserve carbohydrate whi
called hemicellulose. It serves as reserve food or suppo
tissue. From its reactions hemicellulose is considered sir
than cellulose in composition. When boiled with acid the
product of hydrolysis is a hexose. Hemicellulose is also diss(
by.dilute alkali and by means of enzymes, and may be conv
into gums. The formation of galactose on hydrolysis sug
a relationship to the gums.

AGAR

Agar (agar-agar) is a carbohydrate extracted with hot 1
from certain marine algæ which grow mainly along the ea
coast of Asia and Japan. The extract is evaporated anc
product sold in bundles of shreds, or as a powder. It con
practically of the hemicellulose, gelose, $(C_6H_{10}O_5)$, and diss
in 500 parts of water. When boiled with about 500 pai
water' for 10 minutes, it yields a stiff jelly on cooling. It is
principally in the preparation of bacterial culture media,
because of its indigestibility has been recommended as a cath:
In this respect it acts like bran and vegetables rich in celli
Phenolphthalein agar, is agar impregnated with 3 per cent. ph

phthalein to increase its laxative effect. Regulin is another preparation of agar with cascara.

Agar, because of its cheapness and good jelling properties, has been employed as a "coagulator" in the manufacture of cheap jellies. To detect agar in such jellies the product is heated with 5 per cent. sulphuric acid, a little permanganate is added, and after the material settles, diatoms in large numbers will be found if agar has been used.

GUMS

Gums are desiccated exudations of certain plants, obtained by incising the limbs or branches. They are somewhat transparent carbohydrates, isomeric with starch. Acacia and tragacanth are the most important. They have a physical action only and are used mainly as excipients or vehicles (see mucilages and demulcents). Their use is objectionable in cases where they are hydrolyzed by bacteria and the products remain as irritating substances. They are but little used externally for this reason. Pectin or vegetable jelly is closely related to the gums and causes fruit to set or ."gel". Gums lessen the irritation of medicines and are used in enemata where it is desirable to retain the solution in the rectum for some time. The taste of acids or salts is also lessened by being mixed with colloids, as in fruits. Raspberries contain more acid than currants but taste less acid because they contain colloid. These effects are due to lessened absorption and also to protection of the sensory nerve endings by the colloidal material.

Tests for Gums

1. Test the solubility of gum acacia and tragacanth in water and alcohol.

2. Mix watery solution of acacia with an equal volume of alcohol. Result? What has happened? Compare with glucosides under the same treatment. What is the difference?

3. Test a water solution of acacia or tragacanth with Fehling's solution.

4. Test a water solution of a gum with iodine solution. Compare results with starch solution. Note differences.

5. To a solution of acacia in a test tube add a few drops of

H_2SO_4. Boil for two or three minutes. Neutralize with KOH or NaOH and test with Fehling's solution.

6. Compare the taste of a 1 per cent. citric acid in water with 1 per cent. citric acid in 10 per cent. mucilage of acacia. Explain.

7. Mix a small quantity of cottonseed oil with 3 volumes mucilage of acacia and shake until an emulsion is formed. Add alcohol to the mixture and note results. Explain.

8. State the differences between starches, sugars, and gums; between gums and glucosides; glucosides and alkaloids.

PECTINS

Pectins are carbohydrate bodies whose composition is known but slightly. They are associated with cellulose in the plant. It is due to pectin that fruit juices "gel". The phenomenon of gelling is similar to the setting of gelatin, but the composition of the gelling body is different in the two cases. In the case of gelatin it is a protein, while pectin is a carbohydrate.

Pectin is especially abundant in apples, pears, gooseberries and currants. It is also found in abundance in carrots, beet roots, etc., as pectose, which as ripening proceeds is converted into pectin.

The clotting of plant juices is said to be due to an enzyme pectase, but that it will occur without enzyme action is apparent from the gelation after prolonged cooking which destroy enzymes. According to Duclaux and others the clotting of pectin is due to the presence of calcium salts and the presence of an enzyme is unnecessary. The clotting therefore would seem similar in nature to the clotting of blood. According to Freimy (Jour. Pharm. et chim., 1840, 26, 368) the hardness of unripe fruit is due to pectose. When this is boiled with dilute acids or alkalies, pectin, parapectin, metapectin, and pectic acid are formed. Some of these exist in the plant combined with calcium, in the same sort of union as that which occurs in gums.

No very characteristic tests for pectins can be given. Methylene blue and some other substances stain pectins but not pure cellulose, while crocein, napthol black and orseille, stain cellulose, but not pectin. Pharmacologically pectins may exert a vitamin effect, but this is not proven.

METHOD OF PREPARING PECTIN

(C. H. Hunt, Science, 48, 201, 1918)

The object in view was to prepare pectin, so that it could be added to fruit juices which are low in pectin, and so cause a gelling of non-gelatinating juices: The method was as follows:

Dried apple pomace (60 g.) was boiled with 3 successive portions (200 cc. each) of H_2O, and filtered after each boiling. For each 100 cc. of filtrate, 25 g. $(NH_4)_2SO_4$ were added; the resulting solution was heated to 70°; the pectin separated as a grayish white flocculent precipitate which was collected on a filter, dissolved in hot H_2O, again precipitated with $(NH_4)_2SO_4$ and collected on a filter, dried at 60 to 70°, then washed several times with cold H_2O to remove adhering $(NH_4)_2SO_4$, and again dried. The product was tested for gelatinizing power "by adding to a 1 per cent. solution of the pectin 0.5 per cent. solution of citric acid and 65 g. of sugar. This solution was boiled for 10 to 20 minutes and upon cooling a nice stiff jelly was produced. The taste did not indicate the presence of $(NH_4)_2SO_4$ and upon dissolving the jelly in hot H_2O only a slight milkiness was produced when tested for sulphates." If wet pomace be used, in addition to the 25 g. $(NH_4)_2SO_4$ per 100 cc. of filtered extract, that salt must be added in extra portions 5 g. each until precipitation of the pectin occurs; it may also be precipitated by saturation of the filtered extract in the cold $(NH_4)_2SO_4$. The $(NH_4)_2SO_4$ method gave a yield of 6.33 per cent. pectin, the alcohol method a yield of 6.91 per cent. Concentration of the pectin extract either at a temperature below the boiling point or by freezing did not impair the quality of the pectin and reduced the amount of $(NH_4)_2SO_4$ required.

XVII. FATS AND FIXED OILS

Fats and fixed oils are salts of glycerine with fatty acids, the acids being principally palmitic, stearic, and oleic, or mixtures of these. The oils are liquid fats. The consistency of fat depends upon the relative amount of the acids present: if stearic acid only is present, the fat is hard (e.g., oil of theobroma-cocoa butter); if oleic acid is the principle one present, the fat is soft or oily (as in all the ordinary fixed oils). Tallow is the fat from beef and mutton suet, while lard is hog fat. To obtain these

relatively pure, the fats are sometimes kneaded in a muslin b
under hot water. The pure fat separates and floats on the su
face, while the connective tissue is held in the bag. High he
decomposes fats with a resultant formation of irritating su
stances (acrolein acrid oil). Vegetable oils are obtained l
expression of the seeds, which, when the fats are solid, are oft
heated to liquefy the oil and facilitate the process. The fix
oils are entirely different from the volatile oils (*q.v.*).

Fats are sometimes called glycerides, glycerine esters, or ether
salts. Glycerine with stearic acid alone is called stearin,
glyceryl stearate; with palmitic acid, palmitin, and with ole
acid, olein. The combination is represented by the followin
formulas where R represents any fatty acid radical:

$$CH_2O \cdot H \quad HO \cdot OCR \qquad\qquad CH_2O.OCR$$
$$|\qquad\qquad\qquad\qquad\qquad\qquad\qquad |$$
$$CHO \cdot H \quad HO \cdot OCR \quad \longrightarrow \quad CH.O.OCR + 3H_2O$$
$$|\qquad\qquad\qquad\qquad\qquad\qquad\qquad |$$
$$CH_2O \cdot H \quad HO|OCR \qquad\qquad CH_2O.OCR$$

Glycerine + fatty acid $\longrightarrow$	Fat + water
Stearic acid	$C_{17}H_{35}COOH$
Stearin	$C_3H_5(C_{18}H_{35}O_2)_3$
Palmitic acid	$C_{15}H_{31}COOH$
Palmitin	$C_3H_5(C_{16}H_{31}O_2)_3$
Oleic acid	$C_{17}H_{33}COOH$
Olein	$C_3H_5(C_{18}H_{33}O_2)_3$
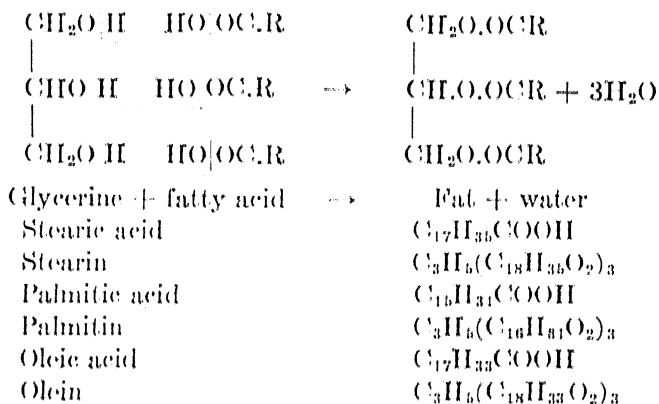
CLASSIFICATION OF OILS

Oils are divided into drying and non-drying. Some oils whic
contain linolenic and linolic acids when exposed to the air absor
oxygen and become resinous and leave a hard elastic film. Th
process is hastened by catalytic agents such as litharge, mang
nese dioxide and the acetates and borates of lead, manganese, ar
zinc. These agents are known as "driers." Oleic acid does no
absorb oxygen. The drying oils are less viscous and less stab
than the non-drying. This drying and unstable property is du
to the unsaturated fatty acids. The drying vegetable oils ar

I. The linseed oil group which includes:

Linseed
Hempseed
Walnut
Sunflower
Poppyseed
Nigerseed

The semi-drying or cottonseed oil group includes:

Cottonseed
Sesame
Beechnut
Maize
Rape
Brazil nut

This group is composed mainly of the glycerides of oleic and linolic acids.

II. The non-drying or *castor oil group* includes:

Castor
Croton

The non-drying *olive oil group* includes:

Olive
Almond
Rape
Peanut
Mustard oils

Most animal fats and waxes are non-drying, but the fats of the rattlesnake and ice bear are drying, while horse fat is semi-drying.

Both animal and vegetable fats and oils are used in medicine. The most important animal fats are lard or swine fat, suet or mutton fat, tallow or beef fat, and butter fat.

The relative amount of the various fatty acids in these different fats varies widely, not only with the species but also with the food of the animal. Lard may contain 90 per cent. olein and melt as low as 28°C. when the diet is corn-meal, or as high as 35°C. when the animal is fed on oats, peas and barley; the fat in this case contains less olein than when the animal is corn fed. Fat

10

from different parts of the same animal may vary in melting point due to differences in composition. Human fat melts as low as 17.5°C. because it is rich in olein, tallow melts at about 45°C., and suet at 45–50°C. If a fat contains only oleic acid with glycerine it is an olein or triolein and is a liquid at 0°C., while palmitin (tripalmitin) melts at 62°C. and stearin (tri-stearin) at 71.5°C.

Butter fat is a mixture of palmitin, stearin and olein, and in addition it contains 6 to 8 per cent. of volatile fatty acids combined with glycerine. These are butyric, caproic, capryllic, capric, with traces of lauric and myristic. No other fat except cocoanut oil contains so high a percentage of volatile fatty acids. This fact aids in the recognition of an adulteration of butter with other fats as in oleomargarine, which consists chiefly of the higher fatty acids. Butter is little if at all used as a medicine, but it is extremely valuable as a food and contains vitamines essential to normal growth, which few if any other fats can adequately supply.

Fats and oils are widely distributed in the vegetable kingdom, chiefly as the glycerides of palmitic, stearic and oleic acids, but the following fatty acids are frequently found:

$$\text{I. Isobutyl acetic or caproic} \quad \begin{array}{c} CH_3 \\ \diagdown \\ \diagup \\ CH_3 \end{array} CH.CH_2.CH_2.COOH$$
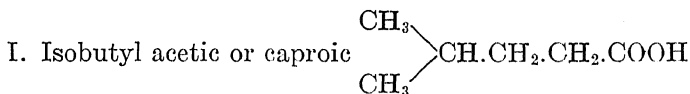
Caprylic	$CH_3(CH_2)_6COOH$
Capric	$CH_3(CH_2)_8COOH$
Lauric	$CH_3(CH_2)_{10}COOH$
Myristic	$CH_3(CH_2)_{12}COOH$
Palmitic	$CH_3(CH_2)_{14}COOH$
Stearic	$CH_3(CH_2)_{16}COOH$
Arachidic	$CH_3(CH_2)_{18}COOH$
Behenic	$CH_3(CH_2)_{20}COOH$

These acids all conform to the general formula

$$(C_nH_{2n}O_2).$$

There are other fatty acids of the oleic or acrylic series that conform to the general formula
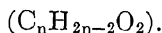
$$(C_nH_{2n-2}O_2).$$

II. These are Tiglic acid $C_5H_8O_2$

Oleic $C_{18}H_{34}O_2$

Elaïdic $C_{18}H_{34}O_2$

Iso-oleic $C_{18}H_{34}O_2$

Erucic $C_{22}H_{42}O_2$

Brassidic $C_{22}H_{42}O_2$

The most important of these in medicine are oleic and tiglic—found in croton oil.

III. The linolic series

$$(C_nH_{2n} - {}_4O_2)$$
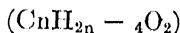
1. open series linolic acid $C_{18}H_{32}O_2$
2. Chaulmoogric acid $C_{18}H_{32}O_2$

a cyclic compound, from chaulmoogra oil, which is used in the treatment of leprosy.

IV. A linolenic acid series of the general formula

$$C_nH_{2n-6}O_2$$

is also known but not important in medicine.

V. A clupanodonic series with the general formula

$$C_nH_{2n-8}O_2$$
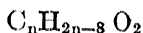
VI. A ricinoleic oleic series, general formula

$$C_nH_{2n-2}O_3$$
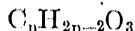
of which the acid from castor oil is the important representative. While many of these are unimportant in medicine, they illustrate because of their unsaturated condition, what is meant by the iodine number—described below. Unsaturated compounds as a rule are also more active physiologically than saturated compounds.

The chief vegetable fats used in medicine are:

Palm oil, which consists almost entirely of palmitin and cocoa butter, contains about

| 40 per cent. stearin, | 20 per cent. palmitin, |
| 30 per cent. olein, | 6 per cent. linolein, |

Linseed oil consists mainly of oleins—a mixture of oleic, linolic, linolenic, and isolinolenic acids.

Cottonseed oil consists chiefly of olein, palmitin, and linolein, with small amounts of linolenic acid.

Olive oil, consists of 72 per cent. of liquid glycerides, made up of olein 94 parts, linolein 6 parts, and about 28 per cent. palmitin.

Castor oil consists mainly of the glycerides of triricinolein, together with ricinisolein, palmitin and dioxystearin.

Croton oil: The composition of croton oil is very complex. The glycerides of at least 10 acids have been found, namely—oleic, palmitic, stearic myristic, lauric, valeric, formic, butyric, acetic, tiglic and croton oleic. It is a violent purgative, a single drop being a dose. When rubbed on the skin croton oil may also produce rubefaction and pustulation. It yields about half as much volatile fatty acids as butter, among these volatile acids are formic, acetic, and valerianic. While these acids are irritating, and it was formerly thought that the irritant and purgative action is due to the irritation caused by the acids liberated on saponification of the oil, it is now believed that these actions of croton oil are due to an acrid resin $C_{13}H_{18}O_4$ contained in the oil.

Most oils are insoluble in alcohol, castor and croton oils are exceptions to this rule. Croton is somewhat soluble and castor is soluble in absolute alcohol. Both are soluble in ether.

A distinguishing property of castor oil is its insolubility in petroleum ether. It is likewise one of the heaviest fats having a specific gravity of 0.960 as against a range of 0.85 to 0.95 for other fats.

Fats are extracted from seeds, or tissues after these have been thoroughly desiccated. They are then placed in extractors and the fat is drawn out with ether, light petroleum, carbon bisulphide or carbon tetrachloride. Ether is the usual laboratory solvent.

These solvents extract also cholesterol, lecithin, essential oils, and the indefinite group of bodies known as lipoids, and the extract for this reason is known as the ether extract. A process of purification must be employed if a pure product is desired.

GENERAL PROPERTIES OF FATS

1. The physical properties depend on the composition—oleins are liquid, stearins are solid, palmitins of a vaseline or tallow consistency.

2. Fats are insoluble in water and but slightly soluble in cold alcohol.

3. They are soluble in ether, benzine, benzene, chloroform, carbon bisulphide, carbon tetrachloride.

4. Fats can be heated from 200° to 250°C. without decomposition. Higher heat may decompose them with the formation of the irritating volatile product of glycerine—acrolein

$$CH_2 = CH - CHO$$

This change is hastened by the addition of $(KHSO_4)$—potassium bisulphate, and is a test for true fats, or anything containing glycerine.

5. Lipases hydrolyze fats into fatty acids and glycerine. This change may also be accomplished by bacteria and by superheated steam. Acids and alkalies greatly accelerate the reaction. This hydrolysis is known as saponification.

6. When boiled with alkalies fats are hydrolyzed, and the combination of the alkali metal with the fatty acid is known as a soap. Green soap is the potassium or soft soap, and is so-called because the oils formerly used contained chlorophyll which gave the soap a green color.

In medicine and pharmacy, antiseptics and other substances are frequently added to, or incorporated in the soap. These are the so-called medicated soaps. Cresol, thymol, tar, sulphur, mercury, salicylic acid, etc. are among the substances added. Castile soap is made from olive oil and sodium hydroxide; green soap from linseed oil and potassium hydroxide. Lead plaster is a lead soap. Resin and sodium silicate are added to soaps mainly as adulterants. Such soaps hold a great deal of water, hence weigh more than a pure soap, and this is the principal reason for the addition.

Explanation of the Cleansing Action of Soap

Ordinary soaps are the sodium potassium salts of fatty acids. These are weak acids, and their salts are decomposed to some extent by water just as sodium carbonate is, and soap solutions are alkaline in reaction for the same reason that sodium carbonate is alkaline. In water soap is hydrolyzed according to the formula:

1. $CH_3(CH_2)_{16}COONa \rightarrow CH_3(CH^-{}_2)_{16}COO + Na^+$

2. $CH_3(CH_2)_{16}COO^- + Na^+ + HOH \rightarrow$

$$Na^+ + OH\ CH_3(CH_2)_{16}COOH +$$

      Stearate ion   Stearic acid
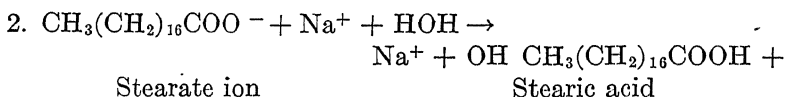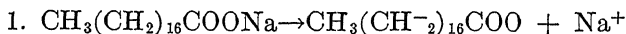
Since stearic acid is insoluble in water, it is removed from solution, and the NaOH ions react alkaline. The amount of free alkali depends on the dilution. In strong solution a soap that will cause just a pink color with phenolphthalein, may be distinctly alkaline on dilution. These hydrolyzed products readily emulsify fats, and such emulsion is readily soluble in or removable by water. This briefly explains the mechanism of soap in washing. Mathews explains the formation of these colloidal solutions as follows:

$$
\begin{matrix}
& O & & & O \\
& \| & & & \| \\
1.\ Na-O-C-(CH_2)_{16}-CH_3 \rightleftarrows & & & \\
& & Na^+ + O^- - C-(CH_2)_{16}-CH_3 \\
\end{matrix}
$$

      Sodium stearate $\rightleftarrows$ Sodium ion + stearate ion

$$
2.\ Na-O-C-(CH_2)_{16}-CH_3 + H_2O \rightleftarrows
$$
$$
\qquad\qquad \|\qquad\qquad NaOH + H-O-C-(CH_2)_{16}-CH_3
$$
$$
\qquad\qquad O\qquad\qquad\qquad\qquad\qquad\qquad \|
$$
$$
\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad O
$$

                           Stearic acid

$$
3.\ Na^+ - \bar{O} - C-(CH_2)_{16}-CH_3 + 2HO-C-(CH_2)_{16}
$$
$$
\qquad\qquad \|\qquad\qquad\qquad\qquad\qquad\qquad \|\qquad -CH_3 \rightleftarrows
$$
$$
\qquad\qquad O\qquad\qquad\qquad\qquad\qquad\qquad O
$$

$$
\begin{array}{c}
+ \\
Na\ + \\
\end{array}
\left\{
\begin{array}{c}
O \\
\| \\
^-O-C-(CH_2)_{16}-CH_3 \\
2HO-C-(CH_2)_{16}-CH_3 \\
\| \\
O \\
\end{array}
\right.
$$
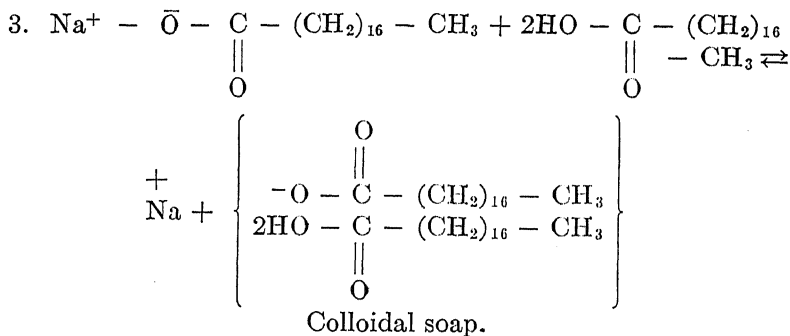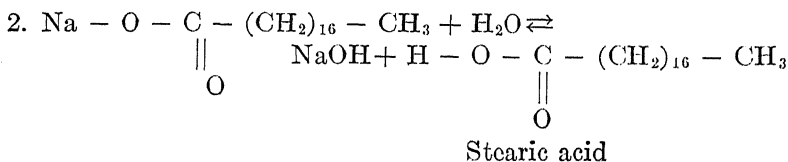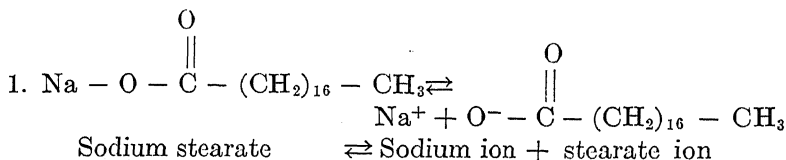
                     Colloidal soap.

This negatively changed colloidal soap is held in solution by the great attraction of the positively changed sodium ion, for

water, and it (colloidal soap) has a great attraction for the fatty acids of neutral fat or grease. Consequently when put on the skin, the fats of the skin adhere to the colloidal soap particles and are held in colloidal solution by the attraction of the sodium ion for water. Large easily removable aggregates may thus be formed. Vaseline, liquid petrolatum and other lipoids that do not form emulsions readily, are for this reason hard to remove.

THE CHARACTERIZATION OF FATS

The following methods are used for the recognition and the evaluation of fats.

1. The melting point is determined. This shows the general nature of the fats—whether they are composed mainly of stearin, palmitin or olein.

2. The acid number. This is the number of milligrams of KOH required to neutralize the free acid contained in one gram of the fat. This is determined by dissolving 1 or 2 grams of the fat in about 20 cc. of a mixture of 1 part alcohol and two parts of ether. Titrate the solution with N/10 solution of KOH in alcohol. Alcohol is used here because water does not mix well with the oil, but causes an emulsion formation, and the end point is not clear. The acid number gives one an idea of the state of freshness of the fat.

3. The saponification number or Koettstorfer number. The saponification number is the number of milligrams of KOH necessary to neutralize (to form a soap), with the fatty acids derived from 1 gram of fat. Since fatty acids are monobasic one molecule of potash neutralizes one molecule of acid, but each molecule of fat required three molecules of KOH—since glycerine esters or fats are tribasic.

The saponification value is determined by dissolving a weighed amount of fat—about 2 grams—in a wide mouthed bottle holding from 250 to 300 cc. Add 25 cc. of half normal alcoholic KOH. Attach a reflux condenser and heat on a water bath for 30 minutes. Cool and titrate the excess of KOH with semi-normal HCl, using phenolphthalein as the indicator. Subtracting the acid necessary to neutralize, from 25 cc. gives the saponification number.

Since fats are glycerine in combination with monobasic fatty

acids, the saponification number will give indirectly the molecular weight of the pure acid.   This relationship is as follows:

	Mol. weight	Saponification number
Butyrin	302	557.3
Palmitin	806	208.8
Stearin	890	189.1
Olein	884	190.4

4. Unsaponifiable residue = Cholesterol and Phytosterol.

These previous numbers are of value in the calculation of the molecular weight of acids only when we are dealing with pure products.   The numbers however are of value in determining the nature of an oil, especially when taken in consideration with other constants.   One of these is the amount of unsaponifiable residue.   This residue consists mainly of cholesterols or phytosterols which are soluble in petroleum ether, while glycerol, and potassium hydroxide are not, and soap only slightly.   Accordingly to determine the unsaponifiable residue, after saponification cool and filter off the soap—shake the solution with petroleum ether in a separatory funnel, and evaporate in a desiccator to constant weight, in a weighed dish.   The residue represents the unsaponifiable residue.

The following table gives the amount of unsaponifiable residue in the more important fats.

	Per cent. of Unsaponifiable Matter
Lard	0.30 to 0.40
Castor oil	0.30 to 0.40
Human fat	0.33 to 0.00
Linseed oil	0.42 to 1.00
Olive oil	0.46 to 1.00
Corn oil	1.35 to 2.90
Wheat fat	4.45 to 0.00
Shark oil	7.00 to 10.00
Sperm oil	37.00 to 41.00
Beeswax	52.00 to 56.00

The isolation and identification of the unsaponifiable residue, is of importance in establishing whether or not a fat is of animal or vegetable origin.

5. The iodine absorption number of fats (Hübls number). This is the amount of iodine (per cent.) that a fat will absorb. It is a measure of the unsaturated fatty acids in the fat. An unsaturated (ethylenic) compound absorbs iodine after the manner of ethylene:

$$C_2H_4 + I_2 \rightarrow C_2H_4I_2$$
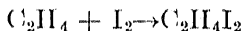
The resulting compound being saturated.

To determine the iodine number the following solutions are needed.

1. 25 grams of pure iodine and 30 grams pure mercuric chloride, in 500 cc. pure alcohol, free from unsaturated compounds.

2. A decinormal solution of sodium thiosulphate.

3. Potassium iodid 20 per cent. in water.

4. A 1 per cent. solution of starch paste as an indicator.

The determination is made as follows:

Weigh 0.3 gram of the fat in a glass stoppered bottle and dissolve in about 20 cc. chloroform and add 25 cc. of the iodine solution. Stopper the flask and set aside in the dark for 4 hours. Wash into a flask for titration, with 10 cc. of the KI solution and titrate with sodium thiosulphate solution. The difference between the volume of thiosulphate needed and 25 cc. of iodine solution used will be the amount of iodine absorbed or the iodine number.

The reactions involved are:

Each cc. N/10 thiosulphate represents 0.0127 gm. iodine

$$I_2 + 2(Na_2S_2O_3 + 5H_2O) = Na_2S_4O_6 + 2NaI + 10H_2O$$
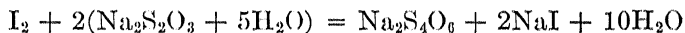
The KI is added to prevent separation of the iodine in the solid state when diluted with water. The mercuric chloride forms:

$$Hg.Cl_2 + I_2 = Hg.ClI + ICl$$
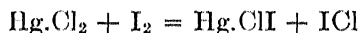
The iodine chloride is perhaps the active agent in the addition, and facilitates the process.

The iodine numbers of pure fats are:

Olein..................... 86.2
Linolein.................... 173.6
Linolenin................. 262.2

Iodine Numbers of natural fats:

Linseed oil... 175–205
Almond oil..................... 145–150
Olive oil....................... 80– 88
Cottonseed oil.................. 108–110
Codliver oil................... 107
Neat's foot oil 67– 73
Palm oil......... 51
Cocoanut oil................... 8–9
Tallow........................ 35– 45
Lard.......................... 50– 70
Butter........................ 26– 38
Japan wax..................... 4– 10
Spermaceti.................... 0.4

Unsaturation as evidenced by iodine absorption is a specific instance or kind of unsaturation and in no sense a general test for unsaturation. The unsaturation in the case of fats and oils is ethylenic—*i.e.* between carbon atoms. In aldehydes, ketones, etc. which contain a carbonyl group $\begin{matrix} R \\ R \end{matrix} \Big> C = O$, there is also unsaturation but iodine is not added to these. If hydrogen be used, however, it reacts with the carbonyl as also with the ethylenic linkage.

The reactivity in the one case and not in the other is due to modification of the unsaturated bonds by attached molecules or atoms. This may be illustrated by the reactivity of the H atom in water, alcohol and acid.

$$H.OH$$
$$CH_3CH_2OH$$
$$CH_3COOH$$
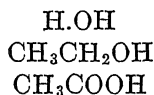
The difference in reactivity in each case being due to the modifying influence of the attached radical.

THE HYDROGEN NUMBER AND HYDROGENATED FATS

Under proper conditions hydrogen may be added to fats much in the same way as bromine. This changes ill-smelling and

tasting, cheap vegetable oils into more palatable products resembling the more expensive animal fats. The process of hydrogenation is of great commercial importance. In some processes finely divided metals such as nickel are used as catalyzer, and some of the metal may remain in the finished vegetable lard. Nickel may be absorbed from the gastro-intestinal tract; and it is toxic, hence fats prepared in this way may be interesting from a pharmacological point of view. The pure products are not toxic, but if nickel remains in oil the latter may become toxic. These hydrogenated fats are important economically.

THE REICHERT MEISSEL NUMBER

This represents the number of cubic centimeters of N/10 KOH required to neutralize the volatile acids liberated from 5 grams of fat under certain special conditions. The process of determining the amount consists in saponifying the fat with an alkali, then adding an excess of a non-volatile mineral acid, distilling and titrating the volatile acids. Phenolphthalein is used as the indicator. This method is especially useful in the examination of butter fat for adulteration.

The Reichert Meissel numbers of the most important fats are:

Linseed oil	0.0
Goose fat	0.2
Tallow.	0.5
Olive oil	0.6
Lard.	0.7
Palm oil	5–7
Cocoanut oil	6–7
Croton oil	12–14
Butter fat	25–30

No other fat contains as much volatile acid as butter.

THE ACETYL NUMBER

This is a measure of the number of hydroxyl groups in a fat. The measurement of these depends upon the fact that substances containing the alcoholic hydroxyl group react with the acetyl group (CH_3CO). The number of OH groups is arrived at by

treating the fat with acetic anhydride and heat; when a reaction takes place as follows:

$$\begin{matrix} R \\ \diagdown \\ \diagup \\ R \end{matrix} CHOH + O \begin{matrix} CO - CH_3 \\ \diagup \\ \diagdown \\ CO - CH_3 \end{matrix} \rightarrow \begin{matrix} R \\ \diagdown \\ \diagup \\ R \end{matrix} HC.OOC.CH_3 + CH_3COOH$$
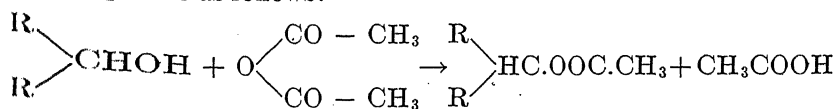
The acetyl derivative of the fat is stable in boiling water, and by boiling in water, excess of acetyl anhydride is converted into acetic acid. The acetylated fat can now be separated by filtration and washed free from the acid. This acetylated fat can be saponified according to the reaction:
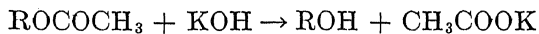
$$ROCOCH_3 + KOH \rightarrow ROH + CH_3COOK$$

In this way the amount of potash required for the saponification can be used as a measure of the acetyl groups, and hence of the hydroxyl groups in the fat.

The number of milligrams of potash required to neutralize the acetyl derivative of 1 gram of fat, is the acetyl value of that fat.

The following table gives the acetyl value of some common pharmaceutic products:

Linseed oil	0.4
Olive oil	10.5
Codliver oil	0.5
Spermaceti	4.5
Lard	2.6
Tallow (Beef)	2.5–9
Beeswax	15.0
Wool wax	0.23
Castor oil	0.15

The Elaïdin Test for Fats (Gr. Elais—Olive Tree)

This test is distinctive for the oleic series. It depends on the fact that oleic acid is changed from the *cis* to the *trans* form on treatment with nitrous oxide, or liquid olein is converted into solid elaïdin—which is an isomeride of olein. Other acids of this series are similarly transformed.

The Elaïdin test is performed as follows:

(I) Place 10 cc. oil in a test tube and add 5 cc. nitric acid sp. gr. 1.38–1.40 underneath it. Place a small piece of copper (0.2

gm.) in the acid.   Leave at a temperature of not over 25°C. until the following day, and observe frequently or

(II) 10 grams of oil are mixed with 5 cc. nitric acid sp. gr. 1.38 and 1 gram of mercury, and the mixture shaken until the mercury is dissolved.   Set aside and shake again after about 20 minutes. Note the time required for solidification.   This reaction is called the "elaidic transformation."

Depending upon the amount of oleic acid present, the oils vary in the length of time necessary for solidification.

> Olive oil solidifies in about 60 minutes.
> Peanut oil solidifies in about 80 minutes.
> Sesame oil solidifies in about 185 minutes.
> Rape oil solidifies in about 185 minutes.
> Lard oil—inside two hours.
> Linseed oil gives a red pasty froth.
> Hempseed oil remains unchanged.

The temperature of the mixture should not exceed 25 degrees. At best the reaction gives only an idea of the character of the oil.

The Bromine Test

This test depends on the fact that linolic, linolenic and other unsaturated drying and semi-drying oils form insoluble addition compounds with bromine containing 6 or 8 atoms of this element, which is insoluble in ether.   Linolenic acid having three double bonds yields a hexabrom derivative.   The avidity of the reaction can be measured also by the heat of bromination, which runs parallel with the amount of bromine or iodine that a fat will absorb.   To determine the amount of bromine absorbed: 1 to 2 cc. of oil are dissolved in 40 cc. of ether and 2 cc. glacial acetic acid.   Cool to about 5°C. and add bromine drop by drop until no more is absorbed.

The precipitate is collected on a weighed asbestos filter and washed 4 or 5 times with ether, and dried in a steam oven.   The weight is directly proportional to the amount of unsaturated acids in the fat.

Maumené or Sulphuric Acid Test

Fats of the linolic series on being mixed with sulphuric acid evolve heat while those of the oleic series do not.

The difference in degrees centigrade between the initial temperature and the temperature after the addition of sulphuric acid under special conditions is known as the Maumené Number: The test is carried out as follows:

Place a beaker of 150 cc. into a beaker of 800 cc. and pack the space between with cotton. Weigh 50 grams of oil into the smaller beaker. Place a thermometer in the oil and run in 10 cc. concentrated H_2SO_4 from a burette at the same temperature as the oil. Stir the oil with the thermometer while the acid is running in. The temperature rises quickly, and remains at the high point a sufficient time to permit observation. The maximum point should be noted. The initial temperature subtracted from the maximum gives the Maumené number.

RANCIDITY OF FATS

Most fats but especially those containing unsaturated acids on exposure to the air become rancid and develop a disagreeable smell and taste. The unsaturated fatty acids are converted into others containing a smaller number of carbon atoms. Among the decomposition products aldehydes, alcohols, hydroxy acids and esters have been found. The actual cause of rancidity is but little understood. Oxygen, light, and heat, and moisture, facilitate the process which is probably initiated by enzymes and bacteria, while free acid is liberated in the process.

Acids may be developed without rancidity as is often seen in cocoa butter which is frequently acid but rarely rancid.

THE SIGNIFICANCE, USES AND FATE OF FATS

Fat is found in varying amounts in all forms of living matter. This may not be seen in microscopic sections or when stained with sudan III, osmic acid and other fat stains but organic substances when extracted with ether and other fat solvents, always yield a lipoid residue on evaporation. After anesthesia for an hour with chloroform, sudan III shows that fat droplets are distinctly present in the cell, while chemical analysis shows that there is no greater amount than before the anesthesia. It is differently distributed after the anesthetic.

In the economy of both plants and animals, fats are connected

with nutrition. They are readily stored and provide a food reserve which in animals is used in cases of food deficiency.

They act as protectors to the proteins of the body, sparing the protein from oxidation. They also act as lubricants to the skin and aid in keeping it soft and pliable. If the lipoid material is too frequently and too vigorously removed from the skin, as is sometimes done by the excessive use of highly alkaline soaps, the skin becomes dry and eczematous. In such cases the judicious use of oils externally is very beneficial. Many fats are used in emulsions for this purpose. Some fats because they are decomposed into slightly irritating materials in the intestines are used as cathartics.
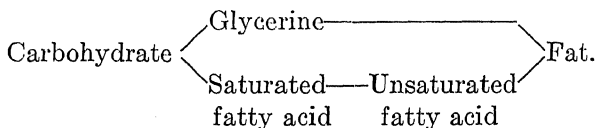
In the protoplasm fats are distributed very finely as in milk. None of the ordinary fat tests will detect fat when it is so finely divided and protected. The fat in the cells in this condition may also act as a protective to the essential part of the cell. In phosphorus poisoning and in other conditions classed as fatty degenerations, the fat is run together and so loses its protective properties. In these conditions there is no increase in the actual body fat, but simply a redistribution of it. Why one person is fleshy—or the body retains a considerable amount of fat—while another, is lean cannot be explained further than that the fundamental properties of the protoplasm is different. This may depend on the physiological activity of some endocrine gland either acting on the seats of oxidation directly or through the nerves. It is known that basal metabolism is distinctly higher in hyperthyroidism, and lower in hypothyroidism, and in other conditions.

Oxidation furnishes the heat necessary for the body and fats are the heat producing foods par excellence, one gram of fat produces 9.3 calories. Fats also act as a mantle and since they are poor conductors they aid in heat conservation by preventing evaporation and radiation. In cases of obesity this property may be a hindrance rather than a benefit. Fats also act as packing material for such organs as the kidney, which is partially embedded and held in place by a cushion of fat.

In plants fats are found in greatest amounts in the seeds and propagative organs. Their function here is protective, to prevent desiccation which would prevent germination, they also serve as nutritive material. Seeds contain lipases which may

either hydrolyse the fat into fatty acids and glycerine or synthesize the fats from the same materials.

Regarding the origin of fat in the plant little is definitely known. In many cases there seems to be strong evidence that it originates from the carbohydrates. Certain seeds like the almond, and castor bean, and olive in the green state are rich in carbohydrates and poor in fats, but as they ripen the carbohydrate decreases and the fat increases. Glucose, sucrose, mannite, starch and other carbohydrates, have been observed to change in this way. Ivanow, in case of flaxseed represents the changes taking place as follows:

$$\text{Carbohydrate} \left\langle \begin{array}{c} \text{Glycerine} \\ \\ \text{Saturated——Unsaturated} \\ \text{fatty acid} \quad \text{fatty acid} \end{array} \right\rangle \text{Fat.}$$

The reverse change is supposed to take place during germination. Miller found in case of the sunflower that the cotyledons in the resting state contained 1 per cent. free fatty acid while in the seedling there was 30 per cent. fatty acid. These fatty acids disappear, that is, are used by the plant in the following sequence; linoleic, linolic, oleic and finally palmitic; that is the more unsaturated acids are used first. There is some difference of opinion as to the changes in the original fat during germination, but one acid may be transformed into another.

It has been suggested that starch may arise from oleic acid as follows:

$$C_{18}H_{34}O_2 + 27O = 2(C_6H_{10}O_5) + 6CO_2 + 7H_2O$$
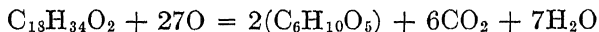
Fats may also arise from protein, but the proof of this is not so definite in the plant as in the animal. Fats may also be transported in the plant from one region to another, similar to fatty infiltration in the animal.
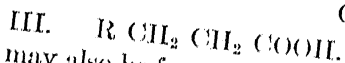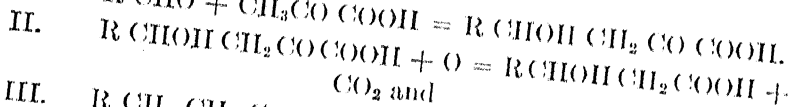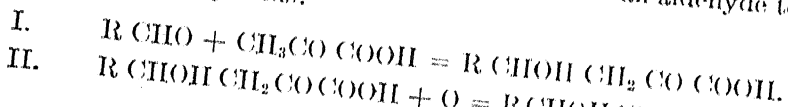
ORIGIN OF FAT IN THE ANIMAL

1. It may arise from the fat of the food. Proof of this is found in the fact that when linseed oil, rape oil, mutton fat and the like are fed to dogs—these fats can be recognized in the fatty deposits of the tissues of the animal. Experiments have shown

that the fat of dogs fed on linseed oil, melts at 0°—while those fed on suet was solid at 50°C.
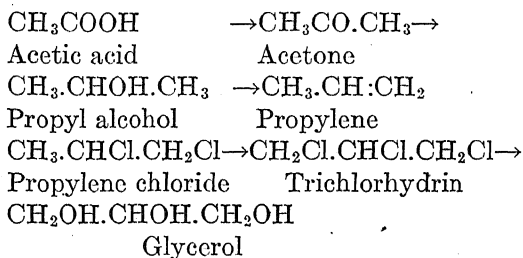
2. From carbohydrates; animals have been fed on a carbohydrate diet, and the carbon retention has been shown to be in the form of fat. For example: Rubner fed a dog weighing 5.89 kg. on starch, sugar, and fat that had a total carbon content of 176.6 grams. During the period the animal excreted 87.1 grams of carbon, there was thus a retention of 89.5 grams. The fat of this diet had a carbon content of 3.6 grams. The animal excreted 2.55 grams nitrogen = 16 grams protein (2.55 × 6.25). On the improbable assumption that all the carbon of this excreted protein was retained in the body, this would be 8.32 grams C (16 × 0.52) (52 per cent. C in proteins) so that 8.32 + 3.6 = 12 grams, could originate from other sources than carbohydrate leaving 89.5 — 12 = 77.5 grams of carbon that could arise only from the carbohydrate and could be retained only as carbohydrate or fat. The greatest possible amount of glycogen that could be stored from this would be 78 grams or 34.6 C so that there would still remain 42.9 grams of C that could be stored only as fat. This calculation is based on the fact that glycogen is stored equally between the liver and the muscles. The liver rarely exceeds 4 per cent. of the body weight and only in exceptional cases will the liver glycogen = 17 per cent. of the weight of the organ.

Numerous other fattening experiments have convinced physiologists that fats can be formed in the animal body from carbohydrate. The chemistry of this change is not understood, and cannot be imitated in the laboratory. See Lusk, Science of Nutrition, 3d Edition. The following hypotheses have been proposed in that the process starts with pyruvic acid. Lactic acid arises from the sugar and may be converted into pyruvic acid by oxidation. The pyruvic acid unites with an aldehyde to form higher fatty acids:

I. $R\,CHO + CH_3CO\,COOH = R\,CHOH\,CH_2\,CO\,COOH.$

II. $R\,CHOH\,CH_2\,CO\,COOH + O = R\,CHOH\,CH_2\,COOH + CO_2$ and

III. $R\,CH_2\,CH_2\,COOH.$

may also be formed on further oxidation.

11

This gives some idea of how higher fatty acids may be formed in the plants. The glycerol necessary to form fat from the fatty acid may be synthesized in the plant in a manner unknown to the chemist. That it may be formed from the elements has been shown by Friedel and Silva through the following steps:

CH_3COOH $\rightarrow CH_3CO.CH_3 \rightarrow$
Acetic acid   Acetone
$CH_3.CHOH.CH_3$ $\rightarrow CH_3.CH:CH_2$
Propyl alcohol   Propylene
$CH_3.CHCl.CH_2Cl \rightarrow CH_2Cl.CHCl.CH_2Cl \rightarrow$
Propylene chloride   Trichlorhydrin
$CH_2OH.CHOH.CH_2OH$
      Glycerol

FATS FROM PROTEINS

It has been shown quite definitely in feeding experiments that fat may be formed from protein. There has been considerable difference of opinion on this question. Pettenkoffer and Voit claiming a distinct formation while Rubner questioned the computation on the basis that they had used the ration of carbon to nitrogen in protein as 3.68 instead of 3.28 which he believed to be the correct figure. Cremer, however, showed by experiment that fat may be formed from protein and his results have been amply confirmed. His experiment is as follows:

A cat was starved for a number of days. It was then fed 450 grams of meat a day. The animal was kept in a respiration chamber and the CO_2 in respiration measured and the excreta analysed. There was a daily excretion of 13.0 grams nitrogen— 41.6 grams of protein carbon (13 $\times$ 3.18). However only 34.3 grams of carbon was eliminated. 7.3 grams or 17.5 per cent. of the carbon taken in was retained. In 8 days 58 grams of carbon was retained. If this were stored as glycogen it would make 130 grams, but in the total animal at this time there was found only 35 grams of glycogen. The balance must have been stored as fat.

This subject has also been investigated by Atkinson and Lusk who have shown by calculations based on respiratory quotients and heat production as measured by the respiration calorimeter that fat is produced from protein in the dog after the ingestion of large quantities of protein.

THE NEED OF FATS IN GROWTH

The normal growth of an animal depends upon something in addition to the requisite number of calories of fats, proteins and carbohydrates. The fat must be of a certain source and contain a growth promoting substance "A," or what has been called vitamine. All fats do not contain this vitamine. It is especially abundant in butter fat, beef fat, egg yolk, and cod liver oil. Animals fed on a diet in which olive oil or almond oil supplies the fat, do not grow, and soon will die if such diet is continued. However, even when death is near, the substitution of vitamine containing fat, immediately restores normal health and growth. The nature of this substance is not known. The term vitamine, suggests that they are amines, but such is not the case. The term vita, McCollum thinks, gives an importance to these essentials, greater than other equally indispensable constituents of the diet. He suggests until more definite knowledge is obtained, the term fat soluble "A" be applied to the vitamine essential growth promoting ingredient of fats, and to other like substances which are soluble in water, water soluble "B."

THE FATE OF FATS IN THE BODY

Fats are easily and completely oxidized in the body and are a great source of body heat. They are absorbed after saponification and resynthesized again in the body, probably by an enzyme. In the dog 10–20 per cent. of the fat of a meal is absorbed in four hours, about 30 per cent. in seven hours and 86 per cent. in 18 hours. After excision of the pancreas, or disease of it, fat absorption is markedly retarded but not abolished.

In man the feces contains 0.5 to 1.5 grams of fat in starvation, while on ordinary diet containing about 120 grams fat, 3 to 7 grams is excreted.

Normal urine contains no fat, but in diseased conditions variable amounts may be found. The condition is known as lipuria and may occur after excessive eating of fat, after cod liver oil, in fat embolism occurring after fractures, in phosphorus poisoning and other fatty degenerative processes, in prolonged suppuration, chronic Bright's disease, diabetes, chronic alcoholism, in wasting diseases, diseases of the pancreas, obesity, leukemia, and in mental diseases.

XVIII. WAXES

The waxes are esters of higher monatomic alcohols or sterols such as cetyl alcohol, $C_{16}H_{33}OH$, myristic alcohol, $C_{30}H_{61}OH$, or cholesterol $C_{27}H_{45}OH$, and one of the higher fatty acids. Spermaceti is a wax, obtained from a cavity in the head of the sperm whale, and consists mainly of cetyl alcohol and palmitic acid or cetyl palmitate. Bees wax consists chiefly of myricil alcohol and cerotic and melissic acids in ester combination.

Waxes are of both animal and vegetable origin. The surfaces of all organisms, both plant and animal, are covered with a layer of wax. The secretion is found in greater abundance in some plants than others. The function of it is to protect the plant or animal from over-wetting or over-drying and against changes in temperature. For these reasons waxes are important in the protection of the eggs and larvæ of insects. It is well known that wax is a poor conductor of heat as well as electricity.

Lanolin or wool fat, or more correctly, wool wax, consists largely of monatomic alcohol, cholesterol in the free state. There is also some of this combined with myristic, cerotic, and lanoceric acids to form true wax.

The fact that waxes generally have a harder consistency than fats has given rise to incorrect nomenclature in some cases. For instance, wool fat, which is in reality a wax, is not usually regarded as such, while Japan wax, produced by a species of Rhus, is actually a fat. True fats are esters of glycerine, but waxes are esters of higher fatty acids and monatomic alcohols. There is a great variation in the alcohols and the fatty acids in waxes as the following list will show:

(COMPOSITION OF THE WAXES—TAKEN FROM MATHEWS PHYSIOLOGICAL CHEMISTRY, 1915, p. 80.)

Acids. Saturated.	Formula	Melting point	Wax
Ficocerylic	$C_{13}H_{26}O_2$	57°C.	Gundang.
Myristic	$C_{14}H_{28}O_2$	53.8°	Wool.
Palmitic	$C_{16}H_{32}O_2$	62.6°	Bees. Spermaceti.
Carnaubic	$C_{24}H_{48}O_2$	72.5°	Carnauba. Wool.
Cerotic	$C_{26}H_{52}O_2$	77.8°	Bees. Wool. Insect.
Melissic	$C_{30}H_{60}O_2$	91°	Bees.
Psyllostearylic	$C_{23}H_{66}O_2$	94–95°	Psylla.

II. Acryllic series.

Physetoleic	$C_{16}H_{30}O_2$	30°	Sperm oil.
Dooglic (?)	$C_{19}H_{36}O_2$		Sperm oil.
Lanopalmic	$C_{16}H_{32}O_3$	87–88°	Wool.
Cocceric	$C_{31}H_{62}O_3$	92–93°	
Lanoceric	$C_{30}H_{60}O_4$	104–105°	Wool.

III. Alcohols. Sterols.

Pisan ceryl	$C_{16}H_{34}O$	78°	Pisang.
Cetyl (Ethal)	$C_{16}H_{36}O$	50°	Spermaceti.
Octodecyl	$C_{18}H_{38}O$	59°	Spermaceti.
Carnaubyl	$C_{24}H_{50}O$	68–69°	Wool.
Ceryl	$C_{26}H_{54}O$	79°	Wool Chinese.
Myricyl (Melissyl)	$C_{30}H_{62}O$	85–88°	Bees. Carnauba.
Psyllostearyl	$C_{33}H_{68}O$	68–70°	Psylla.
Lanolin alcohol	$C_{12}H_{24}O$	102–104°	Wool.
Ficoceryl	$C_{17}H_{28}O$	198°	Gundang.
Cholesterol	$C_{27}H_{46}O$	148.4–150.8°	Wool.
Cocceryl	$C_{30}H_{62}O_2$	101–104°	Cochineal.
Iso-cholesterol	$C_{26}H_{46}O$	137–138°	Wool.

Waxes are soluble in the ordinary fat solvents, benzene, ether, chloroform, etc. but are less soluble than the fats.

When heated, waxes give no smell of acrolein, since they contain no glycerine. They are saponifiable like the fats, but with more difficulty.

STEROLS

These are solid alcohols, "steros," meaning solid, and "ol" the chemical ending signifying, alcohol. Cholesterol $C_{27}H_{45}OH$ was the first discovered member of the group, and the most important. It is a secondary alcohol, since it oxidizes to a ketone. Compounds closely related to cholesterol are found in plants, phytosterols, and also in feces, coprosterols.

Cholesterol can be taken as a type of the sterols, which are important as constituents of waxes. The relation of the sterols to waxes is the same as glycerine to fats.
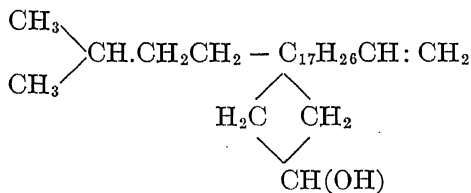
CHOLESTEROL

This sterol was first prepared from gall stones in 1785 by Four-croy and studied by Chevreul in 1814, who named it cholesterin from the Greek chole, bile, and steros, solid. Some gall stones are almost pure cholesterol. It is also found in brain tissue. The important source of it is lanolin or wool fat, "lana,"
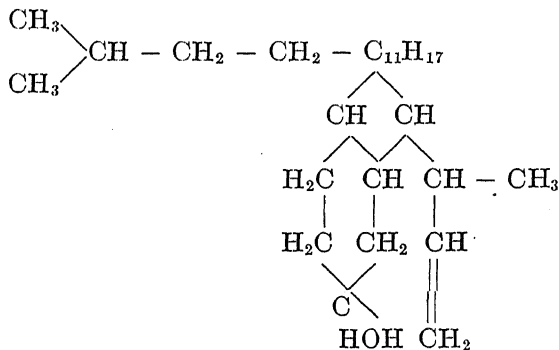
wool, oleum, oil, or adeps lanæ hydrosus. This contains some free cholesterol and some combined with myristic, cerotic, lanoceric, and lanopalmitic acids in the form of wax. Wool wax also contains other sterols, as carnabuyl, and lanolin alcohols.

Cholesterol is insoluble in water and alkalies, sparingly soluble in cold, but readily soluble in hot alcohol, ether, acetone, chloroform, and other organic solvents, slightly soluble in soap solutions and much more soluble in solutions of bile salts. It is readily soluble in oleic acid and oils. Solutions of it react neutral. It is tasteless, odorless, cannot be saponified, and is remarkably stable toward oxidation. These reasons, and the additional one that it does not become rancid, recommend its use in ointments, etc. Because of its penetrative power, it is used as the base to carry drugs through the skin.

Cholesterol is found to some degree in every cell, probably as a protective agent. The structure of it is not satisfactorily known. Mauthner[1] assigns to it the following formula:

$$\begin{array}{c} CH_3 \\ \diagdown \\ CH_3 \diagup \end{array} CH.CH_2CH_2 - C_{17}H_{26}CH:CH_2$$

$$\underset{\diagdown\;\diagup}{H_2C \quad CH_2}$$

$$CH(OH)$$

Windaus[2] gives

$$\begin{array}{c} CH_3 \\ \diagdown \\ CH_3 \diagup \end{array} CH - CH_2 - CH_2 - C_{11}H_{17}$$

$$CH \quad CH$$

$$H_2C \quad CH \quad CH - CH_3$$

$$H_2C \quad CH_2 \quad CH$$

$$C \qquad$$

$$HOH \quad CH_2$$

From these formulas it is seen to be closely related to the terpenes, which are also important in drug chemistry.

[1] Zeit. f. physiologische chemie, 1901, 34, 426.

[2] Ber. Deutsche, chem. gesellschaft, 1912, 45, 2421.

This constitution is not yet definitely settled. It is evidently a terpene compound. The formation of terpenes in the animal body is hard to explain, and it seems probable that it does not originate in the animal organism. Animal cholesterol is apparently plant cholesterol, utilized by the body.[1] The metabolism of it in the body is as unknown, as is its function, though it possesses certain definite properties which are pharmacologic importance. Lecithin accelerates the activity of cobra poison and cholesterol retards the action of lecithin. Snake venom added to washed red blood corpuscles suspended in water, will not cause laking. If, however, a trace of lecithin be added, laking results. A trace of cholesterol dissolved in methyl alcohol will neutralize the influence of the lecithin in this case. Since lecithin and cholesterol exist in all cells and especially in red blood corpuscles, it seems that the function of the cholesterol is protective.

Preparation and Tests for Cholesterol

Place 2 grams of wool fat in a 100 cc. Erlenmeyer flask, add 25 cc. of 25 per cent. alcoholic (KOH) and boil under a reflux condenser for two hours with frequent shaking. This saponifies the fats but not the cholesterol. Pour the mixture into an evaporating dish and evaporate off the alcohol. Dissolve the residual soap in 50 cc. of hot water and transfer to a 200 cc. separating funnel, cool and add 50 cc. of ether and shake several times. The ether dissolves the cholesterol. If separation does not occur readily, add 5 cc. alcohol and shake again. Run off the soap solution and collect the ether solution in a dry evaporating dish and evaporate to dryness on a water bath.

1. Examine the residue under a microscope on a glass slide for the characteristic crystals.

2. Cholesterol on oxidation yields pigments. The Liebermann-Burchard test is the most delicate and characteristic. The test is as follows:

Dissolve a few crystals of cholesterol in 2–3 cc. of chloroform in

[1] Recently, Gamble and Blackfan (J. Biol. Chem., 1920, 42, 401–9), from analysis of the non-saponifiable fraction of the feces of undernourished children for three days found the excretion of cholesterol larger than the amount in the food. They interpreted this result as indicating a synthesis of cholesterol in the body. This is confirmation of an older observation of Mueller, but does not satisfactorily account for the excretion of a probable storage from previous feeding.

a dry test tube or in the depression of a test tablet. Add about 10 drops of acetic anhydride, shake and add concentrated H_2SO_4 drop by drop. A transient pink color first develops, which on the addition of more acid changes to blue and finally to green.

3. **Schiff's reaction**: A few crystals of cholesterol are placed on a porcelain dish and treated with a few drops of a mixture of 1 volume 10 per cent. ferric chloride and 3 volumes of concentrated H_2SO_4. It is then evaporated carefully to dryness over a free flame. A reddish violet residue changing to bluish is obtained.

4. Crystals of cholesterol on a white surface, when moistened with a mixture of 5 parts H_2SO_4 and 1 part water, turn pink. On the oxidation of a drop of very dilute solution of iodine a play of colors violet, blue, green, and red, results.

All animal fats contain cholesterol while vegetable fats contain phytosterol, and sitosterol. The isolation and identification of the unsaponifiable residue, therefore, is of considerable importance, in establishing whether or not a fat is of animal or plant origin. In food products the more expensive animal fats are sometimes substituted by or adulterated with, the cheaper vegetable fats. Recently vegetable fats have been hydrogenated to make them more nearly like animal fats—see p. 154, but such hydrogenated fats are used only as foods.

XIX. VOLATILE, ETHEREAL OR ESSENTIAL OILS

The sources of the volatile oils are mainly the flowers, fruit and leaves of many plants. They differ from the fixed oils chemically, physically, pharmacologically, and economically.

The composition of volatile oils is very variable and not fully understood. Terpene is the most common constituent. Many are composed mainly of terpenes either of the aliphatic or aromatic series. But mixtures of terpene derivatives which include alcohols, aldehydes, ketones, acids, esters, ethers, phenols, lactones, quinones, oxides, nitrogen and sulphur compounds occur. Some non-terpene hydrocarbons have also been found and in some oils no terpene has been found (Attar of Roses). The only common characteristic of the volatile oils as a class is their volatility. They all contain hydrogen and carbon and most of them also oxygen. A few contain nitrogen or sulphur or both.

The characteristic odor of the oil is associated with the oxygenated part of the molecule, and especially with the oxygenated aliphatic terpene.

CHEMICAL CLASSIFICATION

Dumas in 1833, classified volatile oils as follows:

1. Those containing carbon and hydrogen only, like turpentine.

2. Those that contain oxygen, like camphor and eucalyptus.

3. Those that contain sulphur, like mustard oil or

4. Nitrogen, like oil of bitter almonds. While this classification may still be used in a modified form, it is to general to give one any information regarding the composition of any volatile oil.

ALIPHATIC HYDROCARBONS IN VOLATILE OILS

Heptane C_7H_{16} is the lowest member of this series found in volatile oils. It has been found in the distillate of the oleoresin of some California pines. Higher members of this series and of the olefin series occur quite generally in the wax-like secretions of leaves, flowers and fruits. They occur mixed with other homologues and not as pure products. Octylene C_8H_{16} has been found in the oils of bergamot and lemon. A number of terpene hydrocarbons have been isolated.

TERPENES

Terpenes were formerly defined as hydrogenated derivatives of cymene and its substituted products (true terpenes). More recent work however has discovered some olefine terpenes. These can readily be converted into aromatic terpenes. All terpenes are unsaturated compounds and can be hydrogenated readily and yield addition products with halogens. On exposure to the air they are oxidized to resins, and this has given rise to the opinion that natural resins are oxidized products of volatile oils. As a group they appear to be derived from hydrocarbons of the composition C_5H_8. They are classified as:

$$
\begin{aligned}
&\text{Hemiterpenes} \ldots \ldots \ldots \ldots \ldots \quad C_5H_8 \\
&\text{Terpenes} \ldots \ldots \ldots \ldots \ldots \ldots \quad C_{10}H_{16} \\
&\text{Sesquiterpenes} \ldots \ldots \ldots \ldots \ldots \quad C_{15}H_{24} \\
&\text{Diterpenes} \ldots \ldots \ldots \ldots \ldots \ldots \quad C_{20}H_{32} \\
&\text{Polyterpenes} \ldots \ldots \ldots \ldots \ldots \quad (C_5H_8)n
\end{aligned}
$$

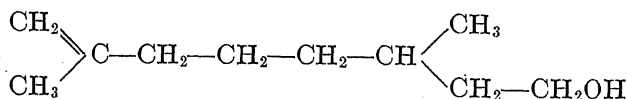These may be divided into two groups:

1. The olefine terpenes.

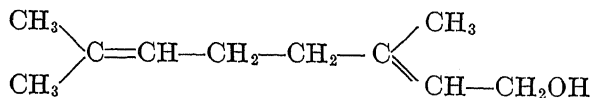2. The aromatic terpenes.

    (a) Monocyclic.
    (b) Dicyclic.

The monocyclic are represented by cymene or menthol and the dicyclic by camphor and camphane.
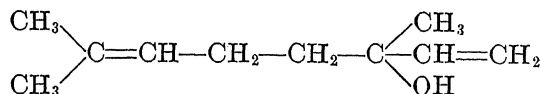
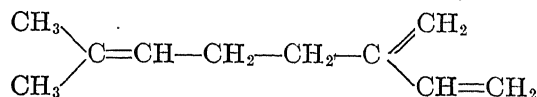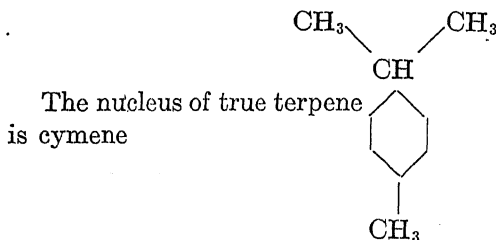The most important terpenes of the aliphatic or olefine series are:

$$\begin{array}{l} CH_2 \\ \rangle C-CH_2-CH_2-CH_2-CH\langle \begin{array}{l} CH_3 \\ CH_2-CH_2OH \end{array} \\ CH_3 \end{array}$$

<div align="center">Citronellol (Lemon oil)</div>

$$\begin{array}{l} CH_3 \\ \rangle C=CH-CH_2-CH_2-C\langle \begin{array}{l} CH_3 \\ CH-CH_2OH \end{array} \\ CH_3 \end{array}$$

<div align="center">Geraniol (Oil of geranium)</div>

$$\begin{array}{l} CH_3 \\ \rangle C=CH-CH_2-CH_2-C\langle \begin{array}{l} CH_3-CH=CH_2 \\ OH \end{array} \\ CH_3 \end{array}$$

<div align="center">Linaloöl (Oil of lavender)</div>

$$\begin{array}{l} CH_3 \\ \rangle C=CH-CH_2-CH_2-C\langle \begin{array}{l} CH_2 \\ CH=CH_2 \end{array} \\ CH_3 \end{array}$$

<div align="center">Myrcene (Oil of lignaloes, etc.)</div>

The nucleus of true terpene is cymene

$$\begin{array}{c} CH_3 \quad CH_3 \\ \diagdown \quad \diagup \\ CH \\ | \\ \text{(benzene ring)} \\ | \\ CH_3 \end{array}$$

or paramethyl isopropyl benzene, which can be derived easily from some of the volatile oils, stearoptenes and camphors.

$$C_{10}H_{16}O + P_2O_5 \rightarrow C_{10}H_{14} + H_2O$$
<div align="center">Camphor   Cymene</div>

$$C_{10}H_{16} + O \rightarrow C_{10}H_{14} + H_2O$$
<div align="center">Turpentine   Cymene</div>
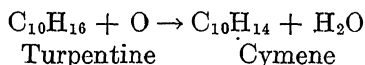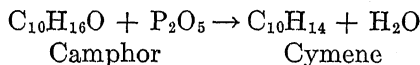
Cymene is a pleasant smelling liquid—specific gravity 0.87 and boils at 175–176°C. On oxidation with dilute HNO_3 the isopropyl end of the ring is first oxidized and para toluic acid is formed $CH_3.C_6H_4.COOH$. Further oxidation yields terephthalic acid $COOH.C_6H_4COOH$ (1:4). In the body the methyl end of the chain is first attacked and cumic acid is formed:

$$C_6H_4 \underset{COOH}{\overset{CH(CH_3)_2}{<}}$$
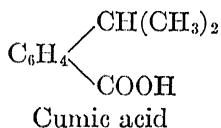
Cumic acid

and excreted as the glycocoll conjugate, cuminuric acid

$$(CH_3)_2CH.C_6H_4CO.NH.CH_2COOH$$

AROMATIC TERPENES

True terpenes have the formula $C_{10}H_{16}$. They seem to be polymerides of the hemi-terpene (C_5H_8). Two or more molecules of this compound may polymerize to form terpenes or polyterpenes.

In the destructive distillation of india rubber, or when turpentine is passed through a tube heated to redness, isoprene (C_5H_9) which is methyl divinyl, is formed

$$CH_3 \underset{CH_2}{\overset{}{>}} C \underset{CH_2}{\overset{CH}{<}}.$$
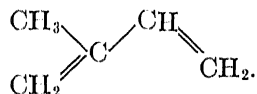
This is a liquid B.P. 37°. It polymerizes readily to the terpene dipentene;

$$2 \; CH_3 \underset{CH_2}{\overset{}{>}} C—CH = CH_2 \rightarrow \; CH_3 \underset{CH_2}{\overset{}{>}}C—CH \underset{CH_2—CH_2}{\overset{CH—CH}{<}} C.CH_3$$

Isoprene   Dipentene
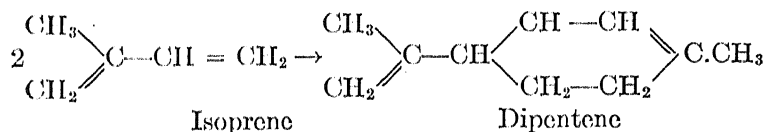
On treatment with acids, isoprene polymerizes, forming rubber again, which is considered as a resin.

The terpenes may be considered as being derived from isoprene or an isomeric hydrocarbon. The true terpenes all contain the dipentene or cymene nucleus.

$$CH_3$$

Cymene
nucleus

$$C$$

$$CH_3 \quad CH_3$$

$$CH_3$$

Dipente
nucleus

$$C$$

$$CH_2 \quad CH_3$$
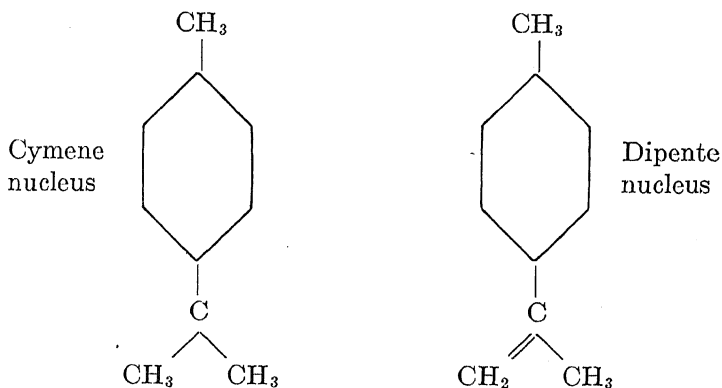
The terpenes being unsaturated bodies, unite with HCl HBr to form addition products. The unsaturated condit also imparts great reactivity to them. They absorb oxy readily and resinify. HNO_3 or iodine and other oxidizing s stances mixed with them may cause explosions. Weaker oxi ing may break them down with the formation of acetic, propio butyric, oxalic, and other acids while bromine and iodine conv them into cymene. One of the easiest ways to prepare cym is to treat camphor with $P_2S_5, ZnCl_2$, or P_2O_5 (p. 170).

The main characteristics of this ill-defined group of t terpenes are:

1. Their composition $C_{10}H_{16}$.
2. Their unsaturated condition:
3. Their great reactivity.
4. Their tendency to polymerize and resinify.
5. On reduction they yield hydroterpenes.
6. On oxidation with potassium, they yield, in many ca benzene derivatives.
7. The presence of the cymene ring or nucleus.
8. They boil without decomposition at 155–180°C.
9. When taken into the body, they as a rule, are excre combined with glycuronic acid, as conjugated glycuronates.

For convenience of study, the true terpenes have been s divided as follows:

1. The terpenogen group
2. Terpan or menthan group

3. Camphan group.

Group I. consists of alcohols, aldehydes, acids, etc., combinations of terpenes from which the hydrocarbon can readily be prepared.

Group II. Menthol is a prominent member of this group, and has certain reactions which distinguish it from the first group. It is not so easily converted into the hydrocarbon.

Group III. Camphor is the typical representative. Camphor yields camphene which is the only solid terpene known.

ALIPHATIC ALCOHOLS IN VOLATILE OILS

Methyl alcohol occurs frequently and has been found in aqueous distillates of the oils of cypress, savin, vetiver, orris, etc. Ethyl alcohol has been observed only in a few instances. *N* butyl, isobutyl, isoamyl, *n* hexyl, heptyl, *n* octyl, *n* nonyl and undecyl have also been found. Various other less known aliphatic alcohols have been reported.

AROMATIC ALCOHOLS IN VOLATILE OILS

Benzyl, phenyl ethyl, phenyl propyl, and cinnamic occur; also salicyclic alcohols, are more or less commonly found.

DIFFERENCES BETWEEN FIXED AND VOLATILE OILS

The chief differences are:

Fixed Oils	Volatile Oils
1. Leave a greasy spot on paper.	Evaporate completely.
2. Can be saponified.	Cannot be saponified.
3. Will not explode when brought together with nitric acid, iodine, or other oxidizing agents.	May explode when brought together with nitric and other oxidizing agents.
4. Chemical composition—esters of glycerine and fatty acids	Chemical composition, mainly terpenes and derivatives.
5. Almost insoluble in alcohol, except castor oil. Soluble in ether, chloroform, benzene, and in other oils.	Soluble in ether, chloroform, benzene, and other oils.

6. More easily emulsified. Not so easily emulsified.

7. Used in medicine as laxatives, emollients, vehicles for ointments, liniments, etc. Used in medicine as flavors, carminatives, stomachics, correctives, rubifacients, deodorants, antiseptics, etc.

8. Are foodstuffs. Are not foodstuffs.

9. Completely oxidized in the body and excreted as CO_2 and H_2O. Not oxidized but are excreted, mainly combined with glycuronic acid.

THE GENERAL ACTION OF THE VOLATILE OILS

All volatile oils attack protoplasm and are antiseptic for this reason. This is a general action of benzene derivatives, and most volatile oils are such. The volatility of the oil aids in its penetration and action. When applied to the skin, they produce itching, redness, some anesthesia, and if volatilization be prevented they will cause blistering. The turpentine stupe, which is essentially, oil of turpentine, sprinkled on a woolen cloth wrung out of hot water, and applied to a part of the body, gives one a good idea of the local action of volatile oils. Some oils, such as oil of mustard act after they are broken down into active ingredients, and others such as menthol have a specific action on the nerves conveying the sensation of cold. In general however the action resembles that of turpentine.

Action on the Alimentary Tract

Oils generally have an agreeable taste. They are slightly irritating and cause a flow of saliva. They are readily absorbed and may increase the appetite. When swallowed small doses increase moderately the activity of the gastro-intestinal tract and act as carminatives. Excessive doses produce symptoms of inflammation with vomiting and diarrhœa.

The oils circulate in the blood for the most part unchanged, but due to their action on the intestine a leucocytosis may be produced. If very large doses are taken the central nervous system is influenced and convulsions may occur. This is readily demonstrated by giving rabbits large doses of camphor which acts like a volatile oil. The harmful effects of absinthe (a volatile oil) are due to its action on the central nervous system. The continued

use of any volatile oil may lead to fatty degeneration of the liver and kidneys.

Volatile oils are excreted mainly in combination with glycuronic acid—as glycuronates, but this is not characteristic as many other substances are excreted in this way.

Substances Excreted Combined with Glycuronic Acid.—In addition to terpenes the following substances, when ingested, may be excreted as glycuronates:

Isopropyl alcohol	Chloral
Methylpropyl carbinol	Butylchloral
Methylhexyl carbinol	Bromal
Tertiary butyl alcohol	Dichloracetone
Tertiary amyl alcohol	
Pinacone	
Saccharin	
Benzene	Turpentine oil
Nitrobenzene	Camphor
Aniline	Borneol
Phenol	Menthol
Resorcinol	Pinene
Thymol	Antipyrine
a-and β-naphthol	Etc.

The Significance of Glycuronic Acid in the Urine

In the normal metabolism of glucose, the aldehyde end of the chain is first oxidized. Glycuronic acid is formed from glucose by oxidation of the CH_2OH end of the chain. It is thought by some to be formed in small quantities in normal metabolism, but this does not seem to be correct, since glycuronic acid administered parenterally appears in the urine quantitatively (Biberfeld, 1914). Its appearance in the urine following the administration of drugs indicates a derangement of carbohydrate metabolism. The formation of the glycuronic acid may be due primarily to the drug uniting with the aldehyde end of the chain which prevents its oxidation.

According to their uses in medicine volatile oils may be classified as:

1. Flavoring agents or carminatives:

Cloves   Peppermint
Coriander   Rose
Lavender   etc.
Lemon

2. Malodorous oils, used mainly for their psychic effect:

Asafœtida
Valerian

3. Genito-urinary disinfectants. All volatile oils are mildly antiseptic but those especially valuable here are:

Copaiba
Cubebs
Sandalwood.

Tests

Any fixed and volatile oil may be used. Oil of turpentine is taken as a representative of the volatile oils and cottonseed as a type of the fixed oils.

1. Place a drop of each on a piece of glazed paper and note the difference.

2. Test the solubility of each in water, alcohol, and acetic acid, chloroform. Repeat this, using croton or castor oil.

3. Add 1 cc. of oil of turpentine to water in a test tube, shake and let settle. Draw off the water and note the odor. What are aquæ?

4. **Saponification.**—In an extractor place 200 cc. of cotton-seed oil and 100 cc. of 10 per cent. alcoholic solution of KOH. Heat on water bath for 30 minutes, cool and add 15 grams of NaCl in 50 cc. of water. This converts the soft green soap into hard soap. Green soap (sapo viridis) was so named because the vegetable oil from which it was first prepared contained enough chlorophyll to color it green. Soft soap as now prepared is not colored green.

5. Heat a little fixed oil with a crystal of KHSO$_4$ in a test tube over a free flame. Note the odor of acrolein (acer, sharp and oleum, oil). Repeat, using glycerine instead of oil.

$$CH_2OH.CH_2OH.CHOH - H_2O \rightarrow CH_2:CHCHO$$
Glycerine   Acraldehyde or acrolein
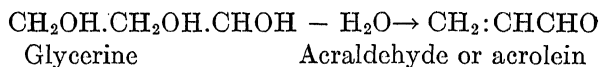
Fats and oils become rancid on standing, especially when ex-

posed to light, of if there is a small amount of protein present. For this reason in the preparation of ointments, benzoinated lard, lanolin, or petrolatum is often substituted.

Lanolin or wool fat, $C_{27}H_{45}OH$, is cholesterol, a monatomic alcohol obtained from sheep's wool. It resembles fat in appearance and solubility, and does not become rancid, but is expensive. It is used in plasters and ointments.

The cholesterols are closely related to the terpenes.

STEAROPTENES

Stearoptenes from their pharmacological action may be considered as solid volatile oils. When volatile oils are allowed to stand at low temperatures, they separate into two layers. The top or lighter layer is known as eleoptene and the lower crystalline deposit, as stearoptene. The latter is an oxidized product of the oil. Camphor, menthol, and thymol are the most important stearoptenes. Some unimportant stearoptenes are liquid at ordinary temperature.

Camphora or camphor is a saturated ketone derived from cinnamomum camphora. It is said to be saturated because it will not form addition products. It has the formula—$C_{10}H_{16}O$. The form of camphor in white masses of crystalline structure which have the same solubilities as the volatile oils.

$$\begin{array}{ccc} CH_2 & \!\!\!\!\!\!\!\! CH & \!\!\!\!\!\!\!\! CH_2 \\ | & | & | \\ & CH_3\!-\!C\!-\!CH_3 & \\ | & | & | \\ CH_2 & \!\!\!\!\!\!\!\! C & \!\!\!\!\!\!\!\! CO \\ & | & \\ & CH_3 & \end{array}$$
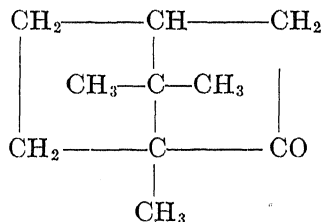
Camphor-menthol of the National Formulary is a solution produced by triturating equal amounts of camphor and menthol. Its uses are as an antiseptic, and as a local anodyne.

Camphor monobromata $C_{10}H_{15}Br.O$ is a substitution product of camphor. It occurs as prismatic needles or scales, the solubility being the same as camphor. Borneol camphor: $C_{10}H_{16}O$ is a secondary alcohol obtained from ordinary camphor by reduction.

$$C_9H_{16}CO + 2H = C_9H_{16}CHOH$$
$$\text{Camphor} \qquad \text{Borneol-camphor}$$

12
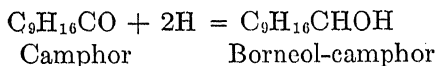
Camphor is oxidized in the body to camphorol,

$$C_{10}H_{16}O \rightarrow C_{10}H_{15}O.OH$$
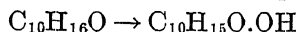
This then combines with glycuronic acid and is excreted as the glycuronate

$$C_{10}H_{15}O.OH + C_6H_{10}O_7 = C_{10}H_{15}O\ O.C_6H_9O_6 + H_2O$$
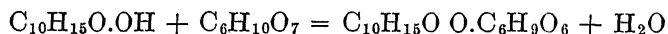
The camphors are used in medicine chiefly in liniments and for stimulation of the respiratory and circulatory centres, as well as the heart muscle in threatening collapse. Externally as a liniment, camphor irritates the skin and dilates the vessels. It is used therefore as a rubifacient. It has a mild antiseptic action and is used to keep away insects. Camphor vapor is a mild paralyzer of all undifferentiated protoplasm. When taken by mouth it has a warm bitter taste and carminative action, much like the volatile oils. Large doses may cause nausea and vomiting. If large doses are taken it may be absorbed and if so has a definite stimulant action on the central nervous system, much like the volatile oils. 10 cc. per kilo of body weight of a 20 per cent. solution of camphor in olive oil given to a rabbit will produce peculiar bucking spasms in which the animal may turn a sommersault backwards.

Menthol.—$C_{10}H_{22}O$. Menthol is a secondary alcohol derived from peppermint-mentha piperita. It occurs in crystals or prisms, the solubility of which is the same as the volatile oils. The dose is about 1 grain, and it is used as an antiseptic, analgesic and stimulant.

$$
\begin{array}{c}
H_3C \quad\ CH_3 \\
\diagdown\ \diagup \\
C\!-\!H \\
| \\
C\!-\!H \\
\diagup\ \diagdown \\
H_2\!=\!\!C \quad C\!-\!H\ OH \\
|\qquad\quad | \\
H_2\!=\!\!C \quad CH_2 \\
\diagdown\ \diagup \\
C\ CH_3 \\
| \\
H
\end{array}
$$

Menthol
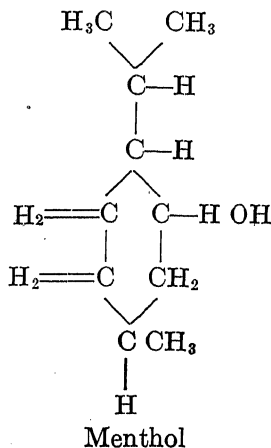
Thymol is a phenol from the oil of thyme. It occurs in large translucent rhombic prisms, its solubilities in general being the same as the other stearoptenes. It is used especially in the treatment of hookworm disease, also as an antiseptic and antipyretic.

Thymolis Iodidum.—Aristol-thymol iodide is a condensation product consisting of two molecules of thymol containing iodine in the phenolic groups. It is a reddish yellow powder and is used for the same purposes as iodoform, i.e. antiseptic.

Menthol has many of the actions of camphor. It is much used as a nasal spray, 1 per cent. menthol in light liquid petrolatum, with volatile oils. When rubbed on the skin it dilates the vessels as camphor does, but it stimulates the "cold" nerves, and there is a sensation of numbness of partial anesthesia due to a paralysis of the sensory nerves, after primary stimulation. For this reason it is sometimes used with benefit in neuralgias. It is excreted in combination with glycuronic acid as menthol-glycuronic acid.
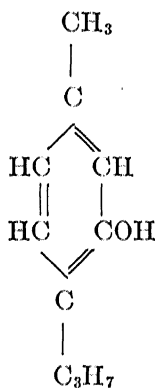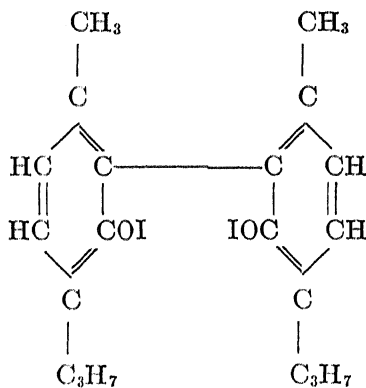
Thymol   Dithymol-diiodide (Thymolis iodidum).

1. Note odor and test solubility in water, alcohol, ether and in fixed oils, of camphor, menthol or thymol.

2. Triturate a small piece of camphor with thymol, chloral, or menthol.

3. Repeat this with any of the stearoptenes and phenacetin, acetanilid or antipyrin.

Carvacrol is an isòmer of thymol.   It has the formula

CH_3

OH

CH

CH_3 CH_3

Carvacrol.
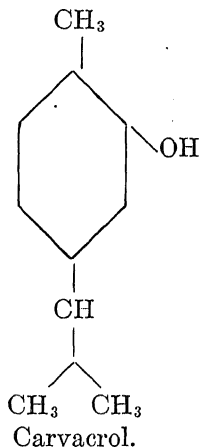
It occurs with thymol in many labiate plants, particularly in
the species origanum and in the oil of thyme it sometimes re-
places all of the thymol.   It has the same pharmacological ac-
tions as thymol and can be used instead of it in hookworm disease.
Because of the great demand for thymol in the treatment of
hookworm disease its supply is inadequate.   Attempts to produce
thymol synthetically have not been successful from a commercial
standpoint.   Carvacrol was first prepared synthetically by Sch-
weitzer (J. Prakt. Chem., 1841, XXIV, 257) and recent work
shows that it may be prepared synthetically from the commercial
point of view.   (Hixon and McKee, Journal of Industrial and
Engineering Chemistry, 1918, X, 982).

Besides its use in the treatment of hookworm disease—thymol
is occasionally used as a parasiticide.   It has been used in ring-
worm with good results.   5 to 10 per cent. solution in alcohol
being applied directly to the growth.   Thymol is excreted com-
bined with glycuronic and sulphuric acids.

XX. RESINS, OLEORESINS, GUM RESINS, AND BALSAMS

Resins are an ill-defined group of amorphous, brittle oxidized
hydrocarbons.   They are not pure chemical bodies, but mix-
tures.   They are allied to, and probably derived from the vola-
tile oils, and occur as exudations of plants excreted in the course

of metabolism. Most natural resins consist of a mixture of peculiar resin acids, which dissolve in alkalies forming resin soaps. These soaps have detergent properties similar to the ordinary soaps, and because of their great water-holding power have been used to adulterate ordinary soaps. The saponification value aids in the identification of resins.

Resins are characterized by being insoluble in water and petroleum ether, soluble in alcohol and volatile oils, and when broken by presenting a smooth shining surface, are amorphous, sticky and fusible and burn with a smoky flame. They are almost invariably a mixture of different substances. When resins occur with volatile oils, they are called oleoresins. When mixed with gums they are gum resins. Balsams are resins or oleoresins that contain benzoic or cinnamic acids. The term resin is also used in chemistry to include such bodies as are formed when a mixture of alcohol and potassium hydrate are allowed to stand. The dark colored material that forms and is soluble in the alcohol is designated as a resin.

The most important resins are those of copaiba, jalap, podophyllum, scammony, guaiacum-wood, gamboge, asafœtida, and caoutchouc. Amber is a fossil resin and consists of two resin acids, and a volatile oil. Caoutchouc is prepared from a number of tropical euphorbiaceæ, apocinaceæ, etc. When purified its formula is $(C_5H_8)n$. On distillation it will polymerize spontaneously to caoutchouc and also to dipentene. It takes up sulphur readily when treated with sulphur chloride (S_2Cl_2) in CS_2 and the product is vulcanized rubber.

1. Test the solubility of resin in water, alcohol, ether, oil of turpentine, dilute boiling NaOH and H_2SO_4.

2. Mix an alcoholic solution of shellac with water; with dilute alcohol.

3. Mix an alcoholic solution of shellac or resin with mucilage of acacia. Shake and let stand.

OLEORESINS

These are solutions of resins in ethereal oils. The chief oleoresins are aspidium, capsicum, cubeb, lupulin, ginger, and black pepper. Aspidium is the most important of the group, and is used in the treatment of tapeworm. It is the principal remedy for this purpose.

Acetone is the solvent used in the preparation of the oleoresins. It is less expensive and less explosive than ether, and is an excellent solvent.

1. Evaporate an alcoholic solution of gum turpentine in a small porcelain dish. Note the odor, and the characteristic residue. Explain.

2. Compare the appearance of the oleoresins and the resins. To what is the physical difference due?

3. Place about 25 grams of ginger, pepper, or powdered aspidium in a Soxhlet apparatus and extract with acetone. When the extraction is complete distil off the solvent and examine the residue-oleoresin. Study the solubility in cotton-seed oil, mucilage and water. Shake.

GUM RESINS

Gum resins are mixtures of resins or oleoresins with gums. Asafœtida, ammoniac, myrrh, gamboge and scammony are the most important.

Triturate a lump of asafœtida in a mortar with water. Note the odor and the character of the mixture. Test the influence of the addition of alcohol. This drug is used in neurasthenic and hysterical conditions. The influence of it, if it has any, is due to the odor, *i.e.* psychic effect.

Boil some of the gum resin with a little H_2SO_4. Neutralize and filter. Test the filtrate with Fehling's solution. Place 5 grams of gum in a distilling flask, add 25 cc. concentrated HCl and distil from a sand bath. Let the distillate drop on a piece of filter paper moistened with aniline acetate. A red color indicates the presence of a pentose, which is converted into furfural by the following reaction.

$$C_5H_{10}O_5 - 3H_2O \rightarrow C_4H_3O.CHO$$
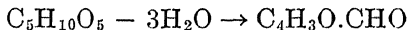
Sugar indicates the presence of a gum. Explain the presence and kind of sugar.

BALSAMS

Balsams are resins or oleoresins that contain benzoic or cinnamic acid. The most important are those of peru, tolu, and storax or styrax. Balsam of copaiba contains neither benzoic or cinnamic acid and is, therefore, not a balsam. On the other hand cranberries and other berries of the Ericaceæ, contain benzoic acid but contain no resin.

XXI. GLUCOSIDES OR COMPOUND SUGARS

Glucosides are substances which on hydrolysis yield glucose or a related sugar, and another substance. In many cases the composition of the other substance is unknown; usually it is an aromatic body. The sugar may be rhamnose, galactose, ribose, arabinose, or any disaccharide that yields a sugar related to glucose. Some glucosides contain only C, H, and O, a few have N, in addition, and one or two contain sulphur. The part remaining after the sugar is split off may be alkaloid, *e.g.* solanine, in which case the term alkaloidal glucoside would be appropriate. Vegetable bases however are rarely found in glucosidic combination. Some of the glucosides are highly toxic, others inert. The characteristic feature is the yield of glucose or related sugar and another substance which is not a carbohydrate (different from gums, starches, sugars polyoses). They are incompatible with free acids, or ferments, since they are decomposed by these agents. Some are also decomposed by alkalies. Many have ferments associated with them in the plant, which are liberated on crushing, and in a water solution hydrolyse the glucoside.

PENTOSIDES, GALACTOSIDES, ETC.

Some writers restrict the term glucoside to compounds yielding hexose sugars, and designate those yielding pentose sugars, as pentosides, while those that give galactose on hydrolysis are galactosides. This is a refinement in classification that may or may not be advisable. Pentosanes, hexosanes, etc. differ from pentosides and glucosides in being polyoses and not compounds. On hydrolysis pentosanes give pentoses only, hexosanes such as cellulose give hexoses only. Other writers taking a wider view include under glucosides, such polyoses as saccharose, raffinose, and gentianose. This is because their combination is ether-like and, similar chemically to artificial glucosides.

CONSTITUTION OF THE GLUCOSIDES

Chemically, glucosides are ether-like combinations of glucose with alcohols, acids, phenols, etc. (see table of composition). Their constitution is analogous in some respects to acetals or aldehyde alcohols:

$$\text{R.—C} = \begin{array}{|cc|} \hline & \text{H} \mid \text{OCH}_3 \\ \text{O} \quad + \quad & \text{H} \mid \text{OCH}_3 \\ \hline \end{array}$$

Aldehyde   Alcohol

$$\text{R.—C} \begin{array}{c} \text{H} \\ | \\ \end{array} \begin{array}{l} \diagup\text{OCH}_3 \\ \diagdown\text{OCH}_3 \end{array}$$

Acetal.
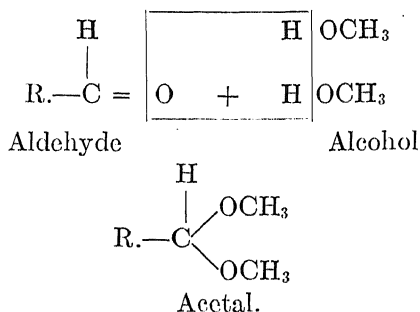
Since they contain no free aldehyde groups they osazones and will not reduce Fehling's solution un-

Some glucosides have been prepared synthetic composition of the synthetic product, gives one an sidic composition in general. The best known synth is the combination of methyl alcohol and glucose. pared by treating a concentrated solution of d. glu alcohol with gaseous hydrochloric acid. Two ison are formed. (1) An alpha, glucoside which is d + 157° and dissolves in 200 parts of alcohol and and beta, glucoside which is levo-rotatory—33° an 67 parts of alcohol and melts at 104°C. They cal by their different solubilities.

The formulas assigned to these different glucosic

a-glucoside   β-glucos
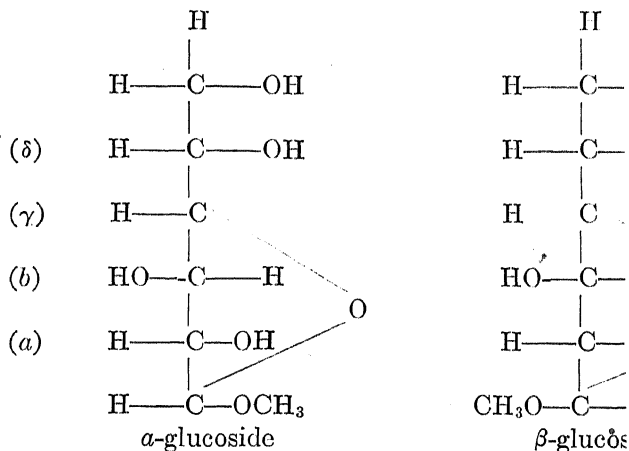
The a, and β glucosides are formed simultaneously, the a, predominating. Equilibrium is established when the mixture contains about 77 per cent. a, and about 23 per cent. of the β isomeride. On standing the β form is slowly converted into the more stable (a) form.

The basis for the assumption of these formulas are:

(I) A single molecule of alcohol reacts with a single molecule of glucose, with the elimination a molecule of water. One of the secondary alcoholic radicals of the sugar must therefore be involved.

(II) These glucosides are readily hydrolysed into their constituents. This indicates that the alcohol radical is joined to the sugar, by means of the oxygen, since if the union were by means of the carbon atoms direct, they would not be so easily hydrolysed. (Compare the action and fate of alcohol and ether in the body.)

(III) The elimination of water is from the $(a$, and $\gamma)$ positions, since other compounds containing $R—CHOH.CO.$ do not yield glucosides. The (a) group does not react therefore, and in favor of the (γ) position is the fact that other such combinations are known; and only combinations containing the (γ) group form glucosides.

From the above, it is seen that there are at least two classes of glucosides, the alpha and the beta. Maltase splits or hydrolyses the a group, while emulsin hydrolyses the β group.

Burquelot's biological method of investigating plants for glucosides, consists in determining the optical rotation and cupric reducing power of extracts before and after incubation with emulsin. A change in these properties indicates the presence of β glucosides, and gives a rough estimate of the amount.

The following table illustrates the hydrolysing action of these enzymes on the different sugars and glucosides.

I.	II.	III.
Invertin	Maltase	Emulsin
Saccharose	Maltose	Aesculin
Raffinose	Methyl-d-glucoside-a	Amygdalin
Gentianose	Ethyl-d-glucoside-a	Androsin
	Benzyl glucoside	Arbutin
	Glycerine glucoside-a	Aucubin
	Amygdalin	Benzyl-glucoside
	Trehalose	Coniferin
	Methyl-d-fructoside	Daphnin
		Dhurrin
		Gentiopicrin
		Glyceryl-glucoside
		synigrin
		Helicin
		Incaratrin
		Indican
		Lactose
		Melatin
		Methyl-d-galactoside β.
		Methyl-d-glucoside δ.
		Oleuropein
		Piccin
		Prunasin
		Prulaurasin

$$
\begin{array}{ll}
 & \text{CH}_2\text{OH} \\
 & | \\
 & \text{H---C---OH} \\
 & | \\
(\gamma) & \text{H---C---O}\boxed{\text{H}} \\
 & | \\
(\beta) & \text{HO---C---H} \\
 & | \\
(a) & \text{H---C---OH} \\
 & | \\
 & \text{C} = \boxed{\text{O}} + \text{H}\,\text{OCH}_3 \\
 & | \qquad \text{Methyl alcohol} \\
 & \text{H} \\
 & \text{Glucose}
\end{array}
$$

$$
\begin{array}{l}
CH_2OH \\
\ | \\
H\!-\!C\!-\!OH \\
\ | \\
H\!-\!C \\
\ | \\
HO\!-\!C\!-\!H \\
\ | \qquad\qquad O + H_2O \\
H\!-\!C\!-\!OH \\
\ | \\
C\!-\!OCH_3 \\
\ | \\
H
\end{array}
$$
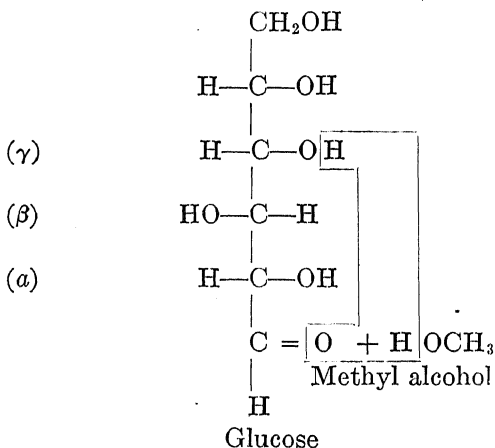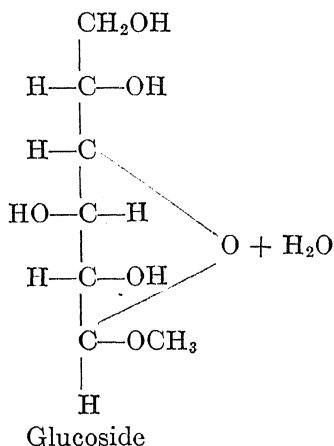
Glucoside

By treatment with methyl-iodide and silver oxide under proper conditions, alpha, and beta pentamethyl glucosides may be prepared with the formula:

$$
\begin{array}{l}
Me.OC\!-\!H \\
\ | \\
H\!-\!COMe \\
\ | \qquad\qquad O \\
Me.OCH \\
\ | \\
HC \\
\\
HCOMe \\
\ | \\
CH_2OMe
\end{array}
$$
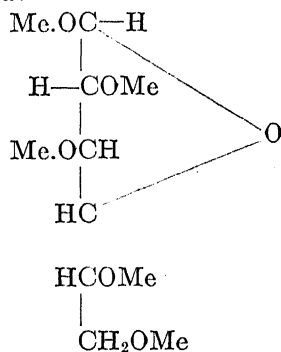
(a) pentamethyl glucoside.

These esters are not acted on by enzymes, but when they are hydrolysed by acids, alpha and beta, tetra-methyl glucosides are formed:

$$
\begin{array}{l}
HO\!-\!C\!-\!H \\
\ | \\
H \quad COMe \qquad O \\
\ | \\
HC \\
\ | \\
H\!-\!COMe \\
\ | \\
CH_2OMe
\end{array}
$$
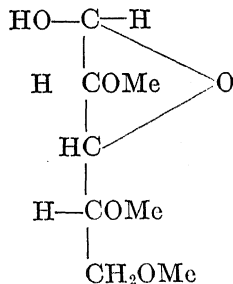
These rapidly change into the same form with constant rotatory power. The alpha tetra methyl glucoside is not fermentable, but the beta form can be hydrolysed by emulsin. This enzyme is especially wide in its action and so far as is known acts only on beta glucosides.

COMPOSITION OF NATURAL GLUCOSIDES

The natural glucosides are generally colorless crystalline solids with bitter taste, and levo-rotatory optical power. All natural glucosides so far isolated are of the beta form. They can all be hydrolysed by acids though some are very resistant. Emulsin will hydrolyse a large number of them. Van Rijn (Die Glucoside) classifies glucosides according to the plants from which they are derived. A complete chemical classification cannot be given, but according to the non-sugar products of hydrolysis, Armstrong (The simple Carbohydrates and Glucosides) gives the following table:

Glucosides		M.p.	Products of hydrolysis
			Phenols
Arbutin............	$C_{12}H_{16}O_7$	187°	Glucose + hydroquinone
Baptisin...........	$C_{26}H_{32}O_{14}$	240°	Rhamnose + baptigenin
Glycyphyllin.......	$C_{21}H_{24}O_9$	175°	Rhamnose + phloretin
Hesperidin.........	$C_{50}H_{60}O_{27}$	251°	Rhamnose + 2 glucose + hesperetin
Iridin.............	$C_{24}H_{26}O_{13}$	208°	Glucose + irigenin
Methyl arbutin.....	$C_{13}H_{18}O_7$	175°	Glucose + hydroquinone methyl ether
Naringin...........		170°	Rhamnose + glucose + narigenin
Phloridzin	$C_{21}H_{24}O_{10}$	170°	Glucose + phloretin
			Alcohols
Coniferin.........	$C_{16}H_{22}O_8$	185°	Glucose + coniferyl alcohol
Populin...........	$C_{20}H_{22}O_8$	180°	Glucose + saligenin + benzoic acid
Salicin...........	$C_{13}H_{18}O_7$	201°	Glucose + saligenin
Syringin..........	$C_{17}H_{24}O_9$	191°	Glucose + syringenin
			Aldehydes
Amygdalin........	$C_{20}H_{27}O_{11}N$	200°	2 Glucose + d-mandelonitrile
Dhurrin..........	$C_{14}H_{17}O_7N$	......	Glucose + p-oxymandelonitrile
Helicin..........	$C_{13}H_{16}O_7$	......	Glucose + salicylaldehyde
Linamarin........	$C_{10}H_{17}O_6N$	141°	Glucose + acetonecyanhydrin
Prulaurasin.......	$C_{14}H_{17}O_6N$	122°	Glucose + racemic mandelonitrile
Prunasin..........	$C_{14}H_{17}O_6N$	147°	Glucose + d-mandelonitrile
Salinigrin........	$C_{13}H_{16}O_7$	195°	Glucose + m-oxybenzaldehyde
Sambunigrin......	$C_{14}H_{17}O_6N$	151°	Glucose + l-mandelonitrile
Vicianin..........	$C_{19}H_{25}O_{10}N$	160°	Glucose + arabinose + d-mandelonitrile

Glucoside		M.p.	Products of hydrolysis
			Acids
Convolvulin........	$C_{54}H_{96}O_{27}$	150°	Glucose + rhodeose + convolvulinolic acid
Gaultherin.........	$C_{14}H_{18}O_8$	100°	Glucose + methylsalicylate
Jalapin............	$C_{44}H_{66}O_{16}$	131°	Glucose + jalapinolic acid
Strophanthin.......	$C_{40}H_{66}O_{19}$	......	Rhamnose + mannose + strophantidin
			Oxycumarin Derivatives
Æsculin	$C_{15}H_{16}O_9$	205°	Glucose + aesculetin
Daphnin...........	$C_{15}H_{16}O_9$	200°	Glucose + daphnetin
Fraxin............	$C_{16}H_{18}O_{10}$	320°	Glucose + fraxetin
Scopolin..........	$C_{22}H_{28}O_{14}$	218°	3 Glucose + scopoletin
Skimmin..........	$C_{15}H_{16}O_8$	210°	Glucose + skimmetin
			Oxyanthraquinone derivatives
Frangulin.........	$C_{21}H_{20}O_9$	228°	Rhamnose + emodin
Polygonin.........	$C_{21}H_{20}O_{10}$	202°	Glucose + emodin
Ruberythric acid...	$C_{26}H_{28}O_{14}$	258°	Glucose + alizarin
			Oxyflavone derivatives
Apiin.............	$C_{26}H_{28}O_{14}$	228°	Apiose + apigenin
Fustin............	$C_{36}H_{26}O_{14}$	218°	Rhamnose + fisetin
Gossypitrin........	$C_{21}H_{20}O_{13}$	......	Glucose + gossypetin
Incarnatrin........	$C_{21}H_{20}O_{12}$	242°	Glucose-quercetin
Isoquercitrin.......	$C_{21}H_{20}O_{12}$	217°	Glucose + quercetin
Lotusin............	$C_{28}H_{31}O_{16}N$	......	2 Glucose + HCN + lotoflavin
Quercimeritrin	$C_{21}H_{20}O_{12}$	247°	Glucose + quercetin
Quercitrin..........	$C_{21}H_{20}O_{11}$	183°	Rhamnose + quercetin
Rutin.............	$C_{27}H_{30}O_{16}$	184°	Glucose + rhamnose + quercetin
Serotin............	$C_{21}H_{20}O_{12}$	245°	Glucose + quercetin
Sophorin...........	$C_{27}H_{30}O_{16}$	......	Rhamnose + glucose + sophoretin
Xanthorhammin ...	$C_{34}H_{42}O_{20}$	......	2 Rhamnose + galactose + rhamnetin
			Mustard oils
Glucropaolin.......	$C_{14}H_{18}O_9NS_2K$	......	Glucose + benzyl isothiocyanate
Sinalbin...........	$C_{30}H_{42}O_{15}N_2 S_2$	138°	Glucose + sinapin acid sulphate + acrinyl isothiocyanate
Sinigrin...........	$C_{10}H_{16}O_9NS_2K$	126°	Glucose + allyl + isothiocyanate + $KHSO_4$
			Various
Aucubin...........	$C_{13}H_{19}O_8$	....	Glucose + aucubigenin
Barbaloin.........	$C_{20}H_{18}O_9$	....	d-arabinose + alocmodin
Calmatambin	$C_{19}H_{28}O_{13}$	144°	Glucose + calmatambetin
Datiscein..........	$C_{21}H_{24}O_{11}$	190°	Rhamnose + datiscetin
Digitalin..........	$C_{35}H_{56}O_{14}$	217°	Glucose + digitalose + digitaligenin
Digitoxin..........	$C_{34}H_{54}O_{11}$	145°	2 Digitoxose + digitoxigenin
Gentiin...........	$C_{25}H_{28}O_{14}$	274°	Glucose + xylose + gentienin
Digitonin..........	$C_{54}H_{92}O_{28}$	225°	Glucose + galactose + digitogenin
Gentiopicrin........	$C_{16}H_{20}O_9$	191°	Glucose + gentiogenin
Gynocardin........	$C_{13}H_{19}O_9N$	162°	Glucose + HCN + $C_6H_8O_4$
Indican...........	$C_{14}H_{17}O_6N$	100°	Glucose + indoxyl
Kampheritrin......	$C_{27}H_{30}O_{14}$	201°	2 Rhamnose + kampherol
Quinovin..........	$C_{30}H_{48}O_8$	....	Quinovose + quinovalic acid
Saponarin..........	$C_{15}H_{14}O_7$	....	Glucose + saponaretin
Saponins...........		....	Glucose + galactose + sapogenins
Vernin............	$C_{10}H_{13}O_5N_5$	....	d-Ribose + guanine

An examination of this table will show that there is little relation between the known chemistry and pharmacological action. As a rule, however, the combination of sugar with another radical increases the action of that radical. This is well illustrated in the action of chloral, which, when combined with glucose to form chloralose, is increased and becomes more like morphine in action. Relatively few glucosides however are used in medicine.

The chief glucosidoclastic enzymes are:

Enzymes	Hydrolyses
Emulsin	Many natural glucosides
	Synthetical β-glucosides
Prunase	Prunasin and many other natural glucosides
Amygdalase	Amygdalin
Gaultherase	Gaultherin
Linase	Linamarin
Myrosin	Sinigrin and sulphur glucosides
Rhamnase	Xanthorhammin

Emulsin from almonds, hydrolyses, æsculin, amygdalin, androsin, arbutin, aucubin, bankankosin, calmatambin, coniferin, daphnin, dhurrin, gentiopicrin, helicin, incarnatrin, indican, melatin, oleuropein, picein, prulaurasin, prunasin, salicin, sambungrin, syningin, taxicatin, verbenalin, etc.

The most important glucosides in medicine are:

Amygdalin
Arbutin
Æsculin
Coniferin
Convallarmarin
Convallarin
Digitalin
Digitoxin
Digitophyllin
Digitalein
Digitonin
Aloin

Helleborein
Jalapin
Phloridzin
Salicin
Saponin
Strophanthin
Scillin
Sinigrin
Sinalbin

Glychyrrhizin was formerly included in this group, but it is not a glucoside.

Another classification, of glucosides based on the chemical groups found in the above is:

1. Ethylene derivatives.
2. Benzene derivatives.
3. Styrolene derivatives.
4. Anthracene derivatives.

The chief representatives of this classification are:

1. **Ethylene Derivatives.**—Sinigrin $C_{10}H_{16}NS_2KO_9 + H_2O$ is the glucoside of black pepper, mustard, horse radish and tropæolum seeds. It is the potassium salt of myronic acid. On hydrolysis it gives allyl mustard oil, dextrose, and potassium bisulphate

$$O—SO_2—OK$$
$$|$$
$$C—S—C_6H_{11}O_5 + H_2O \rightarrow C_6H_{12}O_6 + C_3H_5NCS + KHSO_4$$
$$|$$
$$N—C_3H_5$$
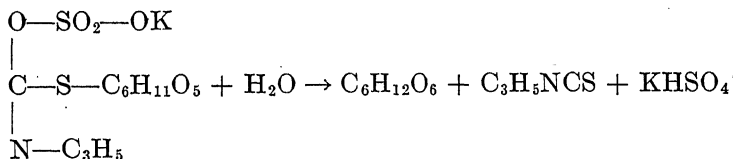
Sinalbin $C_{30}H_{42}N_2S_2O_{15}$, is the corresponding glucoside found in white pepper. On hydrolysis it yields mustard oil, glucose, and sinapin sulphate, which is a compound of choline and sinapinic acid and sulphuric acid:

$$O—SO_2OC_{16}H_{24}O_5$$
$$|$$
$$C—SC_6H_{11}O_5 \qquad + H_2O \rightarrow$$
$$|$$
$$N—CH_2.C_6H_4.OH \qquad\qquad C_7H_7O.NCS$$

Sinalbin   Sinalbin mustard oil

Sinapin   CH : CH − CO.C_2H_4O
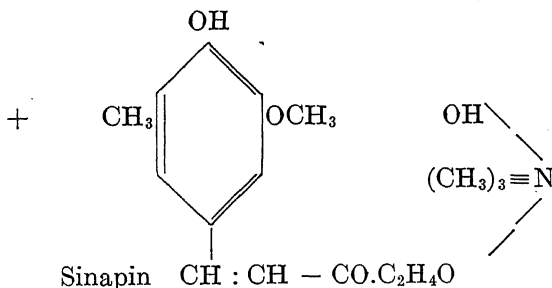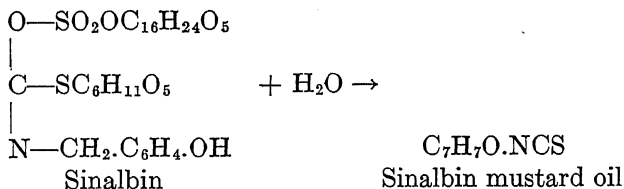
Jalapin $C_{34}H_{56}O_{16}$ is the active principle of scammony, has been assigned the formula

$$\left.\begin{array}{l} CH_3 \\ C_2H_5 \end{array}\right\rangle CH.CHOH.(C_{10}H_{20})COOH$$

Its decompositions are not definitely known.

Jalapin and *Scammonium* are identical. This glucoside is the active principle of scammony (convolvulus scammonia) and Ipomoea orizabensis. It has the empiric formula $C_{34}H_{56}O_{16}$ and when boiled with dilute acids yields Jalapinolic acid and glucose:

$$C_{34}H_{56}O_{16} + H_2O = \left.\begin{array}{l} CH_3 \\ C_2H_5 \end{array}\right\rangle CH.CHOH.(C_{10}H_{20})COOH \\ + 3C_6H_{12}O_6$$
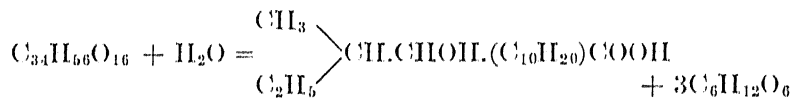
2. Benzene Derivatives.—*Arbutin* $C_{12}H_{16}O_7$ is the glucoside found in bearberry (uva ursi). The leaves are used in medicine and have a diuretic and antiseptic action. The antiseptic action is due to the hydroquinone liberated.

OH
$+ H_2O$
$\longrightarrow$
$O.C_6H_{11}O_5$
Arbutin

OH
$+ C_6H_{12}O_6$
OH
Hydroquinone   Glucose
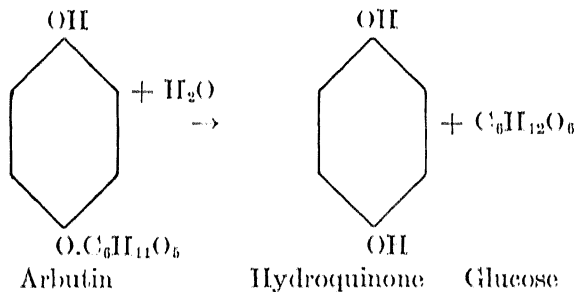
The hydroquinone due to its oxidation imparts a dark color to the urine.

Amygdalin is one of the best known glucosides and is found in bitter almond. After hydrolysis with dilute acids, or ferments, the presence of glucose may be shown with Fehling's solution.

Benzaldehyde may be detected by its odor. The presence of HCN may be shown by its precipitate with $AgNO_3$ or by the Prussian-blue test. When the almond is ground with water, at a temperature below 45°C. the enzyme emulsion contained in the almond will hydrolyse the glucoside;

$$C_{20}H_{27}NO_{11} + 2H_2O = 2C_6H_{12}O_6 + C_6H_5C\diagdown\overset{O}{\underset{H}{}} + HCN$$

Amygdalin   Benzaldehyde.
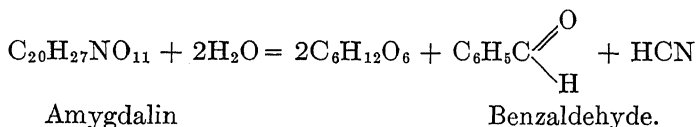
The physiological action of the drug is due mainly to the HCN, that is liberated in the intestine. Amygdalin is thought to be a derivative of the nitrile of mandelic acid:

$$C_6H_5CH\diagup\diagdown\overset{CN}{\underset{O}{}}C_{12}H_{21}O_{10}$$
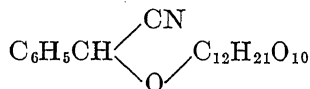
Mandelic acid (Phenylglycollic acid) $C_6H_5CH(OH)COOH$ may be obtained by boiling amygdalin with HCl. It may also be prepared from benzaldehyde by treatment with HCN and hydrolysing the resulting hydroxycyanide:

$$C_6H_5CHO + HCN = C_6H_5CH(OH)CN$$
$$C_6H_5CH(OH)CN + 2H_2O = C_6H_5CH(OH)COOH + NH_3$$
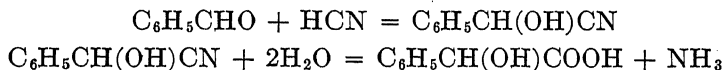
Salicin $C_{13}H_{18}O_7$ is the glucoside of Willow bark. On hydrolysis, it yields glucose and saligenin.

$$C_{13}H_{18}O_7 + H_2O = C_6H_4\diagup\diagdown\overset{OH \quad (1)}{\underset{CH_2OH \quad (2)}{}} + C_6H_{12}O_6$$
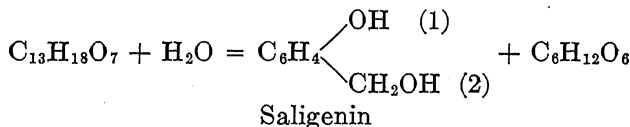
Saligenin

Saligenin is the alcohol corresponding to salicylic acid and on oxidation will yield salicylic aldehyde and salicylic acid.

13

1. Styrolene Derivatives.—This group contains phenylen-ethylene or styrolene $C_6H_5CH:CH$. Strophanthin and phloridzin are the most important representatives.

Phloridzin $C_{21}H_{24}O_{10}.2H_2O$, is a glucoside prepared from the root bark of the apple, pear, plum, cherry, and various other members of the rosaceæ. It is much used in experimental work and its most pronounced action is the production of glycosuria, with a simultaneous hypoglycæmia. It is decomposed by dilute acids into a glucose and phloretin:

$$C_{21}H_{24}O_{10}2H_2O \rightarrow C_{15}H_{14}O_5 + C_6H_{12}O_6$$
$$\text{Phloretin} \quad \text{Glucose}$$
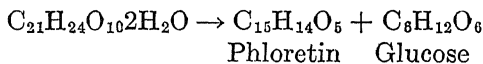
Phloretin has the following formula:
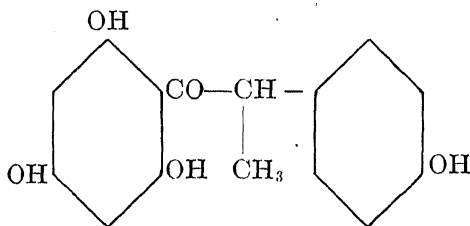
On decomposition, phloretin yields phloroglucin and phloretinic acid:
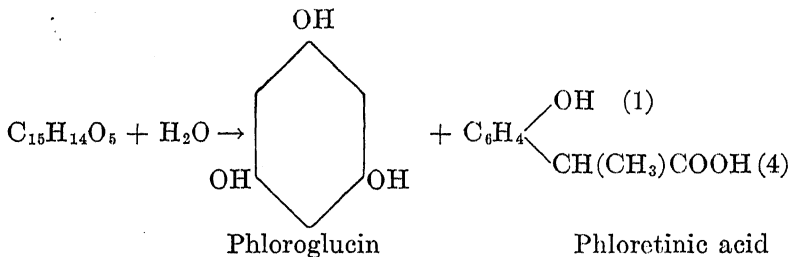
Strophanthin.—Several substances have been described under this term. Strophanthinum or amorphous strophanthin is prepared from strophanthus hispidus and Kombé. Ouabain

from strophanthus gratus, known also as g. strophanthin-crystalline, is considered a purer product than the amorphous forms. The formula $C_{30}H_{46}O_{12}9H_2O$ has been assigned to it.

Arnand, Kohn, and Kulisch isolated a substance from strophanthus Kombé, which gave the formula $C_{31}H_{48}O_{12}$ which on hydrolysis yielded strophanthidin $C_{19}H_{28}O_4$ and a mixture of sugars.

4. **Anthracene or Anthraquinone Derivatives.**—Many of the anthracene purgatives principles belong in this group. Emodin and chrysophanic acid occur as glucosides or rhamnosides. Digitoxin, saponin, and strophanthin may be placed here also, as in the previous group but the chemistry of these bodies is so indefinite.that a final classification cannot be made.

Chrysophanic acid or dioxy methylanthra-quinon
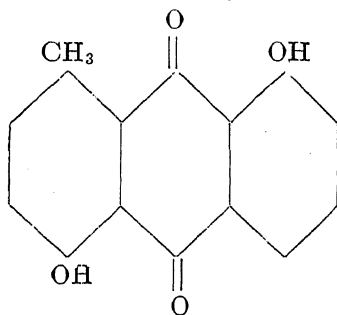
and Emodin or trioxy methyl anthraquinone
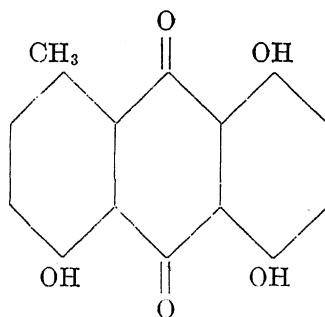
occur in rhubarb, frangula, senna, aloes, etc. The purgative property of these bodies has been attributed to the anthracene group, to the ketone or quinone groups, and to various side chains. Various synthetic bodies of this class have been prepared

commencing with aloin. These are not so efficient as purgatives, as the natural products, because they are too rapidly hydrolysed and absorbed from the intestine. Drugs used for their direct action in the intestine should not be rapidly absorbed. It is by reason of delayed absorption that opium is more efficient in depressing movements of the intestine than morphine.

SAPONIN OR SAPONINS

The term saponin was originally restricted to the specific substance obtained from the root of saponaria rubra and S. alba. The term now includes a series of glucosides of which the empirical formula alone is known. They correspond to the general formula $C_8H_2N_8O_{10}$, and are found in many plants as saponaria officinalis, senega, quillaja, digitalis, sarsaparilla, etc. That isolated from saponaria officinalis has the formula $C_{19}H_{30}O_{10}$. On hydrolysis, it yields sapogenin, $C_{14}H_{22}O_2$. Solutions of saponins foam and become soap-like on shaking. When injected intravenously, they cause laking of the blood. Some are very toxic and are classified as sapotoxins. Fish are very sensitive to saponins. One part of saponin in 100,000 of water will kill fish, but this does not render them unfit for food, since saponin in this concentration has no action in the gastro-intestinal tract.

THE DIGITALIS GLUCOSIDES

The chemistry of these is not definitely known, and in addition to the indefiniteness of the chemistry, the nomenclature is confusing. The principles isolated are probably only approximately pure. Schmiedeberg and Kiliani have done the principal work on this subject, but the field has just been touched.

Digitoxin is the most important glucoside. According to Kiliani, it has the empiric formula $C_{34}H_{54}O_{11}$. On hydrolysis, digotoxin yields digitoxose and digitoxigenin. Digitoxose.

$$C_{34}H_{54}O_{11} + H_2O = 2C_6H_{12}O_4 + C_{22}H_{32}O_4$$
$$\text{Digitoxose} \qquad \text{Digitoxigenin}$$
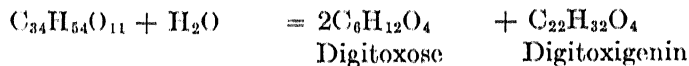
crystallizes in crystals and plates, M.P. 102°C. and is of dextro-rotatory constitution.

Digitalin, $C_{35}H_{56}O_{14}$ or $C_{36}H_{56}O_{14}$, according to Kiliani hydrolysis into digitalose, digitaligenin, and dextrose:

$$C_{35}H_{56}O_{14} = C_6H_{12}O_6 + \quad C_7H_{14}O_5 \quad + C_{22}H_{30}O_3$$
$$\text{dextrose} \qquad \text{digitalose} \qquad \text{digitaligenin}$$
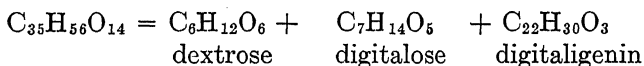
Digitonin, $C_{55}H_{94}O_{28}$ or $C_{54}H_{92}O_{28}$. This is a saponin, soluble in alcohol from which it crystallizes in fine needles m.p. 235°C. On hydrolyses:

$$C_{55}H_{94}O_{28}2H_2O = C_{31}H_{50}O_6 + 2C_6H_{12}O_6 + 2C_6H_{12}O_6$$
$$\text{digitonin} \qquad \text{digitogenin} \quad \text{dextrose} \quad \text{galactose}$$
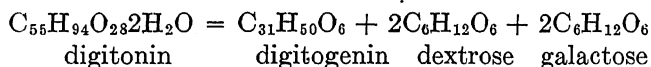
The commercial digitalins are impure and variable mixtures of digitalis principles.

Convallamarin, $C_{23}H_{44}O_{12}$, and convallarin, $C_{34}H_{62}O_{11}$, are two glucosides occurring in convallaria majalis (lily-of-the-valley). Convallamarin is soluble in water and alcohol, insoluble in ether and chloroform, is an acrid glucoside, soluble in water, sparingly soluble in alcohol, and insoluble in ether and is a saponin-like glucoside. Little is known of the split products of these glucosides.

Digitalein, $C_{22}H_{38}O_9$, was supposed by Schmiedeberg to be a pure product but is not now considered a chemical entity. The same is true of digitophyllin.

Glycyrrhizin, $C_{44}H_{63}NO_{18}$, is the sweet principle of licorice root. It occurs as the ammonium salt of glycyrrhizic acid, $C_{44}H_{62}(NH)_4NO_{18}$, and on hydrolysis it yields glycyrrhetin, $C_{32}H_{47}NO_4$, and para saccharic acid, $C_6H_{10}O_8$.

This acid reduces Fehling's solution and for this reason glycyrrhizin was formerly thought to be a glucoside.

Scillin, from squill, is a mixture of glucosides, the chemistry of which is unknown.

Helleborin, $C_{36}H_{42}O_6$, is found in black hellebore. On hydrolysis it gives helleboresin, $C_{30}H_{38}O_4$, and sugar. Helleborein, $C_{26}H_{44}O_{15}$, is another glucoside obtained from the same source. On hydrolysis it yields helleboretin, $C_{14}H_{20}O_3$, and sugar.

CYANOGENETIC GLUCOSIDES

The cyanogenetic glucosides yield hydrocyanic acid on hydrolysis. They are of interest chiefly because they are considered as the connecting link between the carbohydrates and the alkaloids and other nitrogen containing compounds. Their composition differs in different plants. Hydrocyanic acid occurs in many plants sometimes in the free state but mostly in combination. The nature of many of the compounds is unknown. Many are in the form of glucosides and it seems that this is the general condition of hydrocyanic acid in the plant. However, nitrogen may occur in glucosides in other forms. The cyanogenetic glucosides occurs chiefly in the buds, seeds, leaves, and bark.

With regard to the formation of hydrocyanic in the plant nothing is definitely known. Gautier supposes that it may be due to the reduction of nitrates by formaldehyde.

The chief cyanogenetic glucosides are:

Amygdalin   Dhurrin
Amygdonitrile   (Prunasin)
Sambunigrin   Gynocardin and
Prulaurasin   Vicianin
Phaseolunatin
Lotusin

SOLANIN

Solanin is an alkaloidal glucoside found in all parts of the potato plant. Its composition is not definitely known. In its action it resembles the saponins and is a general protoplasm poison killing bacteria and hemolyzing red cells in extreme dilutions. Its salts are amorphous and gummy. It is not affected by alkalies but acids decompose it into solanidin and a mixture of sugars including dextrose, rhamnose and galactose. It dissolves in nitric acid with a yellow color, slowly changing to red. It gives a green tint with sulphuric acid in alcohol and a red color with a mixture of sulphuric acid and sodium sulphate.

CONIFERIN

$C_{16}H_{22}O_8$. This glucoside occurs in various coniferous trees and in asparagus. On hydrolysis with mineral acids or emulsin it yields glucose and coniferyl alcohol.
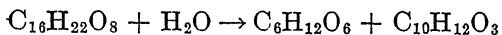
$$C_{16}H_{22}O_8 + H_2O \rightarrow C_6H_{12}O_6 + C_{10}H_{12}O_3$$
<div align="right">Coniferyl alcohol.</div>

When coniferyl alcohol is oxidized with potassium bichromate and sulphuric acid it yields vanillin. Artificial vanillin was formerly prepared by this method. It is now prepared by the oxidation of isoeugenol, which in turn is prepared by boiling eugenol, the chief constituent of oil of cloves. The relationship is shown by the formulas:

Coniferyl alcohol.   Vanillin   Iso-eugenol

Eugenol
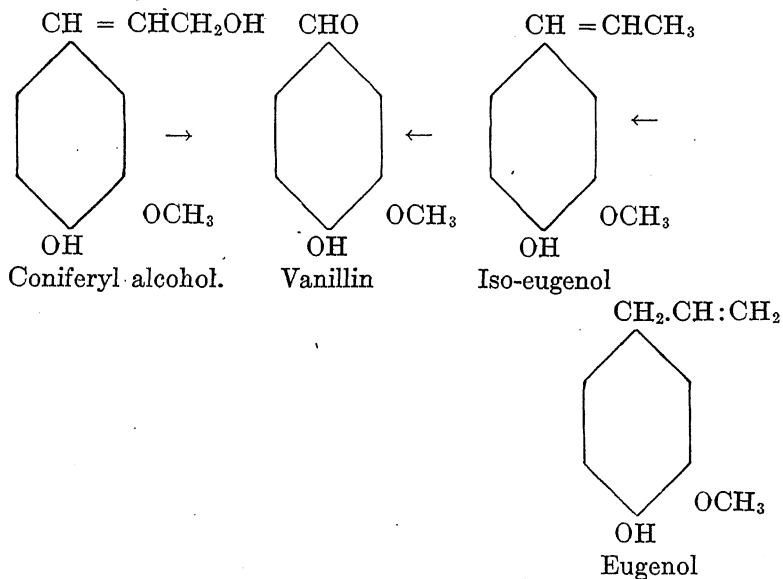
INDICAN

This glucoside occurs in a number of plants, especially indigo fera anil, I. sumatrana, and I. arrecta. It is decomposed on hydrolysis into indoxyl and glucose as follows:

$$C_7H_6NC.O.C_6H_{11}O_5 \rightarrow H_2O$$
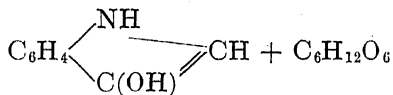
Indoxyl

The dye indigo, is formed from indoxyl by oxidation as follows:
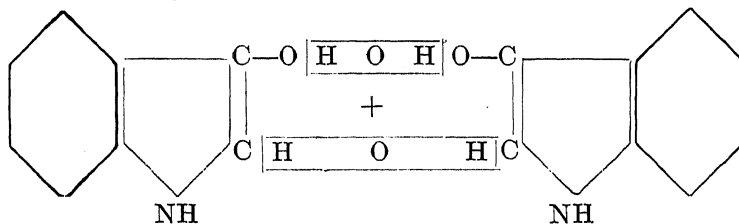
2 Indoxyl
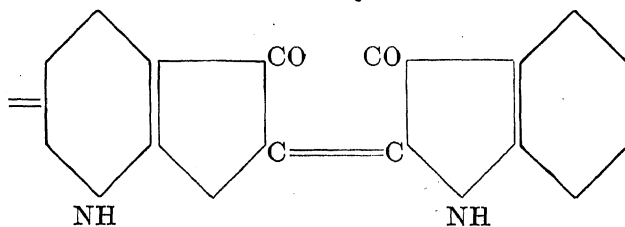
Indigo blue
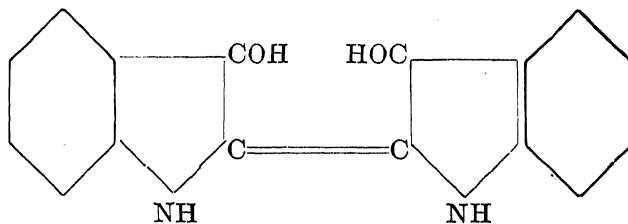
Indigo white

The name indican is also applied to a compound of the formula:
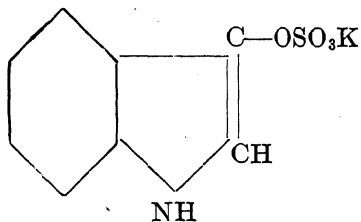
which occurs in the urine in cases of intestinal putrefaction, and is derived from tryptophane, in a manner not yet understood. The relationship is shown by the formula:

Tryptophane

Indole   Indoxyl
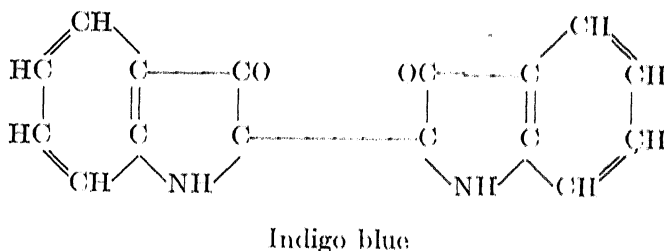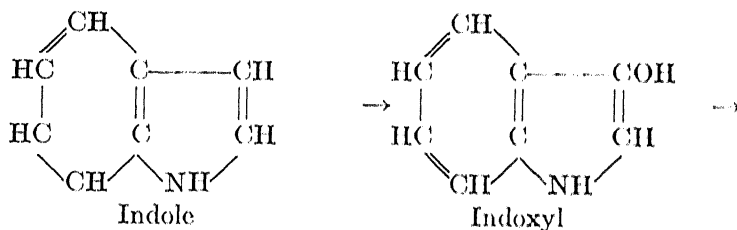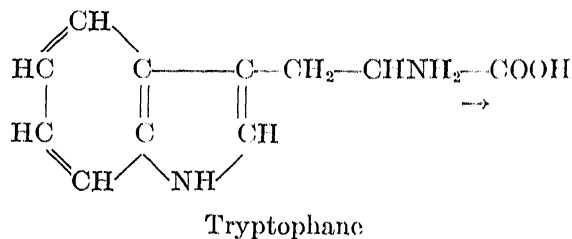
Indigo blue

The indigo blue in this case is the same as derived from glucoside indican. It is now produced synthetically.

ANIMAL GLUCOSIDES

Glucoside like combinations are found in the animal organism. The importance of these is not well understood. The term glucoside itself it must be remembered is not strictly defined. Thierfelder isolated a glucoside like substance from the human brain

which he called cerebron, a galactoside. On hydrolysis this yielded cerebronic acid, sphingosine and galactose:

$$C_{48}H_{93}NO_9 \quad 2H_2O \rightarrow C_{25}H_{50}O_3 +$$
Cerebron   Cerebronic acid.
$$C_{17}H_{35}NO_2 + C_6H_{12}O_6$$
Sphingosin   Galactose.
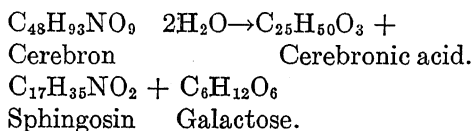
Cerebron appears to be a mixture of two glucosidic bodies which have been named Phrenosin (Phren. brain) and kerasin. Phrenosin yields, sphingosin and galactose kerasin resembles phrenosin, the differences being mainly that kerasin contains lignoceric acid $C_{24}H_{48}O_2$ instead of cerebronic. The chemistry of all these bodies is far from complete. Some of the nucleic acids contain pentosides, and perhaps other glucosides occur in the brain substance. The importance of these in the animal economy for the present cannot be evaluated. That they are very important can be readily seen when we consider the importance of the nucleins to the life of the cell, and the importance of the brain tissue in anesthesia, and other drug action, and to life generally.

THE FUNCTIONS, ACTION, AND FATE OF GLUCOSIDES

The physiological importance of glucosides is not definitely known. They appear again and again in plants under similar conditions and it would seem that like the carbohydrates, they are associated with the metabolism of the plant. As a rule they are found in greatest amount where metabolism is most active as in leaves and shoots. Since the time of the maximum amount of glucosides in plants varies in different plants, their function in the different plants may also vary. They may be of value as food stuffs or as reserve food stuffs. Glucosides as a rule are hydrolysed readily in the upper part of the alimentary tract. In the case of the digitalis glucosides none reach the large bowel unchanged. After large doses some of the glucoside has been found in the liver but not in other organs. The principles have been found in the urine and fæces, so that both kidney and gut

take part in the excretion. The hydrolysed products are active ingredients, though the sugar moiety increases the action. Just how much of the active part is oxidized in the body is unknown.

The galactoside of the brain is interesting in view of the fact that all lecithins of vegetable origin are in glucosidic combination. Galactose, glucose, and pectose, have been identified in these lecithin glucosides of plants.

Tests for Glucosides

1. Test a 1 per cent. solution of salicin or amygdalin with Fehling's solution.

2. Acidify another portion of the glucoside with H_2SO_4, boil for 5 minutes, make neutral or slightly alkaline with NaOH or KOH, and apply Fehling's.

3. To another portion add some saliva and keep at body temperature for 15 minutes, then test for sugar.

4. Pulverize some bitter almonds in a mortar. Note the odor of the dry powder. Divide into two parts. Mix one part with water at 40°C., and set aside for 15 minutes. Boil the other portion for 5 minutes by adding the boiling water directly to it, and continuing the boiling. Test both solutions for HCN as follows: Filter make alkaline with a few drops of KOH, and add a few drops of freshly prepared ferrous sulphate solution. After allowing it to stand for 4 minutes acidify with HCl. A Prussian blue color indicates the presence of HCN. See reaction for N under alkaloids. Difference between the boiled and the unboiled portions? Bitter almonds contain a ferment-emulsin.

5. To 5 cc. of the fluid extract of licorice, add just enough 1 per cent. Na_2CO_3 to make alkaline. Acidify another 5 cc. with H_2SO_4. Compare the taste of the two solutions. Acids are incompatible with glycyrrhiza.

6. Digitalin: Use only a trace of the dry substance in making the tests. (a) The solution in H_2SO_4 is yellow. This turns blood red or violet on adding a drop of HNO_3 or Fe_2Cl_6. (b) Dissolve a trace of the dry substance in a test tube. Add a mere trace of Fe_2Cl_6 with a glass rod. Add an equal volume of conc. H_2SO_4 without mixing. If digitalin is present there is a persistent carmine zone at the point of contact. (c) Place

a small piece of the dry substance on a white plate. Add a drop of Fe_2Cl_6 and conc. H_2SO_4 without mixing. A carmine or violet zone which changes to indigo results (Kiliani). (d) Physiologic test. This must be taken into consideration with the above. The slowing and systolic standstill of the frog's heart is characteristic.

7. To a portion of a glucosidal solution add 2 cc. of saliva. Keep it at 40°C. for 15 minutes and test for sugar as in 2.

8. Guignard's test for cyanogenetic glucosides. Strips of filter paper are dipped in 1 per cent. picric acid solution and dried; they are now moistened with 10 per cent. solution of Na_2CO_3 and again dried. In the fumes of HCN, these papers turn red due to the formation of potassium isopurpurate. If these papers be suspended over a solution containing HCN they become red gradually. The rate depending on the amount of acid present. Hydrogen sulphide gives this same reaction due to the formation of picraminic acid, and sugar heated in a solution of alkaline picric acid also gives the red color.

XXII. BITTER PRINCIPLES

Bitters have nothing in common except their bitter taste, and cannot be classified chemically. All distinctly bitter extractives other than alkaloids, glucosides, and neutral principles that are not toxic, are included under the term bitters. The neutral principles differ from the bitters only in their higher activity and toxicity.

Tests to Distinguish Bitters from Other Bodies

1. They are not precipitated by alkaloidal reagents—different from alkaloids.

2. They do not yield sugar on hydrolysis—different from glucosides.

3. Bitters are physiologically rather inert—different from neutral principles and alkaloids.

Pharmacologic Classification.—Bitters may be conveniently placed under four heads:

I. *Simple Bitters.*—These are practically free from tannin and aromatic oils, and include gentian, quassia, calumba, taraxacum, chirata, pareira, and calendula. The fluid extract and tincture are the most important preparations.

II. *Astringent Bitters.*—These contain tannin, which makes them astringent. Serpentaria, cimicifuga, condurango, and cascarilla are the chief representatives of this class.

III. *Aromatic Bitters.*—These contain more volatile oil than the other classes, and less tannin than the astringent group. The principal representatives are calamus, aurantii amara cortex, anthemis, serpentaria, and prunus virginiana.

IV. *Compound Bitters.*—These are mixtures of simple bitters. Blending is said to improve their action. Tinctura gentina composita, elixir aromaticum, tincture amara, and vinum aurantii compositum belong to this class.

XXIII. PHARMACOLOGY OF THE TASTE AND SMELL

The nerves which mediate taste and smell are the first or *Olfactory* (L. Oleo—smell; facio—to make) and the ninth or *glossopharyngeal.*

Kant defined smell as taste at a distance, taste and smell being related. The olfactory is a nerve of special sensation and hard to investigate because its receptive surfaces are intimately associated with those of the 5th nerve—a nerve of common sensation. For this reason true smells, or those substances which stimulate the olfactory only, are hard to separate from pungent substances like vinegar which also stimulates the 5th nerve.

For the correlation of odor and structure we are indebted mainly to Georg Cohn (Die Reichstoffe, 1904) and Zwaardemaker (Physiologie des Geruchs, 1895).

Zwaardemaker separates pure odors into nine classes which have been arranged by Howell (Text Book of Physiology) as follows:

1. Odores ætherei or ethereal odors, such as are given by the fruits, which depend upon the presence of ethereal substances or esters.

2. Odores aromatici or aromatic odors, which are typified by

camphor and citron, bitter almond and the resinous bodies. This class is divided into five subgroups.

3. Odores fragrantes, the fragrant or balsamic odors, comprising the various flower odors or perfumes. The class falls into three subgroups.

4. Odores ambrosiaci, the ambrosial odors, typified by amber and musk. This odor is present in the flesh, blood, or excrement of some animals, being referable in the last instance to the bile.

5. Odores alliacei or garlic odors, such as are found in the onion, garlic, sulphur, selenium and tellurium compounds. These fall into three subgroups.

6. Odores empyreumatici or the burning odors, the odors given by roasted coffee, baked bread, tobacco smoke, etc. The odors of benzene, phenol, and the products of dry distillation of wood come under this class.

7. Odores hircini or goat odors. The odor of this animal arises from the caproic and caprylic acid contained in the sweat. Cheese, sweat, spermatic and vaginal secretions give odors of similar quality.

8. Odores tetri or repulsive odors, such as are given by many of the narcotic plants and acanthus.

9. Odores nauseosi or nauseating or fetid odors, such as are given by feces, by certain plants and the products of putrefaction.

Beaunis classified all substances which affect the olfactory mucous membranes into three groups (Stewart, Text Book of Physiology), as follows:

1. Those which act only on the olfactory nerves: (*a*) Pure scents or perfumes, without pungency. (*b*) Odors with a certain pungency—*e.g.*, menthol.

2. Substances which act at the same time on olfactory nerves, and on nerves of common sensation (tactile nerves)—*e.g.*, acetic acid.

3. Substances which act only on the nerves of common sensation (tactile nerves)—*e.g.* carbon dioxide.

Haller divided odors into:

   1. Ambrosial or agreeable,

   2. Fetid or disagreeable,

   3. Mixed.

. in every day life the division is usually made into:

Pleasant, or agreeable.

Disgusting, or disagreeable.

CHEMISTRY AND PHYSICS OF ODORS

ʻas formerly believed that before a substance is recognized ʼriferous, particles must reach the olfactory nerve through r. However, odor may be detected when substances are ʼved in saline, or in the pharmaceutic waters, and taken into ʼstrils.

ʼ concentration of the substances in the liquid is of some tance, since cumarin, vanillin, oil of rose, etc., and other ʼnces have different odors in strong and dilute solutions.

ctically, however, volatility is the most essential condition ʼoduction of an odor. Since volatilty is mainly dependent ʼolecular weight, chemistry plays an important part. In ʼcal compounds, it has been found that certain groups or ʼls give rise to rather distinctive odors. These groups are . the osmophore groups (osmo—odor; phero—to bear).

ʼo or more osmophore groups may occur in the same sub- ʼe. Investigation of these groups has not gone far enough ʼssify odoriferous bodies on their chemical groupings. The ʼying influence of associated groups is not yet understood. ʼoxyl, aldehyde, ketone, nitrile, nitro and azoimide groups ʼll osmophoric, but may produce pleasant or unpleasant ʼ, and prediction as to the result is very uncertain. How-ʼcertain facts are established:

ʼ. Homologous derivatives usually have a similar odor.

ʼ. Phenols have characteristic odors.

ʼ. The odor of alcohols is usually pleasant.

ʼ. Unsaturated substances, which are usually chemically ʼive, generally have powerful odors. Triple linked com-ʼds are usually unpleasant.

ʼ. If an aldehyde has a pleasant odor, reduction alters the ʼ, but does not make it disagreeable.

ʼugs that act centrally may stimulate or depress the sensation ʼhe olfactory nerve; strychnine and caffeine stimulate it, ʼ chloral depresses. Cocaine applied to the nasal mucous

membranes paralyzes the sensation of smell entirely. Marked changes in the nerve may occur in disease and the sensation of smell may be entirely abolished (anosmia). Overstimulation because of the fatigue produced, may also cause this.

Fatigue of the nerve is quite common. Odors soon give no sensation when the stimulation is continued, and unpleasant odors, coal gas, etc., by continued action soon lose their effect.

TASTE

Before a substance can stimulate the taste nerves it must be soluble in the fluids of the mouth. Accordingly as they affect the taste, sapid substances have been classified as follows:

1. Sweet
2. Bitter
3. Acid
4. Saline

Regarding the mechanism by which sapid substances stimulate the gustatory nerve endings we know but little, but the stimulus acts on the end organs and not on the nerve trunks. Nerve trunks in general are not stimulated by any pharmacological agent, unless it be applied directly to them; but a sensation of taste is not developed by direct application to the nerve trunk. Attempts have been made to find a chemical group responsible for taste, but little progress has yet been made. Acids and bases owe their characteristic taste to the H, and alkalies to the OH ions.

Sternberg ascribes the bitter taste of alkaloids to their cyclic constitution, but this assertion will not bear analysis. In the Mendeljef periodic classification of the elements, the sweet tasting elements boron, aluminum, scandium, yttrium, lanthanum are found in the third groups, while lead and cerium are in the fourth. Beryllium, another sweet tasting element, is in the second, while chlorine which often gives rise to sweet compounds is in the seventh.

The bitter elements—magnesium, zinc, cadmium and mercury—are found in the second. Sulphur in the sixth group often gives rise to bitter compounds.

The hydroxyl group has often been associated with a sweet taste. Sternberg (Geschmack and Geruch) has pointed out that in organic compounds, in order to have a sweet taste the alkyl groups must not exceed the OH groups, by more than one, or their combination will be bitter.

Thus Rhamnose: $CH_3(CHOH)_4CHO$ is sweet,

$$CH_3$$
$$(CHOH)_3$$

but methyl rhamnoside CH $\rangle O$ is bitter.

$$CH$$
$$OCH_3$$
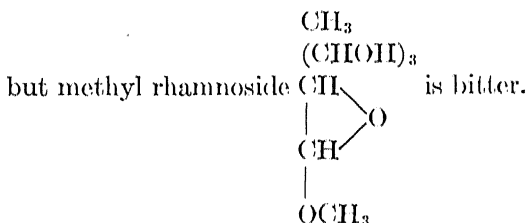
Again, the sweetness in an homologous series increases with the increase of hydroxyl groups, e.g. glycol:

$$CH_2OH$$
$$CH_2OH$$

is sweet, but not so sweet as glycerol:

$$CH_2OH$$
$$CHOH$$
$$CH_2OH$$

and glucose:

$$CH_2OH$$
$$(CHOH)_4$$
$$CHO$$
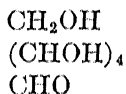
is still sweeter. Most substances with the formula $(CH_2O)n$ are sweet. That other factors than the OH groups enter into the production of a sweet taste is shown by the fact that lead acetate is sweet, yet contains no OH groups; and saccharin, five hundred times sweeter than cane sugar, contains no OH groups. Again the corresponding para compound of saccharin is tastelesss, showing that the architecture of the molecule is perhaps more important than the chemical grouping. It has been suggested that the stimulation of the taste buds is a physical process due to intramolecular vibrations, but we have no way of testing such a suggestion.

Again in those aromatic bodies containing an OH group the position of this in the ring and the relation to other groups is interesting, e.g.:

14
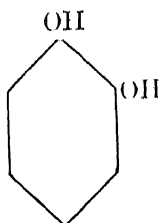
Pyrocatechol
(bitter)
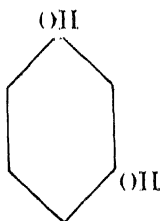
Resorcinol
(sweet)
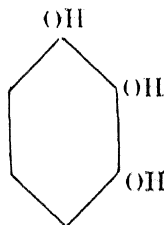
Pyrogallol
(bitter)
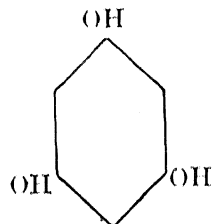
Phloroglucinol
(sweet)
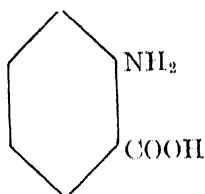
Anthranilic acid
(sweet)
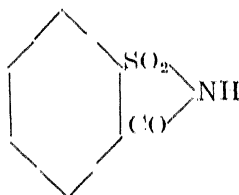
Saccharin
(very sweet)
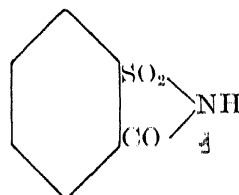
NH_2
Amino saccharin
(very sweet)
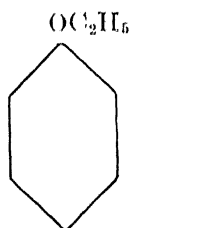
$NH.CO.NH_2$
Para phenetol or
Dulcin (sweet)
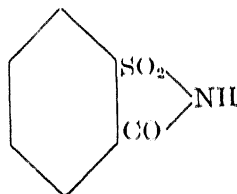
Br
Brom saccharin
(first sweet,
then bitter)
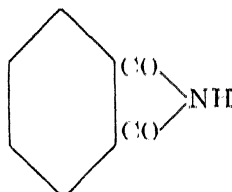
Phthalimide—very similar in com-
position to saccharin—is not
sweet
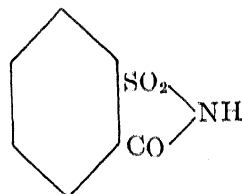
NO_2
Nitro saccharin
(very bitter)

This shows that the arrangement of the molecule is of considerable importance, but we cannot explain taste in relation to structure. Saccharin is an orthocompound; resorcin a meta; and dulcin a paracompound, all of which are sweet. This is further illustrated by the differences in the taste of optical isomers; dextro-asparagin is sweet while levo-asparagin is not; and dextro-glutaminic acid is sweet whereas the levo acid is tasteless.

In a recent study of the chemistry of taste, Oertly and Meyers (Journal of Am. Chem. Society, 1919, vol. 41, p. 855) have worked out a theory relating to the aliphatic sweet stuffs. They think that taste is dependent on two factors, or chemical groups,—a glucophoric and an auxogluc. They define a glucophore as a group of atoms which has the power to form sweet compounds by uniting with a number of otherwise tasteless atoms or radicals. An auxogluc is defined as an atom or radical which combined with any of the glucophores yields a sweet compound. Any glucophore will form a sweet compound with any auxogluc.

The following radicals are found to be glucophores in the sense of their theory:

1. $-CO-CHOH(+H)$,   4. $CH_2OH.CHOH-$,

2. $CO_2H.CHNH_2-$.   5. CH_2ONO_2-

3. $\begin{array}{c} H_3-x \\ C \quad - \\ Hl_x \end{array}$ 6. $\begin{array}{cc} H_3-x & H_2-y \\ C \; - C - \\ Hl_x & Hl_y \end{array}$
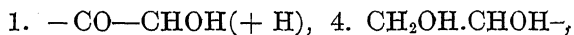
The $(+H)$ in glucophore 1, simply indicates that the group must be united with one hydrogen atom at least, in order to become a glucophore.

In the general formula $\begin{array}{c} H_3-x \\ C \quad - \\ Hl_x \end{array}$ the abbreviation Hl is general for chlorine, bromine, and iodine. Flourine derivatives may be included possibly. The small index (x) refers to the number of halogen atoms in the glucophore. It may vary from one to three, the number of hydrogen atoms in the glucophore meanwhile decreasing from two to zero; e.g., methyl iodide has the glucophore CH_2I-. In this case I limits the abbreviation Hl to a single atom of halogen. The index (x) equals one.

In respect to the hydrogen, the index is 3—x which is equal to two, hence CH_2I—agrees with the general formula. Chloroform has the glucophore—CCl_3 which also agrees with the general formula. The index (y) has the same significance as (x) but varies from one to two.

The following atoms or radicals seem to act as auxoglucs, yielding with glucophores sweet compounds:

(a) H, hydrogen.

(b) The radicals, $C_nH_{2n+1}O$, of saturated hydrocarbons, containing from 1 to 3 carbon atoms. Example CH_3CH_2—

(c) The radicals $C_nH_{2n+1}O$ of monohydric alcohols, n being equal to one or two. Example CH_2OH—

(d) The radicals $C_nH_{2n-1}O_n$ of polyhydric alcohols. Example $CH_2OH.CHOH$—

The following tables indicate more clearly the significance of glucophores and auxoglucs.

TABLE I.—GLUCOPHORE CH_2OH—$CHOH$—

Auxogluc	Name of Compound	Taste
H—..........	Glycol	Sweet
CH_3—	1, 2-Propanediol	Sweetish
CH_3CH_2—.....	1, 2-Butanediol	Sweetish
CH_2OH—.....	Glycerol	Sweet
C_nH_{2n-1}.......	Polyhydric alcohols	All sweet

TABLE II.—GLUCOPHORE, —$CO.CHOH$—H.

H—..........	Glycollic aldehyde	Distinctly sweet
CH_3—	Oxyacetone	Sweet
CH_2OH—.....	Glyceric aldehyde	Sweet and bitter
	monomolecular	Slightly sweet
	bimolecular	Sweet
	Dioxyacetone	Sweet
CH_3CHOH —..	Methyl-glyceric aldehyde, $CH_3(CHOH)_2CHO$	Sweet and bitter
	Methyl-dioxyacetone	Sweetish
$C_nH_{2n-1}O_n$	Sugars, e.g. hexoses	Sweet

Table III.—Glucophore, CO_2H—$CHNH_2$

Auxogluc	Name	Taste
H—..........	Amino-acetic acid	Sweet
CH_3—........	dl-a-Amino-propionic acid	Sweet
CH_3CH_2—....	dl-a-Amino-butyric acid	Sweet
$CH_3(CH_2)_2$—	dl-a-Amino-n-valeric acid	Sweet
CH_2OH—......	dl-Serine, a–amino–β–hy-droxy propionic acid	Sweet
CH_3CHOH— .	dl-a-Amino-β-hydroxy-bu-tyric acid	Sweet
$C_nH_{2n-1}O_n$— ..	d-Glucosaminic acid	Agreeably sweet

Table IV.—Glucophore CH_2ONO_2—

CH_3	Ethyl nitrate	Sweet
$CH_3(CH_2)_{2n}$—..	Butyl nitrate	Sweet
$(CH_3)_2CH$— ..	Isobutyl nitrate	Sweet
$(CH_3)_2CHCH_2$—	Isoamyl nitrate	Sweetish
CH_2OH—	Glycol mononitrate	Sweet

Table V. Glucophore $C\begin{smallmatrix}H_{3-x}\\ \\ Hl_x\end{smallmatrix}$

H	Methyl chloride	Sweetish
	Methylene chloride	Sweetish
	Chloroform	Sweet
	Bromoform	Sweetish
	Iodoform	Sweetish
CH_3..........	Ethyl chloride	Sweetish
	Ethyl bromide	Burning
CH_2OH	Ethylene chloro hydrine	Sweet

$$\text{TABLE VI—GLUCOPHORE C}\quad\begin{matrix}H_{3-x} & N_{2-x} \\ - C - \\ Hl_x & Hl_y\end{matrix}$$

H—..........	Ethylene chloride	Sweetish
	Ethylene bromide	Sweetish
	Ethylene chloro-iodide	Sweet
CH_3—........	2-Chloro-i-iodopropane	Sweet
CH_2OH—.....	2, 3-Dichloro-i-hydroxy—	
	propane	Burning spicy
	2, Chloro-3-bromo-	
	propanei-ol	Sweet

XXIV. TANNIC, DIGALLIC ACID, OR GALLOTANIC ACID

$C_{14}H_{10}O_{29}$, or

occurs in large quantities
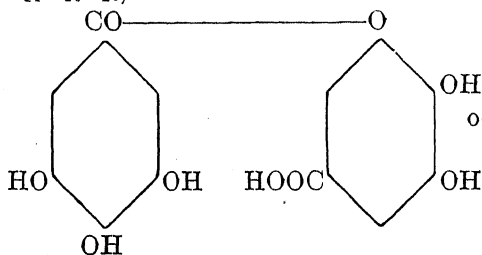
in gall nuts and in all kinds of bark, especially oak. It is the active constituent of all vegetable astringents. Its pharmacologic action is the same as that of metallic astringents and is due to a union with, and precipitation of, proteins. Tannic acid is soluble in water, alcohol, or ether. When boiled with H_2SO_4 it is completely converted into two molecules of gallic acid which shows that it is a gallic acid anhydride,

$$C_{14}H_{10}O_9 + H_2O \rightarrow 2$$
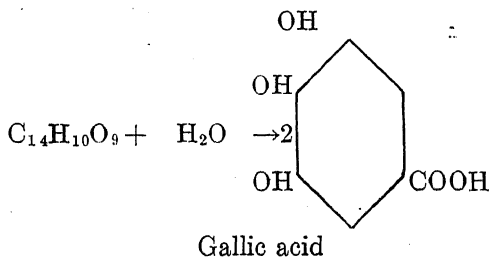
Gallic acid

though it is not known which OH group unites with the carboxyl in the synthesis. All tannins, tannic acid, and gallic acid are reducing agents, and because of this it was formerly thought that they were all glucosides. It is now known that not all of them are *e.g.* pure tannic acid. Ordinary tannin, is impure tannic acid and on hydrolysis yields 7–8 per cent. of glucose. The composition varies, in some, tannins having been found to be the penta digallic ester of glucose.

$$
\begin{array}{l}
\text{CH}_2\text{—t} \\
| \\
\text{CHO—t} \\
| \\
\text{CH} \\
| \\
\text{O} \Big< \begin{array}{l} \text{CHO—t} \\ \text{CHO—t} \\ \text{CHO} \end{array}
\end{array}
\qquad \text{``t'' represents tannic acid.}
$$
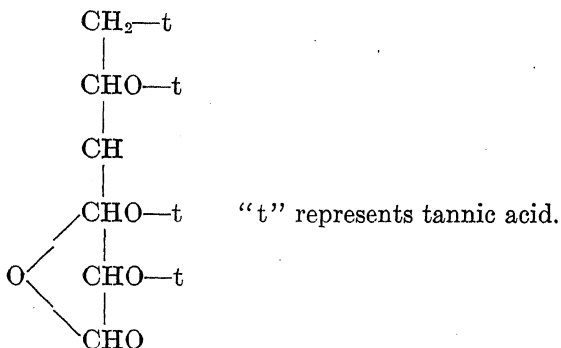
The composition of many tannins has not been determined.

Tannic acid unites with albumin and is an alkaloidal reagent, while gallic acid is not. Animal skins properly treated with it are tanned. Tinctures were formerly detannated by shaking with finely ground animal hides, but this method has been given up. Tannin forms inks with iron salts, and for this reason, tannins and iron salts are incompatible. According to the color of the ink so formed, tannins have been divided into two classes, first—the pyrogallol class, which gives a dark blue color, and second—the catechol class which gives a greenish color.

Tannins differ in the tendency to unite with proteins. A decoction of tea is a much more efficient precipitant than a similar decoction of coffee.

On heating gallic acid CO_2 is given off and pyrogallol formed.—

Gallic acid   Pyrogallol
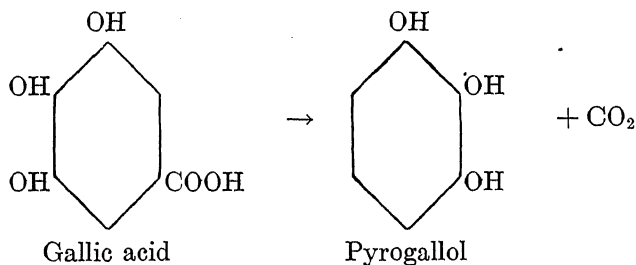
All tannins absorb oxygen readily, but pyrogallol does so to a much greater extent.

Tannic acid is used in medicine for its astringent properties: externally in cases of local sweating or weeping ulcers, and to harden the skin. Lead, zinc, and alum salts are used for the same purpose. In inflammations of the throat, it is used in lozenge form as an astringent. In cases of diarrhœa it is used in the form of tinctures of Kino, Krameria, Gambir, Catechu, etc. Its action in these cases is due to a combination with the material in the gut and also to a similar action on the gut wall, which it protects. It is used as an antidote in cases of poisoning with alkaloids and heavy metals with which it combines. In such cases the precipitated material must be removed or the combination is digested in the body and the action of the alkaloid is only delayed and not avoided. This delay however may prevent an action by the drug, since such delay may enable the body to oxidize or excrete it as fast as it is absorbed. In some individuals, with an idiosyncrasy, tannic acid induces local irritation and inflammation.

FATE IN THE BODY

When tannic acid is taken internally most of it, in some cases all, is oxidized. Traces may be excreted in the urine, and feces. It does not exist in the tissues as such but as the gallate or tannate of sodium. These are devoid of astringent effects. According to Harnack, pyrogallol is sometimes formed from gallic acid in the urine.

Tests for Tannin

1. Test the solubility of tannic acid in water, alcohol, ether, chloroform. Repeat with gallic acid.

2. Add a solution of ferric chloride to tannic acid. Lead acetate added to tannic acid produces a white precipitate; if NaOH is added to this and the mixture shaken, a pink color is formed.

3. Add tannic acid to a solution of albumin (a) excess albumin; (b) excess tannic acid; (c) potassium hydroxide. Repeat with gallic acid.

4. Neutralize a solution of tannic acid with KOH solution. Add to this neutral solution albumin and compare the result with that obtained in 3.

5. Add tannic acid to a solution of 1 per cent. quinine bisulphate. Repeat with 0.1 per cent. strychnine sulphate.

6. To a 1 per cent. solution of gallic acid add a few drops of 1 per cent. KCN, and there will appear a red color which soon fades but reappears on shaking (Young's test). Pure tannic acid does not give this reaction.

7. Boil 1 gm. tannin 15 minutes with 10 cc. of 5 per cent. H_2SO_4. Neutralize and apply Fehling's test. What is the result? Meaning?

8. Permanganate solutions oxidize tannic acid. To 5 cc. tannic acid solution add drop by drop $KMnO_4$ and note results. This fact is used in the quantitative determination of tannin. This is illustrated in the following method—Procter's Modification of Löwenthals—for the determination of tannin in tea.

(A) Preparation of Reagents

1. Potassium permanganate. Make up a solution containing 1.33 grams per liter.

2. Tenth-normal oxalic acid. Make up a solution containing 6.3 grams per liter.

3. Indigo carmine. Make up a solution containing 6 grams of indigo carmine (free from indigo blue) and 50 cc. of concentrated sulphuric acid per liter.

4. Gelatin solution. Prepare by soaking 25 grams of gelatin for one hour in a saturated sodium chloride solution, heat until the gelatin is dissolved, and make up to 1 liter after cooling.

5. Mixture. Combine 975 cc. of saturated sodium chloride solution and 25 cc. of concentrated sulphuric acid.

6. Powdered kaolin.

(B) Determination

Obtain the value of the potassium permanganate in terms of the oxalic acid. Boil 5 grams of the tea for half an hour with 400 cc. of water; cool, transfer to a graduated 500 cc. flask, and make up to the mark. To 10 cc. of the infusion (filtered if not clear) add 25 cc. of the indigo carmine solution and about 750 cc. of water. Add from a burette the potassium permanganate solution, a little at a time while stirring, until the color becomes light green, then cautiously, drop by drop, until the color changes to bright yellow or, further, to a faint pink at the rim. The number of cubic centimeters of permanganate used furnishes the value (a) of the formula given below.

Mix 100 cc. of the clear infusion of tea with 50 cc. of gelatin solution, 100 cc. of salt acid solution, and 10 grams of kaolin, and shake several minutes in a corked flask. After settling decant through a filter. Mix 25 cc. of the filtrate (corresponding to 10 cc. of the original infusion) with 25 cc. of the indigo solution and about 750 cc. of water, and titrate with permanganate. The amount used gives the value b; a − b = c; c equals the amount of permanganate required to oxidize the tannin. Assume that 0.04157 gram of tannin (gallotannic acid) is equivalent to 0.063 gram of oxalic acid.

XXV. NEUTRAL PRINCIPLES

These are physiologically active substances which are neither acid nor basic and have no distinguishing chemical properties. Some are bitter and could, therefore, be classified as bitters, except for their toxicity and pharmacologic actions. They resemble the glucoside closely, but on hydrolysis do not decompose into sugar; although santonin sometimes contains sugar as an impurity. The classification of neutral bases, therefore, is indefinite and includes those chemically nondescript principles of neutral reaction which are physiologically active. Digitalis, strophanthus, and even alkaloidal salts from the chemical standpoint might be included, except that they have chemical proper-

ties that place them in more sharply defined chemical groups. The chief neutral principles are:

1. Santonin
2. Picrotoxin
3. Elaterin
4. Chrysorobin

Santonin, $C_{15}H_{18}O_3$, is obtained from wormseed and forms as crystalline, colorless, bitter, shining leaflets, which melt at 170°C., and are soluble in 500 parts of cold water. It is used as an anthelmintic, especially for roundworms.

It is the internal anhydride (lactone) of santonic acid.

Santonic acid
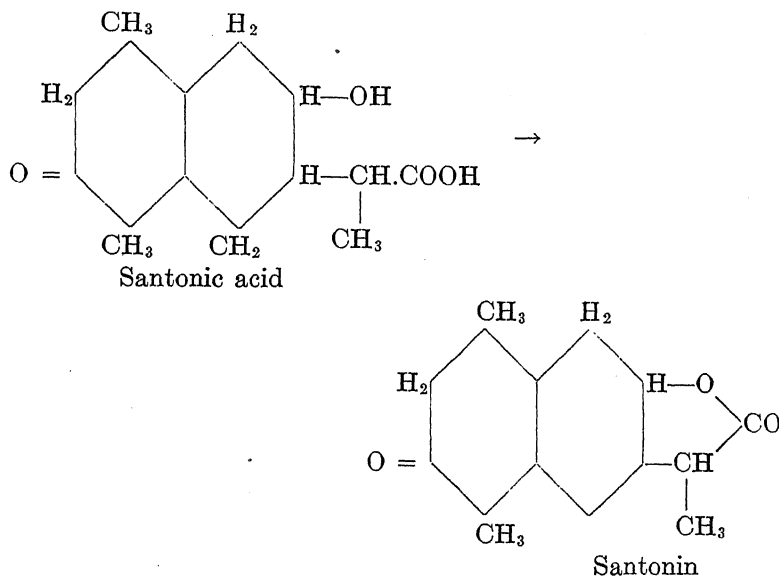
Santonin

Santonin is a ketone and as such, will react with phenyl hydrazine and hydroxylamine. When used as an anthelmintic a slight amount is absorbed and oxidized to oxysantonin $C_{12}H_{18}O_4$. Jaffe found this substance in the urine of dogs to the amount of 5 per cent. of the santonin administered. In rabbits only a small amount could be found. In the rabbit's urine beta-oxysantonin was found which is isomeric with alpha-oxysantonin. After therapeutic doses (0.06 gram) of santonin human urine is reddish and on the addition of KOH, it becomes carmine.

On treatment with lime water, the urine becomes a scarlet or purple color.

TESTS

1. Santonin heated with an alcoholic solution of KOH gives a carmine color, which soon fades through yellow to colorless.

2. Santonin heated with concentrated H_2SO_4 containing a drop of ferric chloride becomes pink; 10 milligrams of santonin to 1 cc. of the acid is sufficient.

PICROTOXIN

Picrotoxin, $C_{30}H_{34}O_{13}$ is the poisonous principle of cocculus indicus. It crystallizes in long colorless needles, M.P. 200°C. It has a very bitter taste, and has a marked action on the medulla producing spasms that have some resemblance to strychnine tetanus. Heated to boiling with 20 times its volume of benzene or chloroform, it decomposes into picrotoxin and picrotin,

$$C_{30}H_{34}O_{13} = C_{15}H_{16}O_6 + C_{15}H_{18}O_7$$
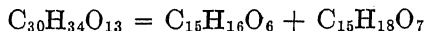
The fate of picrotoxin in the body and the manner of its excretion is unknown.

TESTS

1. Picrotoxin reduces Fehling's solution. Dissolve a little in a test tube by the aid of dilute NaOH, and add to dilute boiling Fehling's solution.

2. If it is warmed with a dilute solution 1 per cent. $AgNO_3$ containing slight excess of ammonium hydroxide a black precipitate of metallic silver will be produced. Where only traces of picrotoxin are present, the precipitate is colored brown.

3. On oxidation with a trace of H_2SO_4 on a porcelain dish, picrotoxin becomes orange red and dissolves to a reddish yellow.

4. **H. Meltzer's Test.**—One to two drops of a mixture of benzaldehyde and absolute alcohol added to some picrotoxin powder on a watch glass, will produce a red color when a drop of concentrated H_2SO_4 is added. The alcohol here is added as a diluent because H_2SO_4 produces a brown color with pure benzaldehyde. 20 per cent. benzaldehyde in absolute alcohol is enough.

5. **Langley's Test.**—Picrotoxin mixed with about 3 times its weight of KNO_3 and moistened with a trace of H_2SO_4 will give an intense red color when an excess of strong NaOH is added.

6. **Physiologic Test.**—Typical convulsions are produced in the frog, but they differ in many respects from those caused by strychnine. Picrotoxin spasms cease when the medulla is removed while strychnine tetanus continues after ablation of the medulla.

ELATERIN

Elaterin, $C_{20}H_{28}O_5$, is the neutral principle of elaterium. It consists of two substances, alpha-elaterin, which is levo-rotary and inert, and beta-elaterin, the active dextro-rotary substance.

Elaterin does not exist as such in fruit, but is formed after expression by a diastatic ferment acting on a glucoside. Little is known of the chemistry of elaterin or its fate in the body.

CHRYSOROBIN

Chrysorobin is a mixture of neutral principles from Goa powder. The chief principle is chrysophanolanthranol $C_{15}H_{12}O_3$, m.p. 204°, an orange yellow, tasteless, odorless powder, very irritating to mucous membranes.

According to Tutin and Clewer, chrysophanic acid has the formula
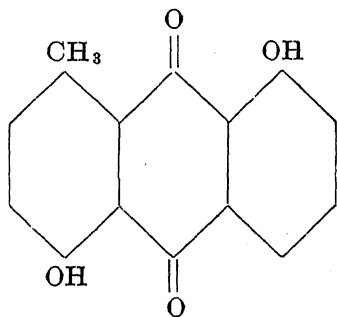
or dioxmethyl anthraquinone.

Chrysorobin is the anthranol corresponding to chrysophanic acid and has the formula
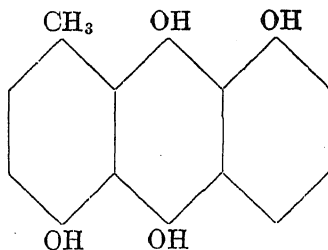
Anthranol is oxyanthracene
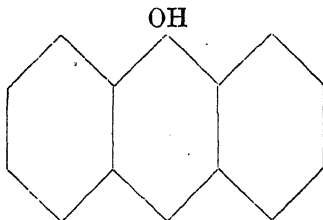
Anthranol

Commercial Goa powder contains a mixture of neutral principles, $C_{30}H_{26}O_7$ and in addition to these described, contains dichrysorobin $C_{30}H_{23}O_7$ and its methyl ester. Aloin and salicin have been classed as neutral principles but they belong definitely to the glucosides.

In the body part of the absorbed chrysorobin is oxidized to chrysophanic acid, but most of it is excreted unchanged by the kidneys and may cause nephritis. In man slight albuminuria has been observed after its application to the skin.

XXVI. ALKALOIDS

NITROGEN BASES; PLANT BASES OR ALKALOIDS

These are all synonymous terms and not sharply defined. The property of N in some compounds to change its valence from 3 to 5, and to unite with acids to form salts is the reason for the term nitrogen base. The isolation of a number of such bases from plants, led to the term vegetable alkaloids or "plant bases," a term which was formerly restricted to those bases in which the nitrogen was in combination of pyridine, quinoline, or isoquinoline. This excluded many nitrogen bases of obvious alkaloidal

reactions, including the caffeine or purine bases, which are now generally conceded to be alkaloids.   Alka- loid mèans an alkali-like substance.   For convenience of study, nitrogen bases or alkaloids in the broad use of the term may be divided as follows:

	Nature of Nucleus	Examples
	Group 1. Pyrrole	Hygrine Stachydrine
	Group 2. Pyridine	Coniine ·
	Group 3. Diheterocyclic, with a common nitrogen atom	Atropine, Sparteine
(1) Vegetable alkaloids derivatives of . . .	Group 4. Quinoline	Strychnine
	Group 5. Isoquinoline	Papaverine
	Group 6. Glyoxaline	Pilocarpine
	Group 7. Purine	Caffeine
	Group 8. Cyclic or acyclic derivatives of aliphatic amines	Choline, arginine
	Group 9. Alkaloids of unknown constitution	
(2) Animal bases or Alkaloids ˉ	Epinephrine—a catechol or pyrocatechol derivative.	
(3) Ptomaines or putrefactive alkaloids.	Choline Muscarine Betaine Neurine Trimethyl amine. Parahydroxylethylamine and other ergot amines.	
(4) Purine Bases also included under 1.	Purine Hypoxanthine Xanthine Guanine Theobromine Caffeine Uric acid	

| (5) Artificial Bases or synthetic alka- loids. | Antipyrine Epinephrine Cocaine substitutes |

In describing these we will not follow this order in detail.

GENERAL CHARACTERISTICS OF ALKALOIDS

1. All alkaloids contain C, H, and N, most of them O, also. Those containing O, are solid and crystalline, while those lacking O, are liquid and volatile. The liquid and volatile alkaloids may be regarded as amines, or substituted ammonias and the solid and crystalline, as amides. See test for N, p. 8.

2. All true alkaloids have an alkaline reaction. The purine bases are neutral, to litmus.

3. All have a bitter taste.

4. Most of them have marked physiologic or toxic properties.

5. They form salts by direct addition, as ammonia does.

6. The free alkaloids are relatively insoluble in water and soluble in ether, chloroform, carbon bisulphide, etc. The salts have opposite solubilities, they are soluble in water, insoluble in ether, chloroform, carbon bisulphate and the like.

7. The majority are optically active, and turn the plane of polarized light to the left. A few, coniine, pelleterine, laudanosine, and pilocarpine are dextrorotary.

8. They are precipitated by a large number of bodies, which because they are much used for this purpose, are called alkaloidal reagents. The most important are:

1. Iodine in KI (Lugol's solution)
2. HgI_2 in KI (Meyer's reagent)
3. Tannic acid
4. Phosphotungstic acid
5. Gold chloride
6. Platinum chloride
7. Picric acid
8. Picrolonic acid

The shapes etc. of the salt crystals, aid in the identification of the alkaloid.

9. Many give color changes on being oxidized with nitric acid, potassium chlorate, potassium bichromate, etc. These color reactions may be characteristic.

10. Since all contain N, they will give the tests for N.

11. In cases of poisoning, they leave no characteristic post mortem change.

CHEMISTRY OF ALKALOIDS

The vegetable alkaloids are related to ammonia and nearly all are tertiary amines. The basicity of the alkaloids, like ammonia, is due to the property of nitrogen, changing its valence from 3 to 5. This is illustrated in the formation of ammonium chloride.

$$N\!\!<\!\!\begin{array}{c} H \\ \\ H \end{array}\!\!- H + HCl = N\!\!<\!\!\begin{array}{c} H \\ H \\ H \\ H \\ Cl \end{array}$$
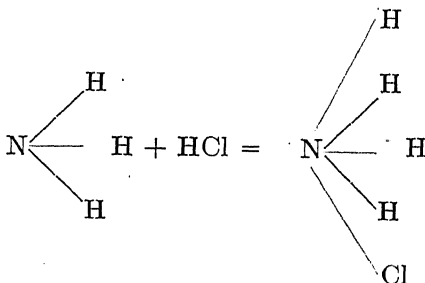
The alkaloids form salts in a similar way.

XXVII. AMINES OR SUBSTITUTED AMMONIAS

Amines are derivatives of ammonia in which the hydrogen has been replaced by alkyl groups. Depending on whether one, two, or three hydrogens are replaced, the amines are named primary, secondary or tertiary.
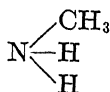
$N\!\!<\!\!\begin{array}{c}H\\H\\H\end{array}$	$N\!\!<\!\!\begin{array}{c}CH_3\\H\\H\end{array}$	$N\!\!<\!\!\begin{array}{c}CH_3\\CH_3\\H\end{array}$	$N\!\!<\!\!\begin{array}{c}CH_3\\CH_3\\CH_3\end{array}$
	Methylamine (primary amine)	Dimethylamine (Secondary amine)	Trimethylamine (Tertiary amine)
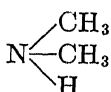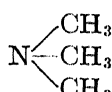
It is hard to draw a sharp dividing line between the simple amines and the alkaloids.
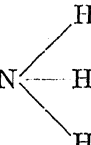
Secondary and tertiary amines are also known in which the N takes part in the formation of a ring. For example, in pyridine

15
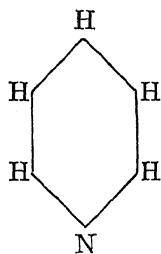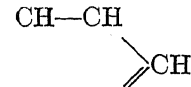
or quinoline
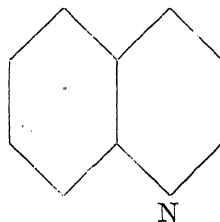
the three

hydrogen atoms of $N \begin{smallmatrix} H \\ \longleftarrow H \\ H \end{smallmatrix}$ may be regarded as being replaced

by a group $\begin{smallmatrix} CH-CH \\ =CH-CH \end{smallmatrix}\!\!>\!\!CH$

which may be considered a tertiary amine.

Piperidine,
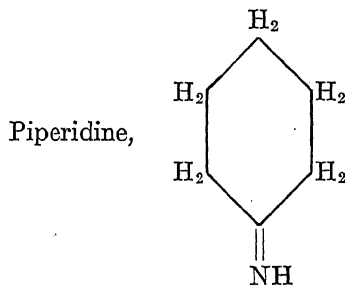
may be classed as a secondary

amine.

Tests for Amines

1. Like ammonia, they form white clouds of finely divided salts, when brought in contact with HCl or other volatile acid. The amines differ from ammonia in being combustible.

2. The amines can be separated from ammonia, if in solution together, by making strongly alkaline with NaOH or Na_2CO_3. Then the addition of very fine amorphous mercuric oxide, which will precipitate the NH_3, as follows:

$$2HgO + NH_3 = Hg_2N.OH + H_2O$$
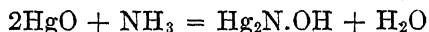
The precipitate may be separated from the amines by filtration.

3. Primary and secondary amines will condense with formaldehyde while tertiary amines do not. The free bases can then be regenerated by hydrolysis, and the difference in the distillation temperature allows separation of primary from secondary.

4. Primary amines all give Hoffman's carbylamine reaction; secondary and tertiary amines do not.

$$R - NH_2 + CHCl_3 + KOH = R - N = C + 3KCl + 3H_2O$$
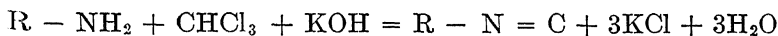
The disagreeable, indescribable odor is characteristic.

Another method of distinguishing primary, secondary and tertiary amines is to determine the number of alkyl groups with which the substance can combine. For example: A substance having the formula C_3H_9N. might be:

(a) $C_3H_7NH_2$—propyl amine—primary

(b) C_2H_5
$\diagdown$NH—methyl ethyl amine—secondary or
CH_3

(c) CH_3
CH_3—N—trimethyl
CH_3

If when heated with an e
should be formed in eacl

would be:

$$(CH_3)_3$$

With the secondary it would be: $\begin{matrix} C_2H_5 \\ \diagdown \\ (CH_3)_3 \end{matrix}$ NI or $C_5H_{14}NI$
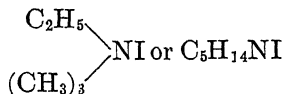
with the tertiary: $(CH_3)_4NI$ or $C_4H_{12}NI$

The determination of the amount of iodine added will decide the question. The titration of the iodine may be done in a manner similar to that described under thymol iodide.

Other tests for the different amines are as follows:

First.—Primary amines $N\diagdown\begin{matrix} R \\ H \\ H \end{matrix}$

When primary amines are treated with nitrous acid HNO_2, they yield alcohols and nitrogen is evolved:

$$R. \begin{vmatrix} N & H_2 \\ & \\ +HO & N & O \end{vmatrix} \longrightarrow R.OH + H_2O + N_2$$

This reaction is analogous to the reaction of nitrous acid with ammonia, which yields nitrogen and water:

$$NH_3 + HNO_2 = H.N.H_2 = N_2 + 2H_2O$$

$$HON\;O$$
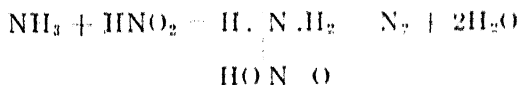
Second.—Secondary amines. When these are treated with nitrous acid they yield nitroso amines:

$$\begin{array}{c} R \\ \diagdown \\ R \diagup \end{array} N.HHO - NO = \begin{array}{c} R \\ \diagdown \\ R \diagup \end{array} N - N - O + H_2O$$
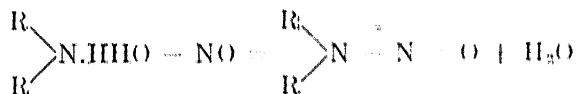
Third.—Tertiary amines either do not react with nitrous acid or are oxidized by it without the formation of definite products.

QUATERNARY AMMONIUM BASES

Ammonia, NH_3, will unite directly with HCl to form

$$N \diagdown \begin{array}{l} H \\ H \\ H \\ H \\ Cl \end{array}$$

In a similar way, tertiary amines unite with alkyl iodide to form quaternary ammonium iodides or quaternary ammonium bases. The physiological action of these quaternary bases differs from the trivalent type. The characteristic action is a paralysis of the motor nerve ending to striated muscle. This action seems to depend more on the physical configuration of the molecule than upon the chemical elements, since phosphorus or arsenic may be substituted for nitrogen. This paralytic action is also exerted by alkaloids in which the nitrogen is quinquivalent, such as curare, methyl strychnine, methyl quinine, methylmorphine, ethyl brucine, and ethyl nicotine.

Sources of Amines

Amines occur in nature as the decomposition products of proteins, and the decarboxylation of amino acids, *e.g.*:

$$CH_2NH_2COOH \rightarrow CH_3NH_2 + CO_2$$
$$CH_3CH_2NH_2COOH \rightarrow CH_3CH_2NH_2 + CO_2.$$
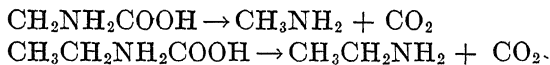
In this way amines corresponding to all the known amino acids are thought to have arisen. This process is favored by the presence of some peptone which serves as a source of nitrogen for the bacteria and in this way prevents deaminization. They may also be prepared synthetically; if a concentrated solution of ammonia be heated in a sealed tube with an alkyl iodide, the corresponding amine is formed:

$$NH_3 + CH_3I \rightarrow NH_2(CH_3) + HI$$
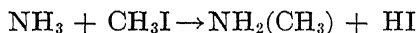
By further action of the methyl iodide, the other H atoms of the ammonia may be substituted.

$$NH_3 + CH_3I = CH_3.NH_2.HI$$
Methylamine hydriodide.

$$CH_3.NH_2 + CH_3I = (CH_3)_2 NH.HI$$
Dimethylamine hydriodide.

$$(CH_3)_2NH + CH_3I = (CH_3)_3N.HI$$
Trimethylamine hydriodide

$$(CH_3)_3N + CH_3I = (CH_3)_4N.I$$
Tetramethyl ammonium iodide.
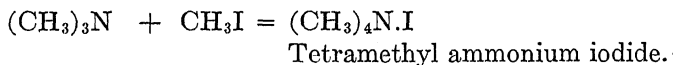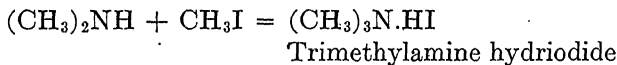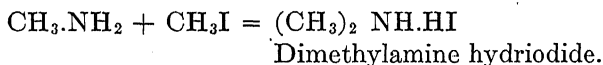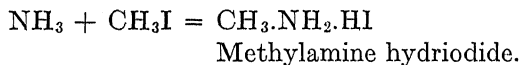
Trimethyl amine can also be formed by heating ammonium chloride with formalin in an autoclave at 120–160°C. (cf. urotropine)

$$2NH_3 + 9CH_2O \rightarrow 2(CH_3)_3N + CO_2 + 3H_2O$$

Amines may also be prepared by the reduction of nitro compounds

$$CH_3NO_2 + 3H_2 \rightarrow CH_3NH_2 + 2H_2O$$
Nitro methane   methylamine
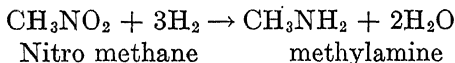
This is a common method of obtaining phenyl amine or aniline

$$C_6H_5NO_2 + 3H_2 \rightarrow C_6H_5NH_2 + 2H_2O$$
Nitro-benzene   Aniline
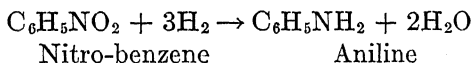
These aromatic amines may also be primary, secondary or tertiary as in case of the alkyls

Primary	Secondary	Tertiary

$$N\overset{\textstyle C_6H_5}{\underset{\textstyle H}{\vphantom{|}\text{---}H}}$$

Primary

$N{<}\begin{array}{l}C_6H_5\\ H\\ H\end{array}$

phenylamine or Aniline

Secondary

$N{<}\begin{array}{l}C_6H_5\\ CH_3\\ H\end{array}$

phenyl Methylamine

Tertiary

$N{<}\begin{array}{l}C_6H_5\\ CH_3\\ CH_3\end{array}$

phenyl Dimethylamine

$N{<}\begin{array}{l}C_6H_5\\ H\\ H\end{array}$

Aniline or phenyl-amine

$N{<}\begin{array}{l}C_6H_5\\ C_6H_5\\ H\end{array}$

Diphenylamine

$N{<}\begin{array}{l}C_6H_5\\ C_6H_5\\ C_6H_5\end{array}$

Triphenylamine
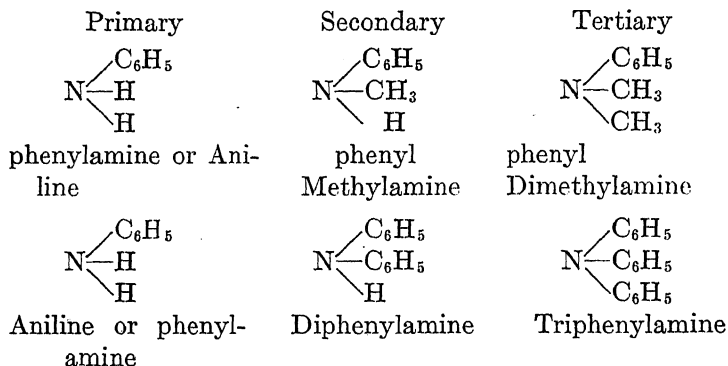
The aromatic amines are more active pharmacologically than the aliphatic.

Amines may also be prepared by reduction of nitrils

$$CH_3 CN + 4H \rightarrow CH_3CH_2NH_2$$
Methyl nitrile
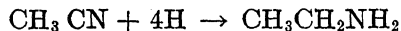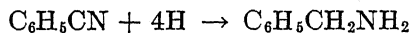
$$C_6H_5CN + 4H \rightarrow C_6H_5CH_2NH_2$$
Benzo nitrile   Benzyl amine

The Physiological Action of the Amines

When ammonia is injected intravenously or when given otherwise in rather strong solution it stimulates respiration and by stimulation of the central nervous system may cause convulsions. As the H atoms of ammonia are replaced by alkyl radicals, the stimulating action is much diminished, and the extent of the diminution increases with the molecular weight of the substituted alkyl.

Alkyl groups are cerebral depressants and the hypnotic action of alcohol, ether, etc., is due to the alkyl groups. When quaternary amine bases are formed, the action becomes paralytic due to a paralysis of the motor nerve ends in a manner similar to that effected by curara. The nitrogen atom in the quaternary amine has little to do with the curara action, since the corresponding phosphorus and arsenic compounds have a like action.

Many amines (substituted ammonias) raise the blood pressure

after the manner of nicotine and epinephrine. Barger and Dale have made a rather exhaustive study of the physiological effects of the amines on the rise in blood pressure, the action on the uterus, pupil, etc. (Journal of Physiol., 1910, 41, p. 19) and have compared the action on these locations with that of epinephrine. Of the aliphatic amines, only the higher open chain primary amines such as amyl amine, $C_5H_{11}NH_2$, and hexyl amine, $C_6H_{13}NH_2$, produced a marked rise in blood pressure. Isobutyl amine, $C_4H_9NH_2$, is the first to cause any significant rise. The normal straight chained compounds were more effective than the isocompounds. Cadaverine, $NH_2(CH_2)_5NH_2$, the only diamine examined, caused a fall of blood pressure instead of a rise. Trimethyl amine and tetramethyl amine were inactive, and of little physiological importance.

A large number of aromatic compounds *without* a phenolic OH and containing an amine aliphatic side chain were investigated, and it was found that only when the amino group in the side chain is attached to the second carbon from the ring is there a marked epinephrine—like action. Beta-phenyl ethyl amine produced all the actions of epinephrine.

Amines *with one phenolic hydroxyl group* in the ortho position, such as ortho hydroxyphenyl ethyl amine

$CH_2.CH_2NH_2,$

HO
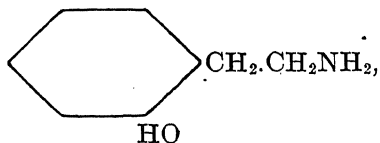
are no more active than phenyl ethyl amine itself. The para compound which is present in ergot (tyramine) and may also be prepared by heating tyrosin

HO

$CH_2CH.COOH$

NH_2
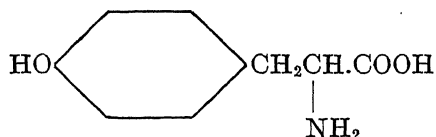
has a similar action.

The pressor or blood pressure raising property in this case depends on the basic property of the substance, for acetyl p. hydroxyethyl amine

$$HO-\langle\ \rangle-CH_2.CH_2NH\ CO.CH_3$$
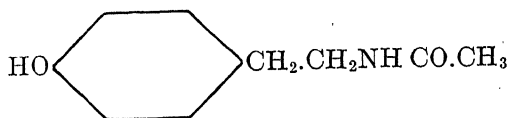
is inactive. The tyrosin ester

$$HO-\langle\ \rangle-CH_2.CH\langle\begin{matrix}COOC_2H_5\\NH_2\end{matrix}$$
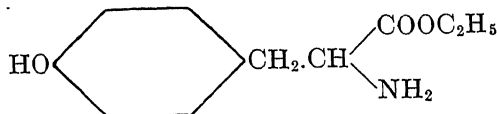
is also inactive. Methylation or ethylation of the amino group

$$HO-\langle\ \rangle-CH_2.CH_2NH.R$$
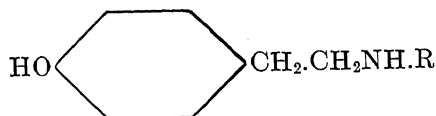
changes the action but slightly and the alkaloid hordenine, which is the tertiary base, has a very weak action

$$HO-\langle\ \rangle-CH_2.CH.N(CH_3)_2$$
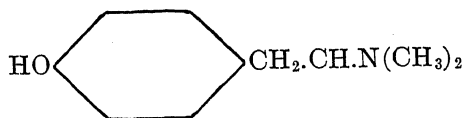
Amines with two phenolic hydroxyl compounds were tested and their comparative effect on the blood pressure is as follows (arranged after Percy May Synthetic Drugs):

Amines with Two Hydroxyl Compounds.—The following compounds in which the two hydroxyl groups are in the 3–4 position were tested:

(a) DERIVATIVES OF ACETO-CATECHOL (KETONES)

	Ratio of Activity
(1) Amino-aceto-catechol, $(HO)_2C_6H_3$—CO—CH_2—NH_2.	1.50
(2) Methylamino-aceto-catechol— $(HO)_2C_6H_3$—CO—CH_2—NH—CH_3.	
(3) Ethylamino-aceto-catechol— $(HO)_2C_6H_3$—CO—CH_2—NH—C_2H_5.	2.25
(4) Propylamino-aceto-catechol— $(HO)_2C_6H_3$—CO—CH_2—NH—C_6H_7	0.25
(5) Trimethylamino-aceto-catechol chloride— $(HO)_2C_6H_3$—CO—CH_2—$N(CH_3)_3Cl$.	

(b) Derivatives of Ethyl-catechol

(6) Amino-ethyl-catechol,
  $(HO)_2C_6H_3$—CH_2—CH_2—NH_2.   1.00

(7) Methylamino-ethyl-catechol—
  $(HO)_2C_6H_3$—CH_2—CH_2—NH—CH_3.   5.00

(8) Ethylamino-ethyl-catechol—
  $(HO)_2C_6H_3$—CH_2—CH_2—NH—C_2H_5.   1.50

(9) Propylamino-ethyl-catechol—
  $(HO)_2C_6H_3$—CH_2—CH_2—NH—C_3H_7 0.25

(10) Trimethylamino-ethyl-catechol chloride—
  $(HO)_2C_6H_3$—CH_2—CH_2—$N(CH_3)_3Cl$

(c) Derivatives of Ethanol-catechol (Secondary Alcohols)

(11) Amino-ethanol-catechol—
  $(HO)_2C_6H_3CH(OH)$—CH_2—NH_2.   50.00

(12) Methylamino-ethynol-catechol (adrenaline)—
  $(HO)_2C_6H_3CH(OH)$—CH_2—NH—CH_3 35.00

The main conclusions of Barger and Dale from their Investigation of the amines are:

1. An action simulating that of the true sympathetic nervous system is not peculiar to adrenine, but is possessed by a large series of amines, the simplest being primary fatty amines. We describe all such amines and their action as "sympathomimetic."

2. Approximation to adrenine in structure is, on the whole, attended with increasing intensity of sympathomimetic activity, and with increasing specificity of the action.

3. All the substances producing this action in characteristic manner are primary and secondary amines. The quaternary amines corresponding to the aromatic members of the series have an action closely similar to that of nicotine.

4. The optimum carbon skeleton for sympathomimetic activity consists of a benzene ring with a side chain of two carbon atoms, the terminal one bearing the amino group. Another optimum condition is the presence of two phenolic hydroxyls in the 3–4 position relative to the side chain; when these are present, an alcoholic hydroxyl still further intensifies the activity. A phenolic hydroxyl in the 2 position does not increase the activity.

5. Catechol has no sympathomimetic action.

6. Motor and inhibitor sympathomimetic activity vary to some extent independently. Of the catechol bases those with a methylamino group, including adrenine, reproduce inhibitor sympathetic effects more powerfully than motor effects: the opposite is true of the primary amines of the same series.

7. Instability and activity show no parallelism in the series.

The amines are very slightly toxic and their ultimate fate especially that of the lower members in the body is perhaps similar to ammonia, urea and carbon dioxide being the ultimate products. In some cases various intermediate products are formed. Ewins and Laidlow found that one-half the amount of p. hydroxy phenyl amine given by mouth to dogs was excreted in the urine as para hydroxy phenyl acetic acid. This same conversion of the amine into the acid occurred when it was perfused through the rabbit's liver, but when perfused through the isolated heart it was completely destroyed without the formation of acid. In the vast majority of the cases, however, little is known of the fate in the body. In view of the great activity of histamine and its probable relation to anaphylactic shock and to the toxicity of proteins as emphasized by Vaughan, many think that a detailed investigation of the fate of the higher amines, especially those like histidine and the more complex peptamine will go far to explain symptoms now classified as ptomaine poisoning or other equally vague terms.

ALKALOIDS DERIVED FROM ALIPHATIC AMINES

A number of important alkaloids are aliphatic derivatives or combinations. The most important in pharmacology are:

1. Epinephrine
2. Arginine
3. The putrefactive alkaloids { Betaine   Putrescine
                                Choline
                                Muscarine   Cadaverine

4. Ergot alkaloids { Tryamine,
                     Histamine,
                     Ergotoxine,
                     Isoamylamine.

5. Sinapine
6. Hordenine

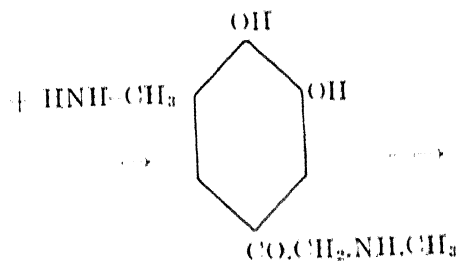Epinephrine or the pressor principle of the adrenal glands is a derivative of para hydroxyphenylethyl amine

$$HO \bigcirc CH_2CH_2NH_2$$

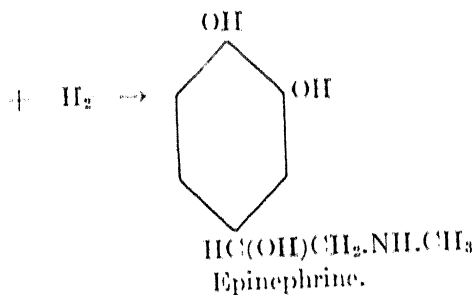and has the formula

$$OH- \bigcirc CH(OH)CH_2.NH.CH_3$$
$$OH$$
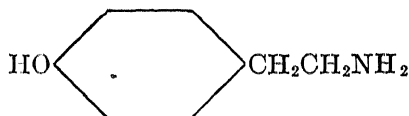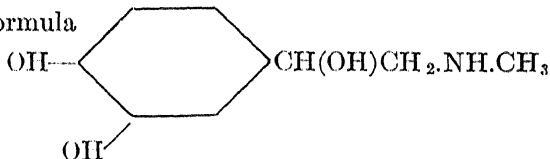
It was first isolated by Abel in 1879 and 1899 (Zeit. f. Physiol. Chem., 1898, 28, 318; and Am. Jour. Physiol., 1900, 3, XVII) and by Takamine who obtained it in crystalline form and from its decomposition thought he obtained catechol and pyrocatechuic acid. These products have been used in the preparation of synthetic epinephrine. It has since been isolated and analyzed by others. It has also been prepared synthetically. The natural product is a slightly yellowish powder, and levo-rotatory. The synthetic product is optically inactive and resolvable into a dextro and levo form. Th natural product is twice as effective as the synthetic judged by its action in raising the blood pressure. The levo form is about 12 times as active as the dextro. The action on the blood pressure is due to a stimulation of the sympathetic nerve endings to the heart and blood vessels. Its action in any location can be predicted if we know the result of stimulation of the regional sympathetics. In the *intestine* and bronchioles, stimulation of the sympathetics causes a *relaxation* and *dilation;* and in these regions, epinephrine has a like effect. Because it mimics the action of the sympathetics, Barker and Dale suggest the term *sympath-o-mimetic*, to describe its action.

The synthesis of epinephrine has been effected by Friedman as follows:

$$OH \qquad\qquad OH$$
$$\bigcirc OH + Cl.CO.CH_2Cl \qquad \bigcirc OH$$
$$\qquad\qquad\qquad\qquad\qquad CO.CH_2Cl$$

Catechol + Chloracetylchloride → chloracetyl catechol

$$+ \text{ HNH·CH}_3$$
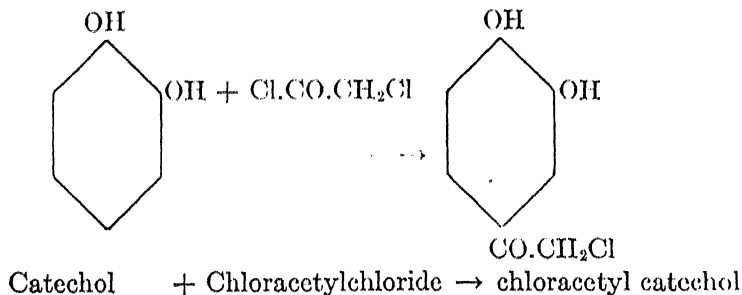
Methylamine   Methyl amino aceto catechol or adrenalone

OH
OH
CO.CH$_2$.NH.CH$_3$

$$+ \text{ H}_2 \rightarrow$$

OH
OH
HC(OH)CH$_2$.NH.CH$_3$
Epinephrine.

Epinephrine has been prepared by another method, starting with pyrocatechuic aldehyde

OH
OH
CHO + HCN →
Pyrocatechuic
aldehyde

OH
OH
CHOH.CN + Reduction

OH
OH
CHOH.CH$_2$.NH$_2$ which on methylation
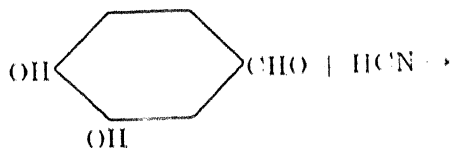
OH
OH
CHOH.CH$_2$.NH.CH$_3$.
Epinephrine
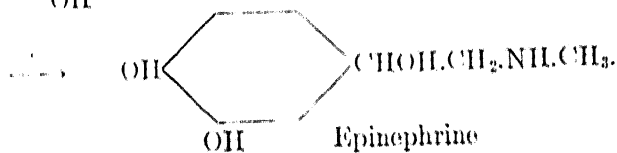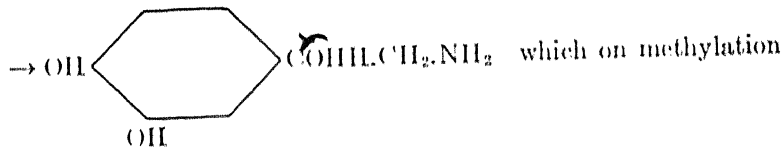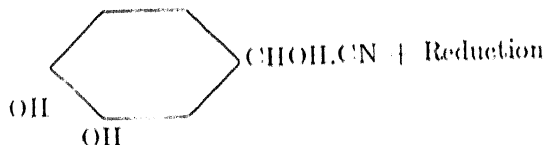
This is the accepted formula—others suggested are:

II $\hspace{1em}$ [hexagon with OH, OH substituents] $CH_2CHOH.NH.CH_3$ and

III $\hspace{1em}$ [hexagon with OH, OH substituents] $CH.NH.CH_3$
$\hspace{8em}$ CH_2OH
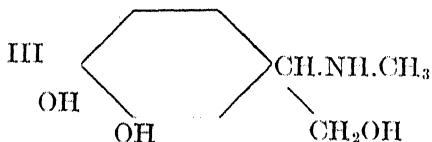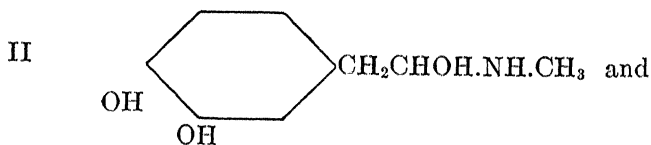
In favor of the accepted formula I is the fact that methyl-amino aceto catechol or adrenalone from which adrenaline may be prepared by reduction, is formed by the action of methyl amine on chloracetyl catechol

HO [hexagon] $—CH_2—CH_2.N(CH_3)_2$
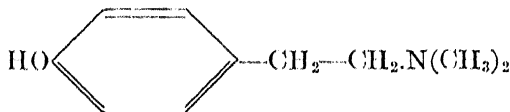
$$\text{Hordenine.}$$

Hordenine, an alkaloid in malt, is very closely related to epinephrine in structure, but its action is more like phenol than epinephrine. It is only slightly toxic:

1 gram per kilo per os in a dog or rabbit causes some rise in blood pressure and acceleration of the pulse. It acts both on sympathetic and para sympathetic endings, and also centrally. After a fatal dose, which for a dog is 0.3 gm. per kilo intravenously, death occurs from respiratory failure—similar to phenol.

Epinephrine Tests

1. To a dilute solution of adrenaline chloride or an extract of the gland, add a few drops of ferric chloride. An emerald green color develops but this is quite transient (phenolic reaction).

2. To a solution add some sodium carbonate. A reddish color is formed. Alkalies destroy the physiologic effect of the substance rapidly.

3. Physiological test: 1 cc. 1–10,000 solution injected into the vein of a mammal will cause a great rise in blood presure.
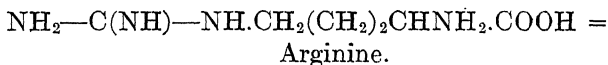
ARGININE

Arginine is physiologically inactive in animals, consequently is of little interest from a purely pharmacodynamic point of view. Chemically it is alpha amino guanidine valerianic acid.

$$
\begin{array}{c}
NH_2 \\
| \\
C = NH \\
| \\
N\text{—}H \\
| \\
H\text{—}C\text{—}H \\
| \\
H\text{—}C\text{—}H \\
| \\
H\text{—}C\text{—}H \\
| \\
H\text{—}C\text{—}NH_2 \\
| \\
O = C\text{—}OH
\end{array}
$$
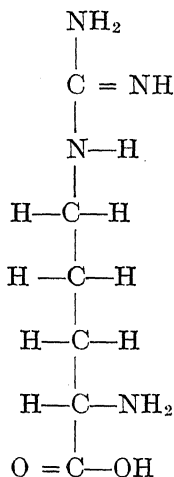
All proteins contain arginine, and the head of salmon sperm yields nearly 90 per cent. Arginine, lysine and histidine have been called hexone bases, by Kossel, because they contain 6 carbon atoms, and he thought proteins were built up of such amino acids in a manner similar to the formation of complex carbohydrates from hexoses. The relationship of proteins to alkaloids is again apparent here.

The Fate of Arginine in the Body

By the action of so-called carboxylase bacteria, which decarboxylate arginine, agmatine is formed:

$$NH_2\text{—}C(NH)\text{—}NH.CH_2(CH_2)_2CHNH_2.COOH =$$
Arginine.

$$CO_2 + NH_2.C(NH).NH.CH_2(CH_2)_2.CH_2NH_2$$
Agmatine.
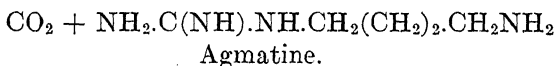
Agmatine has also been obtained from ergot and has been synthesized by Kossel. It is regarded as amino butylene guanidine. According to Dale and Laidlow agmatine contributes but

little to the activity of ergot. It acts like histamine but is only 1/50 as active. Arginine may also be split in the body by an enzyme into urea and ornithine, *i.e.* alpha d-diaminovaleric acid.

$$NH = C \diagup \begin{matrix} NH_2 \end{matrix}$$
$$HO \diagdown NH—CH_2—(CH_2)_2—CH—COOH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad NH_2$$

$$\begin{matrix} NH_2 \\ | \\ CO \\ | \\ NH_2 \end{matrix} + NH_2—CH_2—(CH_2)_2—CH—COOH \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad NH_2$$
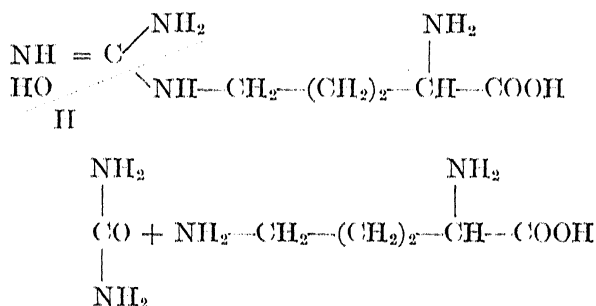
This change may also be accomplished by boiling with alkali. A further decomposition of the ornithin to ammonia and carbon dioxide may occur.

PTOMAINES OR PUTREFACTIVE ALKALOIDS

Ptomaines or putrefactive alkaloids are products of the putrefaction of meat. They are basic bodies, usually amines of simple constitution, such as methyl amine CH_3NH_2—dimethyl amine $(CH_3)_2NH$ or trimethyl amine $(CH_3)_3N$.

Many ptomaines are toxic, others non-toxic. The toxicity may be due in part to ptomaines directly and in part to associated unknown toxins.

In their reactions ptomaines may resemble some alkaloid. This pharmacologic and chemical resemblance may make the identification of the alkaloids difficult. The similarity, however, is usually confined to one of the reactions of the alkaloid, and never extends to all the reactions characteristic of any particular alkaloid. Ptomaines have been found that show certain resemblances to coniine, nicotine, codeine, strychnine, veratrine, atropine, hyoscyamine and morphine; but as stated above these resemblances are frequently confined to one reaction and never in any case agree with all the characteristic reactions of the alkaloid.

Ptomaines are of limited importance as medicines, having a toxicologic interest only. Their great toxicity is probably due

to the inability of the body to oxidize them, even in minute amount.

The most important ptomaines are:

Putrescine	$NH_2(CH_2)_4NH_2$
Cadaverine	$NH_2(NH_2)_5NH_2$
Choline	$\begin{array}{l} N(CH_3)_3OH \\ \mid \\ CH_2CH_2OH \end{array}$
Muscarine	$\begin{array}{l} N(CH_3)_3OH \\ \mid \\ CH_2CHO \end{array}$
Betaine	$\begin{array}{l} N(CH_3)_3 \\ \mid \quad\quad \searrow O \\ CH_3CO \nearrow \end{array}$
Neurine	$\begin{array}{l} N(CH_3)_3OH \\ \mid \\ CH = OH \end{array}$

Choline, muscarine, betaine, and neurine are sometimes called the betaines.

Putrescine: (from putresco, to rot or putrefy), or tetramethylene diamine—

$$NH_2.CH_2.CH_2.CH_2.CH_2.NH_2$$

occurs associated with cadaverine. It was first obtained from putrefying human internal organs. It has also been found in the excreta of cholera patients, and in the urine in cases of cystinuria. Carbohydrate diet lessens the amount excreted in these cases, while meat diet increases it. This points to protein as the source of putrescine. Normal feces do not contain it. The use of salol, sulphur, and other intestinal antiseptics does not appreciably influence the amount excreted. Garcia, however, has shown that when cane sugar is added to putrefying meat and pancreas in vitro, less diamine is formed. The bacteria forming the diamines apparently live on the sugar in preference to the protein. Sugar or carbohydrate for this reason has been

advocated as the preferable diet in many cases of gastro-intestinal putrefactions.

The relation of putrescine to cystinuria is but little understood. It was suggested that putrescine and other diamines united with cystin to prevent its oxidation. When diamines are fed to dogs no cystinuria occurs, and the formula of cystine

$$
\begin{array}{cccc}
& H & & H \\
& | & & | \\
H & -C-S- & S & C-H \\
& | & & | \\
NH_2 & -C-H & H-C & NH_2 \\
& | & & | \\
\cdot O = & C-OH & O = C-OH
\end{array}
$$
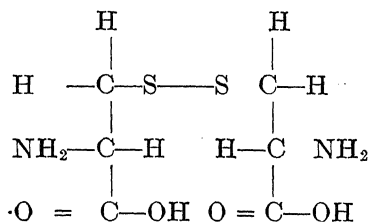
does not suggest an origin from the diamines.

The source of putrescine is most probably directly from ornithine or α, ϵ, diamino valeric acid.

$NH_2.CH_2.CH_2.CH_2.CH_2.NH.COOH \rightarrow$
ornithine
$NH_2.CH_2.CH_2.CH_2.CH_2.NH_2. + CO_2$
putrescine.
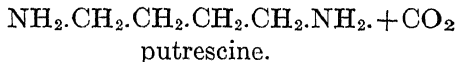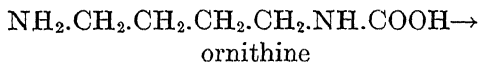
Putrescine has also been prepared synthetically. Addition or substitution products can be readily formed. The tetramethyl derivative $N(CH_3)_2(CH_2)_4N(CH_3)_2$, is much more poisonous than putrescine, and resembles muscarine in action. The symptoms are: nausea, vomiting, salivation, increase then decrease of respiration, contracted pupils, diarrhœa and collapse. Atropine will counteract many but not all of these symptoms.

Cadaverine or penta-methylene diamine is found associated with putrescine and is formed similarly. It is probably formed from lysine or α, ϵ, diamino caproic acid by decarboxylation:

$NH_2.CH_2.CH_2.CH_2.CH_2.CHNH_2COOH -$
lysine
$NH_2.CH_2.CH_2.CH_2.CH_2.CH_2.NH_2. + CO_2$
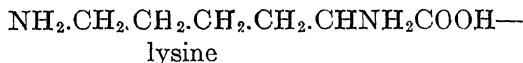
and is probably identical with so-called animal coniine which has been isolated from cadavers. It may produce marked inflammation and necrosis, and like turpentine and some other

16

drugs, can cause suppuration in the absence of bacteria. With putrescine it probably causes the cystitis of cystinuria. It is not very poisonous however,—large doses will kill mice, but it is relatively non-poisonous to dogs.

By heating pentamethylene hydrochloride piperidine may be formed which has a definite toxic action:

$$CH_2\!\!<^{CH_2.CH_2NH|\overline{H}}_{CH_2.CH_2}\quad\Big|NH_2 \quad + HCl \rightarrow$$

$$\begin{array}{c} CH_2 \\ \diagup\ \diagdown \\ CH_2 \qquad CH_2 \\ | \qquad | \qquad\qquad + NH_4Cl \\ CH_2 \qquad CH_2 \\ \diagdown\ \diagup \\ NH \end{array}$$
Piperidine.
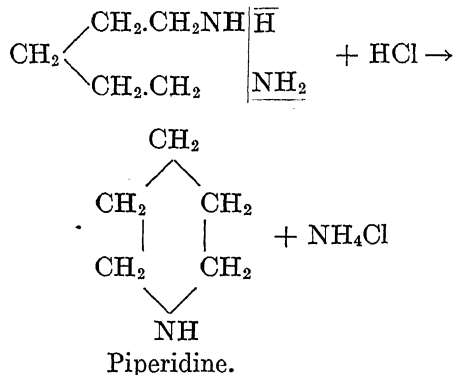
By oxidation of piperidine to pyridine the toxicity is again markedly reduced.

Choline (chole-bile).— Choline is partly amine and partly alcohol. It is found as a constituent of lecithin, which occurs especially in nervous tissue, egg-yolk, seeds, and elsewhere. It is also found in ergot, and in many-plants. Its composition is shown by its synthesis from trimethylamine and ethylene oxide in aqueous solution

$$(CH_3)_3N + CH_2.\underset{\diagdown O \diagup}{CH_2} + H_2O = (CH_3)_3N\!\!<^{CH_2.CH_2OH}_{OH} \qquad Choline$$
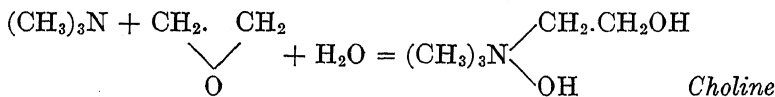
It is related to muscarine and to neurine:

$$(CH_3)_3N\!\!<^{CH_2.COH}_{OH} \qquad\qquad\qquad (CH_3)_3\,N\!\!<^{CH:CH_2}_{OH}$$
Muscarine   Neurine

While choline is but slightly toxic, its dehydrated product neurine is extremely toxic. In the formation of neurine from choline, by the elimination of a molecule of water, a double-bonded carbon

combination is formed. If this double-bond is changed to a triple bond by the formation of

$$(CH_3)_3 N \diagdown \begin{array}{l} C\vdots CH \\ OH \end{array}$$
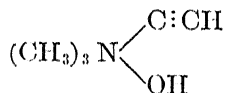
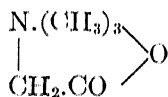the product is still more toxic. See p. 148 for influence of triple bond.

The formation of choline from lecithin can be seen from the formula of lecithin, R and R' being similar to dissimilar acid radicals:

$$
\begin{array}{l}
CH_2OR \\
| \\
CHOR' \\
| \\
CH_2O \cdot P \diagdown \begin{array}{l} OH \\ = O \\ O \quad CH_2.CH_2.N(CH_3)_3.O.H \end{array}
\end{array}
$$
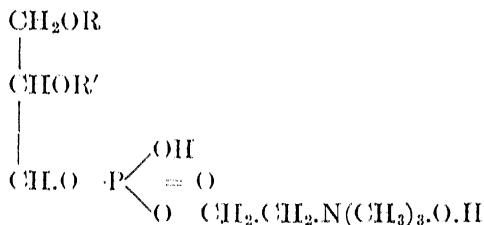
Lecithin, however, cannot be regarded as the only source of choline in plants because it occurs where no lecithin has been found—as in the seeds of white mustard, sinapin giving rise to choline as follows:

$$C_{16}H_{23}NO_5 + H_2O = C_5H_{15}NO_2 + C_{11}H_{12}O_5$$

Sinapin   Choline   Sinapic acid
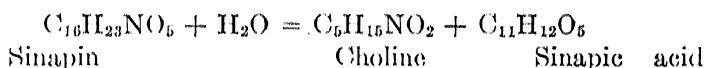
Betaine or trimethyl-glycocol

$$
\begin{array}{l}
N.(CH_3)_3 \diagdown \\
| \qquad\qquad O \\
CH_2.CO \diagup
\end{array}
$$

gets its name because it is found free in the sap of the sugar beet Beta vulgaris. Betaine is the anhydride of hydroxytrimethylamine-acetic acid:

$$
\begin{array}{l}
N.(CH_3)_3 - OH \\
| \\
CH_2.COO - H
\end{array}
$$
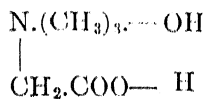
The alkaloid stachydrine

$$CH_2 \!\! < \!\! \begin{array}{c} CH_2 - CH.CO \\ | \\ CH_2 - N.(CH_3)_2 \end{array} \!\! > \!\! O$$
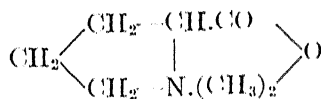
one of the pyrrolidine alkaloids, is also a derivative of this substance being a dimethyl betaine of pyrrolidine. Betaine is physiologically inactive when given by mouth, hypodermically it acts like choline. It occurs in large amounts in the muscles of cephalopods and has been isolated from human urine and has been prepared synthetically. Betaine is excreted unchanged and cannot therefore act as a food.

Muscarine is a tertiary amine and an aldehyde, while choline is the corresponding amine with an alcohol. Very few amino aldehydes or amino ketones are known.

Amino acetaldehyde $CH_2NH_2.CHO$ is a very unstable compound. Muscarine is thought to be the corresponding trimethyl ammonium base:

$$CH_2 - N(CH_3)_3.OH$$
$$| \qquad H$$
$$C \!\! < \!\! \begin{array}{c} \\ \end{array} + H_2O$$
$$O$$

or

$$\begin{array}{c} CH_3 \\ CH_3 \\ CH_3 \end{array} \!\! > \!\! N \!\! < \!\! \begin{array}{c} CH_2.CH(OH)_2 \\ OH \end{array}$$
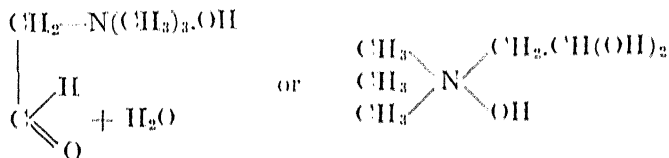
The action of muscarine is very similar to pilocarpine or to arecoline. It causes:

1. A marked slowing of the heart by stimulation of the vagus endings.

2. A constriction of the pupil, due to stimulation of the third nerve endings.

3. Marked gastric and intestinal peristalsis leading to vomiting and diarrhœa, also asthmatic respiration.

4. Marked salivation due to stimulation of the endings of the chorda tympani nerve.

Most of these actions may be neutralized by a small dose of atropine.

ERGOT ALKALOIDS

In recent years much has been done to make clear the composition of the active principles of ergot. These active principles

consist of alkaloids and amines. The chief alkaloids are ergo-
tinine and ergotoxine. These are readily interconvertible.
Ergotinine is inactive, but its hydrate ergotoxine is active—

$$C_{35}H_{39}O_5N_5 + H_2O \rightarrow C_{35}H_{41}O_6N_5$$

$$\text{Ergotinine} \qquad \qquad \text{Ergotoxine}$$
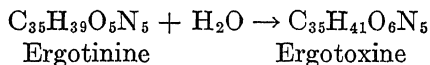
Both of these alkaloids on destructive distillation give isobutyl
form amide—$(CH_3)_2CH.CO.CO.NH_2$.

Beyond this little is known of their constitution. Their fate
in the body is also unknown. Ergotoxine, along with hista-
mine, is responsible for practically the whole action of
ergot in therapeutics. It acts very much like adrenaline
from which it differs by stimulating only the motor myoneural
junctions of the sympathetic nerves while it does not act on the
inhibitors. Dale found that in large doses ergotoxine paralyzes
the augmentor elements only, and that adrenaline after ergo-
toxine often causes a fall of blood pressure. This phenomenon he
called "vaso motor reversal."

ERGOT AMINES

Isoamylamine

$$\begin{array}{c} CH_3 \\ \diagdown \\ CH\ CH_2\ CH_2 . NH_2 \\ \diagup \\ CH_3 \end{array}$$
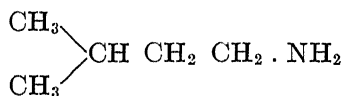
is an ergot amine, and results from the putrefaction of proteins.
It probably arises from leucine,

$$\begin{array}{c} CH_3 \\ \diagdown \\ CH\!-\!CH_2CH.COOH \\ \diagup \\ CH_3 | \\ NH_2 \end{array}$$
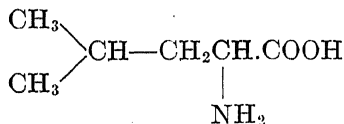
by a splitting off of carbon dioxide.

When injected intravenously isoamyline raises the blood pres-
sure. The amount present in ergot is too small to be of any
significance in ergot action. Isoamylamine hydrochloride has
been employed to some extent as an antipyretic.

Beta-iminoazolylethylamine-4-meta-amino, ethyl glyoxaline or
histamine is another ergot amine. It is derived from histidine
by the action of putrefactive bacteria—

$$
\begin{array}{ll}
\begin{array}{c}
\text{CH---NH} \\[-2pt]
\parallel \quad\quad \diagdown\text{CH} \\
\text{C -----N} \\
\mid \\
\text{CH}_2 \\
\mid \\
\text{CH.NH}_2 \\
\mid \\
\text{COOH}
\end{array}
\quad\longrightarrow\quad
&
\begin{array}{c}
\text{CH--NH} \\[-2pt]
\parallel \quad\quad \diagdown\text{CH} \quad + \text{CO}_2 \\
\text{C -----N} \\
\mid \\
\text{CH}_2 \\
\mid \\
\text{CH}_2.\text{NH}_2
\end{array}
\end{array}
$$

Histidine or α, amino β, imino-   Histamine β,
      azole propionic acid   iminoazole ethyl-amine
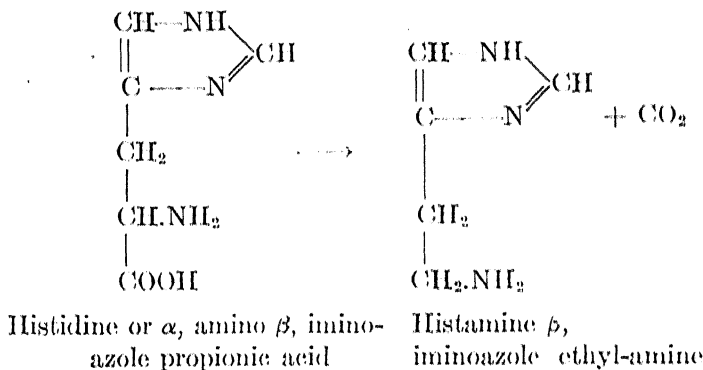
Histamine stimulates the uterine muscle directly, and is one of the important ergot principles. It also stimulates the bronchioles which are highly sensitive; less so, the intestine arteries and spleen. Its action resembles pituitrine. Histamine dihydrochloride, $C_5H_9N_3.2HCl$, is readily soluble in water, and is used in the standardization of pituitrine. One part of betaiminoazolylethylamine hydrochloride (histamine hydrochloride) in $1:20,000,000$ has the same activity on the isolated uterus of the virgin guinea pig as 1 to 20,000 solution of standard pituitary extract.

Histamine is precipitated by phosphotungstic acid, by ammoniacal silver solutions, and by mercuric chloride in alkaline solution. On boiling with bromine water it gives a claret color.

Parahydroxy phenyl ethylamine or tyramine:

$$\text{OH}\hexagon\text{CH}_2.\text{CH}_2.\text{NH}_2$$
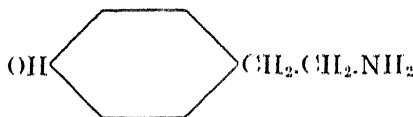
is of especial interest in medicine as being one of the active ingredients of ergot. It has also been isolated from putrid meat. It gets the name tyramine from the fact that it may be prepared from tyrosin:

$$\text{OH}\hexagon\text{CH}_2\text{---CH}\diagup\begin{array}{l}\text{COOH}\\ \text{NH}_2\end{array}$$
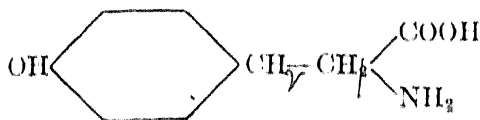
which eliminates CO_2 on heating. Tyramine like epinephrine acts on the sympathetic endings, and unlike epinephrine it apparently acts more on the constrictor endings and little on the dilators.

PYRIDINE ALKALOIDS

Pyridine is a colorless mobile liquid, sp. gr. 1.003 at 0°C. B.P. 115°. It is an exceedingly stable and chemically inactive substance with a pungent characteristic odor, and may be heated with nitric or chromic acid without undergoing change. It is formed by the destructive distillation of many nitrogenous organic substances, especially coal tar and bone oil.

Pyridine, like nicotine, is a highly toxic substance.
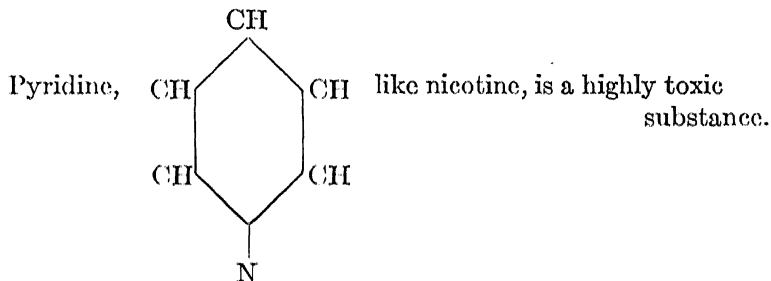
In order to name the substitution products, its various positions are named in relation to the (N):
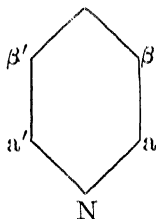
Since piperidine is formed from pyridine by reduction, the reverse change can also be made and pyridine formed from piperidine by oxidation. In the formation of pyridine, pentamethylene diamine hydrochloride is converted into piperidine and this in turn is oxidized to pyridine:

Pentamethylene-diamine
hydrochloride

Piperidine

+ 30

→
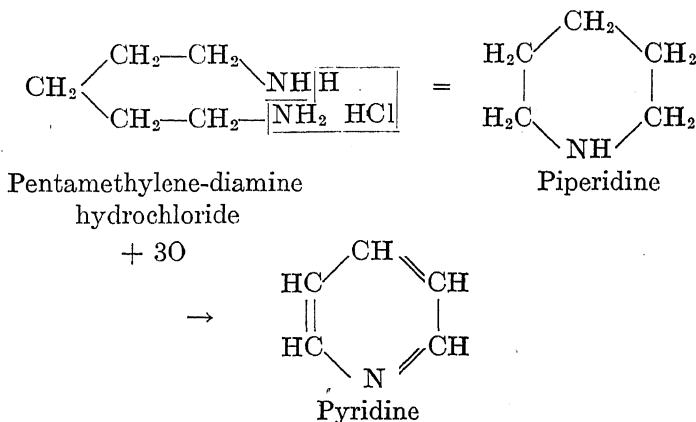
Pyridine

The toxicity of the pyridine homologues increase with increase in molecular weight through picoline or methyl pyridine, lutidine or dimethyl, collidine or trimethyl to parvoline $C_5NH(CH_3)_4$ or quatramethyl pyridine, which is eight times as toxic as pyridine.

Pyridine can be formed synthetically, by dry distillation of pentamethylenediamine. It may be prepared by boiling the alkaloid piperine with alcoholic potash. The decomposition is expressed by the formula:

$$C_{17}H_{19}O_3N + H_2O = C_5H_{11}N + C_{12}H_{10}O_4$$
Piperine   Piperidine   piperic acid.
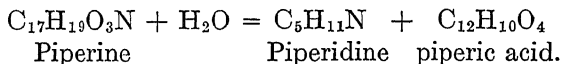
Methyl pyridine may occur in small quantities in the tissues probably derived from vegetable foods and from pyridine—containing plants, like tobacco. His (Arch f. exp. pharm., 1894, vol. 22, p. 247, 281) confirmed by Cohn (Zeit. physiol. Chem., 1894, vol. 18, p. 112) found that pyridine is eliminated in the urine as methy pyridil ammonium hydroxide
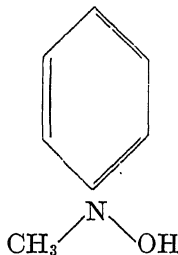
This occurrence of methylation in the animal body is a rare

and interesting phenomenon. Hoffmeister states that after feeding an animal tellurium compounds, tellurium dimethide $Te(CH_3)_2$. is excreted in the urine. Methylated compounds as a rule when introduced into the body are demethylated. Caffeine loses successively one, two and three methyl groups. Since methylation increases the toxicity of pyridine one must feel some doubt of its methylation in the body.

NATURAL METHYLATED COMPOUNDS IN THE BODY

Creatine is methyl guanidine acetic acid. Creatinine is the anhydride of this. These are the most important methylated bodies that occur normally in the urine. Creatine is unquestionably formed from amino acids, but no methylated amino acids occur in the body and the process of methylation though not known is perhaps similar to that occurring in plants. Methylation in plants is a common occurrence and it appears probable that methyl compounds are formed by the action of ammonia and formaldehyde:

$$2NH_3 + 3CH_2O = 2NH_2 : CH_3 + CO_2 + H_2O$$

This reaction can be readily carried out in the laboratory. Formaldehyde has been demonstrated in plants; but its presence in the animal body, however, has not been proven. Consequently, if this be the mechanism in plants, there is still some doubt how methylation takes place in animals.

In the plant, photo chemical reactions must play an important part in such vital processes.

The Fate of Creatine and Creatinine in the Body

As stated above some of these bodies occur in the urine. The amount of creatinine in the urine remains constant no matter how the protein of the diet varies. This led Folin to distinguish between exogenous metabolism or the metabolism of food stuffs and endogenous metabolism or that due to the breaking down of the body protein. Creatinine represents the endogenous metabolism. Creatine is destroyed in the tissues. The mechanism of this oxidation is not known, but it has been suggested that it is first converted into · creatinine and then destroyed. Folin found, however, that creatinine administered is not oxidized; but all is eliminated in the urine.

Hydrogenation of pyridine results in the formation of piperidine or hexahydro pyridine or

$$
\begin{array}{c}
H_2 \\
H_2 \qquad H_2 \\
H_2 \qquad H_2 \\
NH
\end{array}
$$
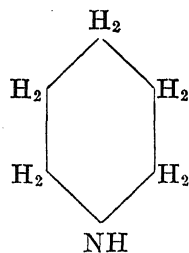
which has an imide group NH and is a secondary amine. Piperidine is a colorless oil, with unpleasant odor and strong basic properties. Pyridine is but slightly toxic and lowers the blood pressure, but piperidine is very toxic and raises the blood pressure with general paralysis of central origin. Its total action is much like coniine, which is propyl piperidine. Large doses exert a curara action on the motor nerve ends. The action of piperidine compared with related compounds shows the toxic influence of the imide group in the molecule.
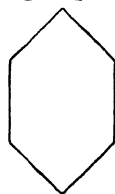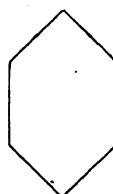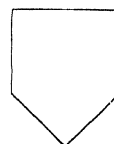
N	NH	NH
Pyridine	Piperidine	Pyrrole

Pyridine is less toxic than either piperidine or pyrrol, and collidine is less toxic than coniine.

CH_3

CH_2 ... CH_2

N

Collidine

$CH_2 CH_2 CH_3$
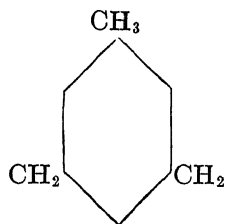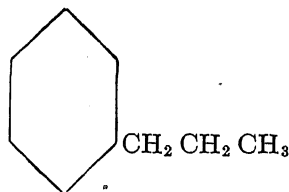
NH

Coniine

Piperidine because it is readily oxidized in the body, does not give the methyl synthesis that pyridine undergoes in the body.

The principal pyridine alkaloids are:

> Coniine from conium maculatum
> Nicotine from nicotina tabacum
> Atropine from atropa belladonna
> Cocaine from Erthroxylon coca
> Morphine from Papaver somniferum
> Narcotine from Papaver somniferum
> Quinine from Cinchona and remija
> Strychnine from Strychnos nux vomica
> Brucine from Strychnos nux vomica

It is possible to place some of these alkaloids also under other heads, because they may contain other nuclei. For example quinine and strychnine also contain the quinoline nucleus, which is a combination of pyridine and benzene.

The tests for the pyridine nucleus are:

1. Potassium ferrocyanide precipitates the base. This product is rather insoluble and the pure base can be prepared from it.

2. When the pure base is treated with platinum chloride a double salt, $(C_5H_5N)_2H_2Pt.Cl_6$, is formed. This is soluble in water, but hydrochloric acid is evolved and a yellow insoluble compound $(C_5H_5N)Pt.Cl_4$ is formed.

3. When the free base is warmed with methyl iodide, an addition product $C_5H_5N.CH_3I$ is formed. When this is warmed with solid KOH, it gives a very pungent disagreeable odor. This is a delicate test for pyridine.

Coniine is propyl piperidine and is the alkaloid of conium maculatum
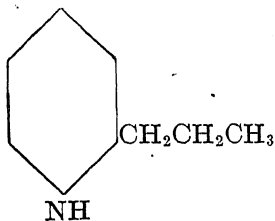
It is still more toxic than piperidine and is the cause of the poisoning of cattle which have eaten the plant or in some cases, browsed

on the roots, or drunk water contaminated with the alkaloid. The drug raises blood pressure by a local action on the peripheral vessels and slows the heart rate by central vagus stimulation. In fatal cases death is due to paralysis of the nerves to the respiratory muscles. Chemically it is one of the simplest known alkaloids, one of the few liquid alkaloids, and closely resembles nicotine in composition and action.

The substance is a colorless oil, boils at 167°C and like nicotine is readily soluble in water, to which it imparts an alkaline reaction (note the solubility in water). It has a peculiar mouse-like odor. As a rule free alkaloids are rather insoluble in water. Coniine was formerly much used, but at present is not used in medicine. It is excreted in the urine.

Tests

1. It gives the pyridine tests p. 251.
2. Test the solubility in water and note reaction and odor.
3. Place a drop of coniine on a watch crystal. Add 2 drops of concentrated HCl and evaporate to dryness on a water bath. Needle like or columnar yellow crystals of coniine hydrochloride frequently in star shaped clusters are deposited. They are doubly refractive.
4. Dissolved in concentrated HNO_3 or H_2SO_4 the crystals are not colored.
5. The alkaloidal reactions especially delicate for coniine are —iodopotassium iodide (1:8000); phosphomolybdic acid (1:5000); potassium mercuric iodide (1:8000).

Nicotine, is a more complicated alkaloid than coniine and is probably a pyridyl-β, tetrahydro-N methyl pyrrole and may be represented by
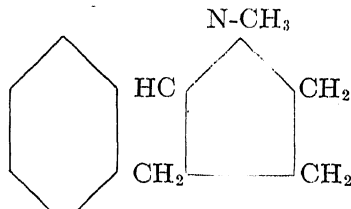
It is a colorless liquid, oily, with a pungent characteristic odor, boils at 241°C., and rapidly turns brown on exposure to the air. The drug is very toxic and raises blood pressure much like adrenaline but by an action on the peripheral ganglion cells, while adrenaline acts on the sympathetic endings. Nicotine also resembles coniine in action. Death results from a stimulation and paralysis of the central nervous system.

On standing, due to partial oxidation, a double-bonded compound (nicoteine) may be formed which is more toxic than nicotine.
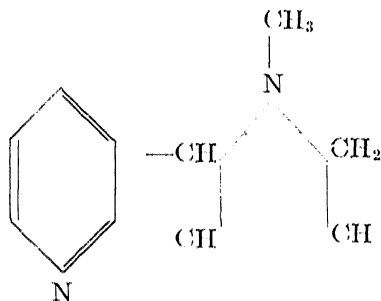
On further oxidation oxynicotine

and metanicotine,
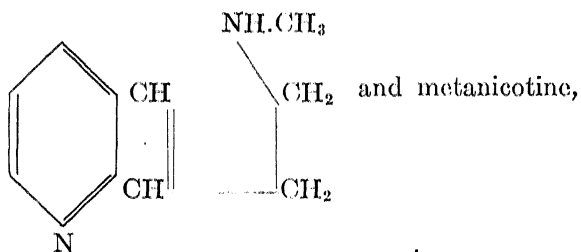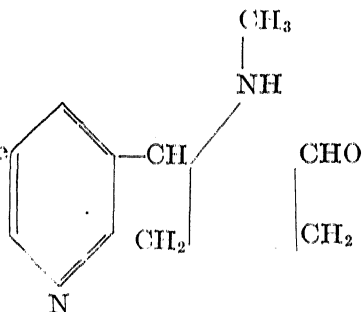
much less toxic derivatives, are developed.

When nicotine is oxidized with chromic or nitric acid, or potassium permanganate, β. pyridine carboxylic acid is formed.

COOH   (nicotinic acid)

N
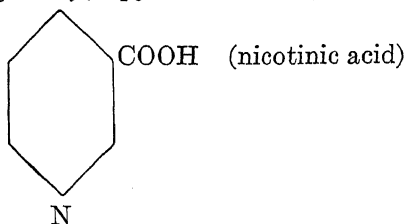
This shows that nicotine is a pyridine derivative with the side chain in the β. position.

The blood pressure raising action of nicotine is very great, small doses injected into the circulation will raise the pressure as much as adrenaline. There is however, quick paralysis of the nervous system and a second dose may have no action, or even cause a fall of pressure or death of the animal. This blood pressure raising seems to be due to the pyrrolidine moiety and not to the pyridine ring since the action is not shown by pyridine or nicotinic acid, but is produced by piperidine, pyrrolidine and N, methyl pyrrolidine.

Nicotine occurs in plants in combination with malic and tartaric acids. At least three other alkaloids also occur in tobacco. These are nicotimine, nicoteine and nicotelline. The natural nicotine is levo-rotatory, synthetic nicotine like most synthetic products, is racemic. This synthetic product has been separated by Pictet from the tartrate into the optical antipodes, and the levo-form corresponded in every way to the natural product. The lethal dose of l. nicotine for guinea pigs, is only one-half that of the dextro-form, and the toxic symptoms are different from the dextro (Mayer Verichte, 1905, 38, p. 597).

Nicotine is extremely poisonous. Four milligrams (about 1/10 drop) in man have produced severe toxic symptoms manifested by giddiness, ringing in the ears, disturbance of respiration, sleeplessness and tetanic spasms. One drop on the tongue of a small cat will cause death in a few minutes. It is absorbed from the tongue, eye, or rectum very rapidly. The harmful effects of tobacco are due to its action on the nervous system, heart and digestive apparatus. The other rather unknown alkaloids of nicotine perhaps also play a role.

The end products of oxidation are not well known because of the small fatal dose, but when minute amounts are inhaled, as in case of smoking it is probably completely oxidized, though after toxic doses some excretion takes place by the lungs and kidneys.

NICOTINIC ACID

The a, β, and γ mono carboxylic acids of pyridine, are known as

Picolinic acid   Nicotinic acid   Isonicotinic acid
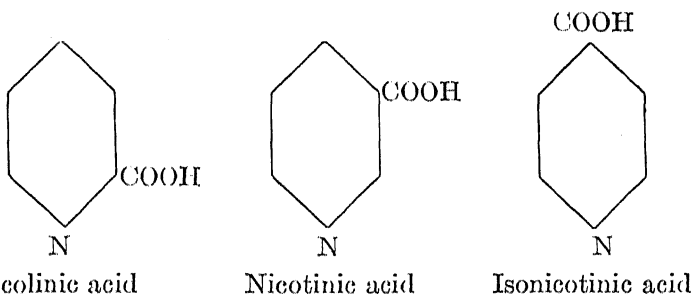
These can be obtained by oxidation of the corresponding ethyl derivatives of pyridine. Their chief interest in pharmacology lies in the fact which Funk has suggested that a mother substance of nicotinic acid is the vitamine of rice and is removed by polishing. Nicotinic acid has been found in the unpurified product, but the pure acid is inactive in the treatment of beri beri.

TESTS FOR NICOTINE

1. It gives the pyridine tests page 251.

2. When a drop of nicotine and a few drops of conc. HCl are evaporated slowly in a watch glass, on a water bath it remains amorphorus. No crystals, or only a suspicion of crystallization, occur when the mixture is kept in a desiccator over sulphuric acid. It differs in this respect from coniine.

3. **Roussin's Test.**—Dissolve a drop of nicotine in 5 cc. of dry ether in a test tube. Add an equal volume of ether containing iodine in solution. Stopper, shake and set aside—in time ruby red crystals—Roussin's crystals—appear. Old resinous nicotine may not give this test until after redistillation.

4. Schindelmeiser's Test.—Fresh nicotine with one drop of formaldehyde free from formic acid, and one drop of concentrated sulphuric acid gives a rose red color. If too much formaldehyde is used a green color results.

5. Physiological Tests.—Nicotine first stimulates then paralyzes all autonomic ganglion cells. When injected into an animal, the heart and respiration are first stimulated, but are paralyzed by larger doses. The blood pressure is raised enormously by the first dose later the drug is inactive because of paralysis of the ganglion cells.

STRYCHNINE

The chemistry of strychnine is not understood. Perkin and Robinson (Jour. Chem. Society, 1910, 305) have suggested as a tentative formula
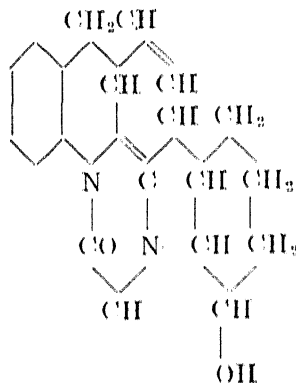
Strychnine

From a therapeutic point of view the effect of strychnine is perhaps over estimated. Toxic doses have a pronounced action, but the actions after therapeutic doses are mild. Respiration is accelerated, the heart rate is slowed, vasomotor tone is increased, due to an action on the central nervous system. Brucine has a similar action but only $\frac{1}{30}$ as strong. Thebaine, one of the opium alkaloids, has a similar action.

The Fate of Strychnine

The greater part of strychnine is excreted unchanged in the urine. A small amount is oxidized in the body. This oxidation has been shown indirectly by injecting strychnine into rabbits, whose kidneys were removed, thus preventing excretion. It was

this way that in small divided doses much more than the
e can be given without causing spasms.   The difference
mount given and the amount excreted is hard to deter-
:urately because of the small fatal dose.

Tests for Strychnine and Brucine

'mate Test.—Place a trace of strychnine on a white glass
ish.   Add a drop of concentrated H_2SO_4, then a small
'f potassium bichromate.   Draw this crystal over the
th a glass rod.   An intense purple or violet color
;radually becoming red, then yellow, or a blue-violet-red-
cllow play of colors, appears.   This is a characteristic
olors and is one of the most beautiful and delicate tests
stry.

'logic Test.—One-tenth of a milligram injected into a 30
)g will cause a characteristic tetanus in about 10

e.—This alkaloid occurs in nux vomica with strychnine:
:i little powdered nux vomica, add a few drops of con-
l HNO_3.   The orange color is due to brucine.
:i small portion of brucine in a test tube add a drop of
A blood red color which turns yellow on heating is the
[t turns to violet when a few drops of sodium thio-
(hyposulphite), $Na_2S_2O_3$, stannous chloride or colorless
:m sulphide are added.   Excess of HNO_3 must be
    The violet color changes to green when NaOH is
These changes are given only by brucine.
ne, $C_8H_{13}NO_2$, is the chief alkaloid of the nut arecoline
und occurs together with arecaine, arecaidine and guva-
is a colorless volatile oily liquid which boils at about
Arecoline is the methyl ester of arecaidine.

CH   CH .

I_2C C.COOH H_2C C.COOCH$_3$

I_2C CH$_2$ H_2C CH$_2$

N.CH$_3$ N.CH$_3$
Arecaidine   Arecoline
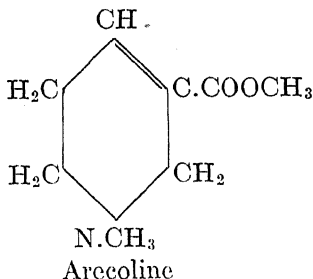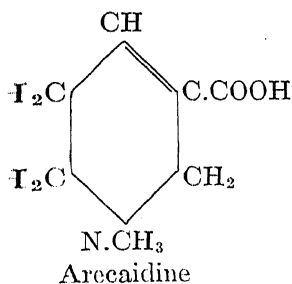
Arecoline has been prepared synthetically by Wohl and Johnson (Berichte, 1907, 40, p. 4712) commencing with acrolein. The synthesis is complex.

Arecoline and its salts are highly toxic and resemble nicotine and pilocarpine in action, while arecaidine is non-toxic. They act on the nerve endings of the para sympathetic system causing a marked flow of saliva. It also resembles nicotine in action and it may be said from its action to be a combination of nicotine and pilocarpine. Large doses may cause convulsions which soon pass into paralysis. Some European pharmacopœias recognize arecoline as a sialogogue and diaphoretic.

Little is known regarding the fate of these alkaloids in the body.

Quinoline—Quinoline is a colorless oil having a specific gravity of 1.095 at 20°C. and boiling at 239°. It occurs together with isoquinoline, in coal tar and bone oil. It may be considered as a condensation of benzene and pyridine rings.
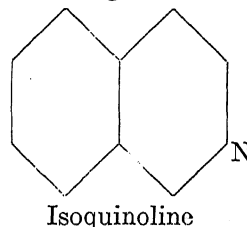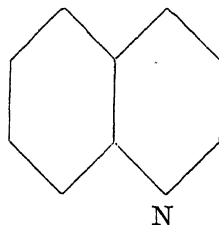
N   Isoquinoline

Both are found in coal tar and bone oil distillates. They are hard to separate pure and are, therefore, made synthetically. The formation of quinoline from aniline and allyl aldehyde proves its formula:
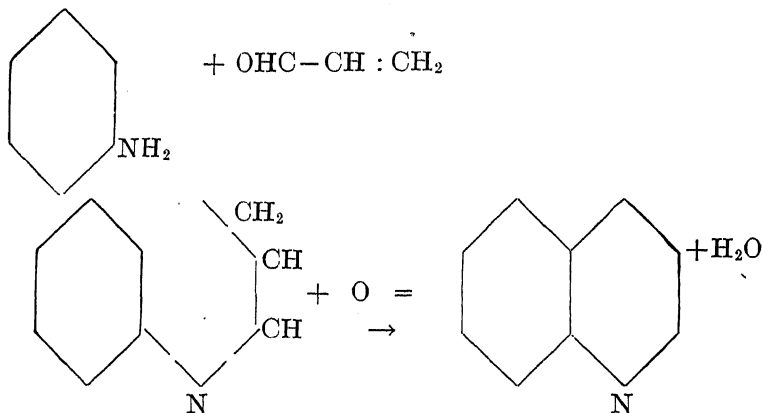
Quinoline Alkaloids.—The important representatives under this head are the strychnine and quinine alkaloids. Quinoline itself has antiseptic and antipyretic properties. Compared with quinine it is, however, feebly antipyretic. The structure of quinine has not yet been confirmed, but is represented by:

$$CH_2 \text{------} CH$$
$$CH_2 \quad CH\text{---}CH = CH_2$$
$$CH_2 \quad CH_2$$
$$CHOH\text{---}CH\text{------}N$$

$$\text{---}OCH_3 \qquad \text{Quinine}$$

N
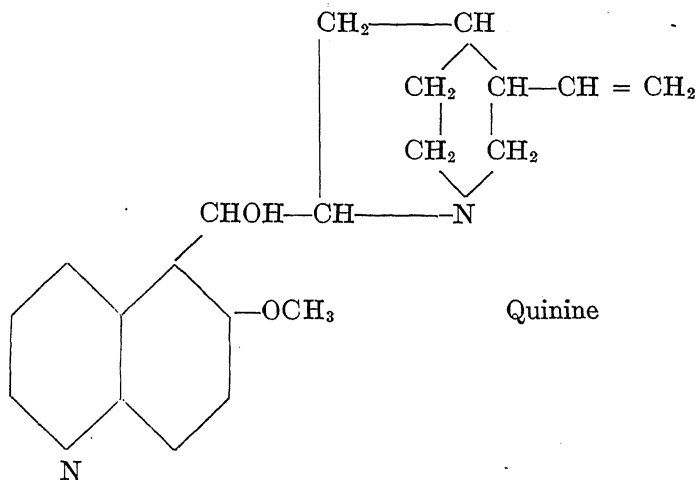
Action

Quinine is toxic to all kinds of protoplasm, but has a specific or selective toxic action on undifferentiated protoplasm such as white cells and malarial plasmodia. Its use in medicine is due to this action. It reduces heat formation by an action on the cells where heat is generated, though it to some extent increases heat loss. This antipyretic action is, however, small in amount. The action of quinine is thought to be due mainly to the piperidine ring portion of it, which Fränkel has called the "Loiponic acid portion." The vinyl side chain on this ring is not considered important in its action.

The Fate of Quinine in the Body

70 to 75 per cent. of it is oxidized and disappears. The remainder is excreted in the urine, only traces being found in the feces. No tolerance for it is gained by the body, and the rate of oxidation remains the same after prolonged usage.

Schmitz (Schmidebergs Arch., 1907, 56, 301) gives the following experiments to show the excretion of quinine:

Exp.　I. 0.817 g. quinine given, 0.217 g. recovered—26.6 per cent.
Exp.　II. 0.817 g. quinine given, 0.244 g. recovered—29.9 per cent.
Exp. III. 1.226 g. quinine given, 0.346 g. recovered—29.7 per cent.

When given subcutaneously the excretion is slower.

Day	Quinine given daily	24-hour urine, cc.	Quinine recovered	Per cent.
Second..................		1400	0.108	17.9
Third...................		1700	0.120	19.8
Fourth.................	0.605	1400	0.083	13.7
Fifth...................		1450	0.128	21.1
Sixth...................		1600	0.076	12.6
Seventh................		1500	0.071	11.7

ASSAY OF THE ALKALOIDS IN CINCHONA BARK

The Calisaya bark is most easily worked and is crystallized most readily by the Keller-Haubensack method: Put 12 grams of calisaya bark in fine powder in a flask and add 120 grams of ether. Shake thoroughly and add 10 cc. ammonia hydroxide—10 per cent. NH_3. Shake frequently during 30 minutes. Then add 15 cc. water and shake thoroughly. Pour 100 grams of the clear ether extract into another flask and add 40 cc. of 1 per cent. sulphuric acid. Shake thoroughly and allow to settle. The acid aqueous solution contains the alkaloidal sulphates. Pour off most of the ether without losing any of the water solution. Transfer the acid solution to a separatory funnel and make alkaline with ammonium hydroxide (6 cc. 10 per cent. solution). Extract with a mixture of $\frac{1}{4}$ ether and $\frac{3}{4}$ chloroform, using about 40 cc. of the mixture. Separate this extract and transfer it to a dry flask. Repeat the extraction with 20 cc. of the ether chloroform mixture. Separate and transfer this also to the flask containing the first extract. To get rid of the water filter through a dry filter into a weighed dry flask and allow to evaporate. The

alkaloids will crystallize out. After the solvent has evaporated, weigh and calculate the percentage of alkaloids in the bark.

Tests for Quinine

A solution of quinine in sulphur, acetic or tartaric acids shows a beautiful light blue fluorescence. The addition of a small amount of these acids increases the fluorescence. Solutions of the alkaloid in hydrochloric or hydrobromic acids are not fluorescent. Salts diminish it. The fluorescence is best seen by drawing the solution into a pipette.

Thalleioquine Test.—(Thallos—green). To 10 cc. of a solution of quinine bisulphate add a few drops of freshly prepared chlorine or bromine water and an excess of ammonia. Stir. A characteristic emerald green color develops. Urea, antipyrine and caffeine, interfere with this test. Morphine, pilocarpine, cocaine, atropine, codeine, strychnine, phenol, and chloral have no influence. It is very important that the chlorine or bromine water be freshly prepared as the presence of HCl or HBr may prevent the development of the color.

Isoquinoline Alkaloids.—The most important are papaverine, hydrastine, narcotine, cotarnine, and berberine.

The formula of none of these is definitely established. Skeleton formulæ for papaverine and berberine are:
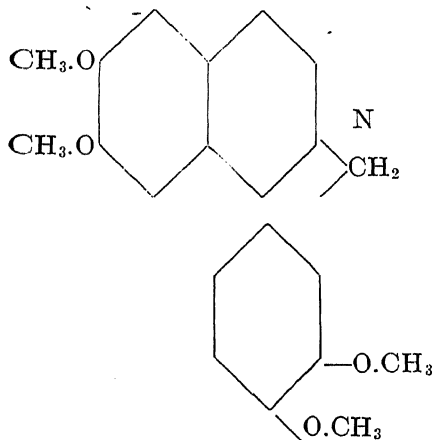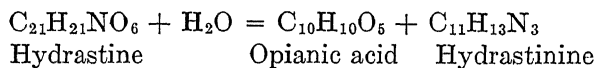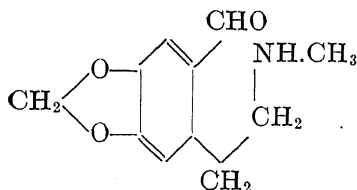

Papaverine
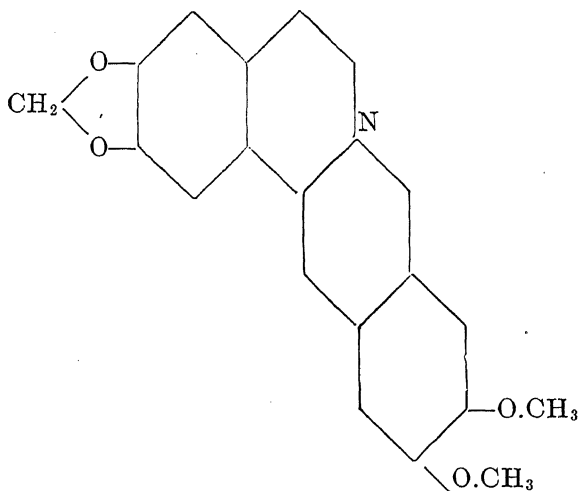
Berberine

They are of little importance in medicine and their fate in the body is not well known.

Hydrastine and Hydrastinine.—These are isoquinoline alkaloids prepared from the root of hydrastis canadensis. On decomposition, hydrastine takes up water and hydrastinine and opianic acid are produced:

$$C_{21}H_{21}NO_6 + H_2O = C_{10}H_{10}O_5 + C_{11}H_{13}N_3$$

Hydrastine   Opianic acid   Hydrastinine

Opianic acid has the formula:
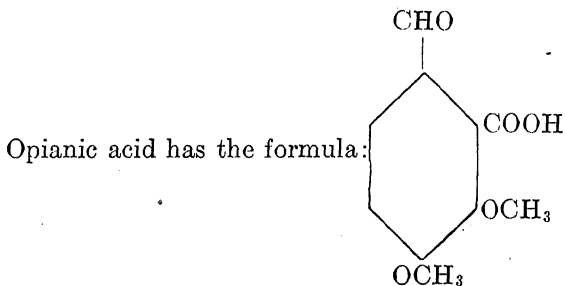
Formulas assigned to hydrastinine and hydrastine are:

Hydrastinine
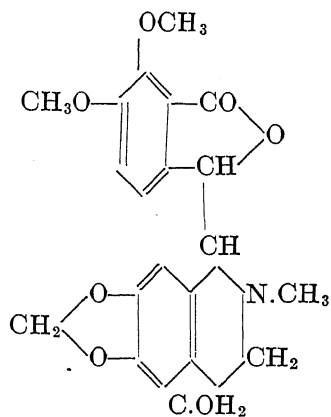
Hydrastine

Narcotine, an opium alkaloid, is methoxy hydrastinine and yields opianic acid on hydrolysis. Hydrastinine has been synthetized by Fritsch and its synthesis throws light on the structure of hydrastinine. Hydrastinine increases the reflex irritability of frogs leading to tetanus resembling that produced by strychnine, and finally to paralysis. In mammals the small amounts slow the pulse; larger doses cause convulsions and tetanus. The pulse is slowed by stimulation of the vagus center, and blood pressure rises for the same reason. It also causes contraction of the uterus. It is excreted unchanged in the urine.

Hydrastinine.—The hydrolysis of hydrastine changes its action markedly. Hydrastinine causes but a small increase in blood pressure. It has no convulsant action but instead is a central depressant and does not weaken the heart, but stimulates it by direct action. Its most important action is on the uterus—due to a direct action on the muscle though there is some action through the nerves.

Hydrastine Tests

1. Concentrated sulphuric acid dissolves hydrastine without color until warmed when the solution becomes violet.

2. When dissolved in dilute sulphuric acid, and very dilute potassium permanganate added, drop by drop, hydrastine is converted into hydrastinine, and the solution shows a beautiful blue fluorescence.

3. Froehde's reagent dissolves hydrastine with a rose red changing to brown color.

4. Soluble chromates precipitate insoluble hydrastine chromate which gives a fleeting red color with sulphuric acid.

HYDRASTININE

1. It crystallizes from light petroleum in colorless glancing needles which melt at 116°–117°C.

2. It is optically active.

3. It is soluble in alcohol, sparingly soluble in water, forming yellow fluorescent solutions.

4. It forms salts with hydrochloric acid—which is the form of the alkaloid used in medicine. The aqueous solutions show a blue fluorescence. Bromine water gives a yellow precipitate.

Narcotine.—Narcotine is an opium alkaloid; in composition it is methoxy-hydrastine. It crystallizes from alcohol in color-less needles which melt at 176°C. When hydrolyzed with dilute acids it yields opianic acid and hydro-cotarnine.
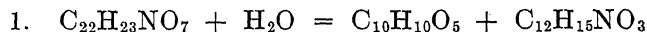
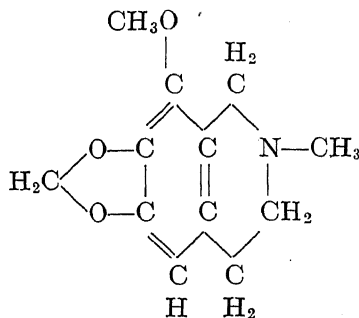1. $C_{22}H_{23}NO_7 + H_2O = C_{10}H_{10}O_5 + C_{12}H_{15}NO_3$
     Narcotine   Opianic acid   Hydro-cotarnine.

2. With dilute HNO_3 narcotine gives opianic acid and co-tarnine the constitution of which are

Opianic acid

Narcotine

$$CH_3O$$
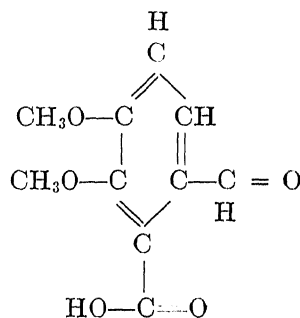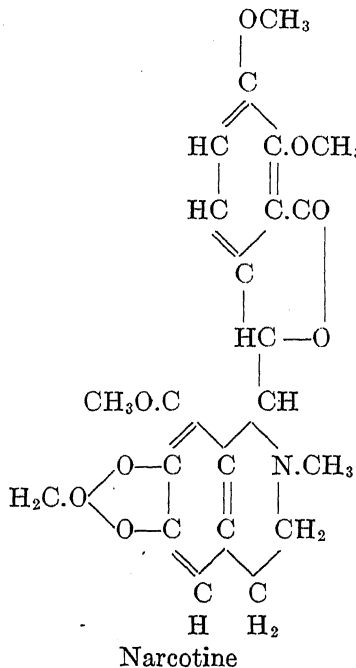
Hydro-cotarnine

In action narcotine resembles morphine but is less hypnotic and has some strychnine-like action though the hypnotic action predominates (see page 256). Mohr states that in cats convulsions precede the narcotic stage. It is but little used in therapeutics, although it has some antipyretic action.

Tests for Narcotine

1. The alkaloid dissolves in concentrated sulphuric acid with a greenish color changing to reddish violet and after several days to a raspberry red.

2. When narcotine is dissolved in concentrated sulphuric acid and a trace of nitric acid added a red color is produced.

3. A solution of narcotine in sulphuric acid gives a blue color on warming with gallic acid (Labat).

Cocaine is the alkaloid of coca leaves. It is a white crystalline solid that melts at 98°C. The hydrochloride is the most important salt. The formula of cocaine is.
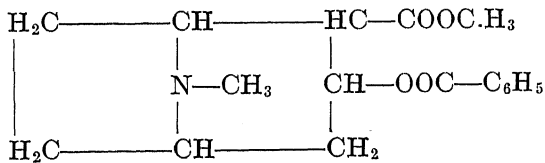
Cocaine or methyl benzoyl ecgonine

On hydrolysis cocaine gives methyl alcohol, benzoic acid and ecgonine:

$$CH_2 \text{————} CH \text{————} CH.COOH$$

$$N.CH_3 \qquad C\begin{matrix} H \\ OH \end{matrix}$$

$$CH_2 \text{————} CH \text{————} CH_2$$
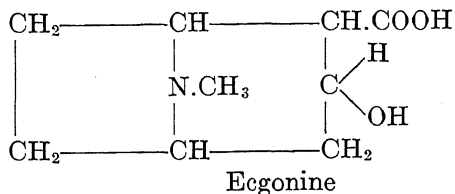
Ecgonine

Cocaine can be prepared from ecgonine by benzoylation and methylation; and ecgonine has been synthetically prepared from tropine, but so far the synthetic product has not been separated into its optical isomers. The natural product like most natural alkaloids is levorotatory. A dextrotatory (isococaine) isomeride of l. cocaine has been prepared from coca leaves, but this is now thought to be formed from the l. cocaine by the action of alkalies.

L. cinnamyl cocaine $C_{19}H_{23}O_4N$ is the chief alkaloid of the Java cocoa leaves. The d. isomeride does not occur in the coca leaves but has been prepared synthetically.

Action of Cocaine

The chief action of cocaine is its local anesthetic effect. This is due to its general protoplasm action, though it acts more strongly on the sensory nerves than on motor ends. The effect is due to the benzoyl group. Large doses first stimulate, then paralyze the central nervous system, chiefly in a descending direction. The heart muscle is directly stimulated by small doses and paralyzed by larger doses. The striated muscles are also stimulated by a direct action. There is a marked mydriasis, formerly thought to be due to stimulation of the sympathetics locally, but later work questions this location. The toxic dose of cocaine varies enormously. Swabbing the tonsils with 4 per cent. has proved fatal in some cases while over 1.5 grams have been taken per os with recovery.

The Fate of Cocaine in the Body

Neither man nor dog eliminates in the urine more than 5 per cent. of the cocaine ingested, and since the urine contains no ecgonine it is thought to be profoundly changed in the organism. In the oxidation in the body it is thought to be first decomposed into ecgonine, benzoic acid and methyl alcohol, and these are
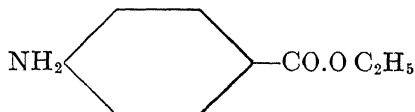
then oxidized. Proells could not detect cocaine in cadaveric material after 14 days.

ARTIFICIAL COCAINES

A large number of artificial cocaines have been prepared. All these contain a benzoyl radical. The most important artificial cocaines are:

Anesthesine, or para amino ethyl benzoic acid:

$$NH_2 \text{—} \langle \bigcirc \rangle \text{—} CO.O\ C_2H_5$$

Pro-cocaine or novocaine is the hydrochloride of the diethylamine derivative of anesthesine or para amino benzoyl di-ethyl amino ethanol and has the formula.

$$NH \langle \bigcirc \rangle CO.O.CH_2CH_2N(C_2H_5)_2HCl$$
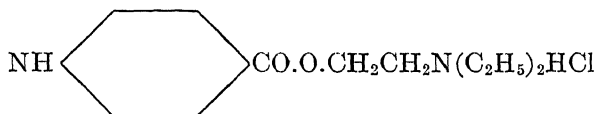
A number of other substitutes have been prepared.

Tests for Cocaine

1. Heat a few milligrams of cocaine with a few drops of alcohol and concentrated H_2SO_4. Note the odor of ethyl benzoate.

$$C_6H_5COOH + C_2H_5OH = C_6H_5COOC_2H_5 + H_2O$$
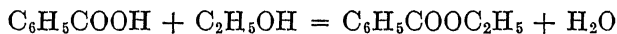
2. Boil a solution of cocaine with a drop of H_2SO_4 and add a drop of Fe_2Cl_6. Ferric benzoate is precipitated.

3. Physiological tests: Local anesthesia and dilation of the pupil, when applied locally.
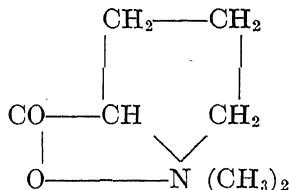
THE PYRROL OR PYRROLIDINE GROUP OF ALKALOIDS

1. This includes, in addition to pyrrol and pyrrolidine, hygrine, a derivative of n. methyl pyrrolidine:

$$\begin{array}{l} CH_2.CH\text{———}CO.CH_2.CH_3 \\ | \qquad\qquad \diagdown N.CH_3 \\ CH_2\ CH_2 \diagup \end{array}$$
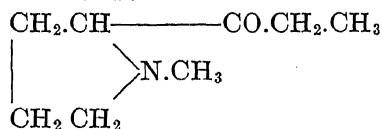
and kuskhygrine from the leaves of erythroxylon coca.

2. Stachydrine from stachys tuberifera has the formula.

$$CH_2\text{---}CH_2$$
$$CO\text{---}CH \quad CH_2$$
$$O\text{---}N\ (CH_3)_2$$

which is a dimethyl betaine of pyrrolidine.

The atropine and cocaine group of alkaloids may be considered in this group or in the tropane group. They may be regarded as a combination of a piperidine and a pyrrolidine nucleus, which is tropane

$$CH_2\text{---}CH\text{---}CH_2$$

pyrroli- N-CH$_3$ piper- CH$_2$
dine   idine

$$CH_2\text{---}CH\text{---}CH_2$$

Tropane
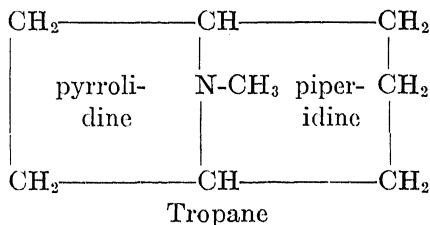
Pyrrol—(pyros, fire-ol., oil) is a constituent of coal tar, and a product of the distillation of bones. It has the formula: C_4H_5N or
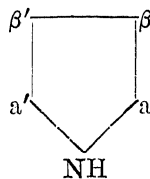
$$CH\text{---}CH$$
$$CH \quad CH$$
$$NH$$
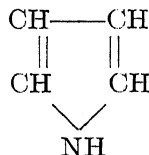
It is more toxic than pyridine or piperidine. It resembles benzene in action.
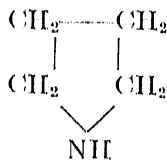
Blood coloring matter, chlorophyll and protein decomposition products contain a pyrrol nucleus. The derivatives of pyrrol are classified according to the scheme
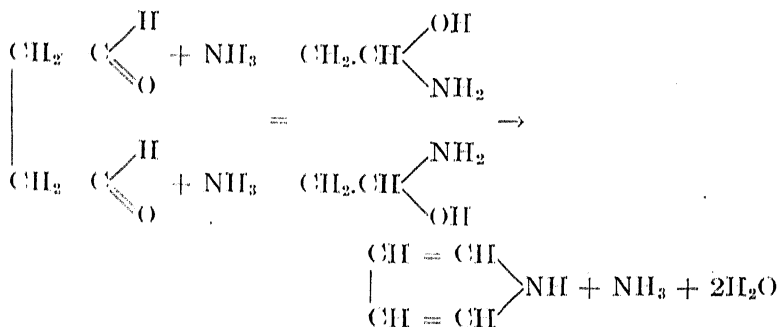
4———3
5   2
1
NH

or

β'———β
a' a
NH
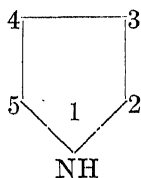
On reduction with hydriodic acid and phosphorus, pyrrol yields pyrrolidine:

$$\begin{array}{ccc}
CH_2 & \!-\! & CH_2 \\
| & & | \\
CH_2 & & CH_2 \\
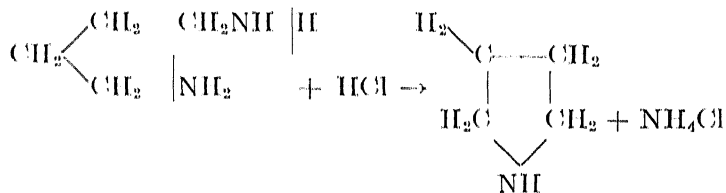& \searrow \ \swarrow & \\
& NH &
\end{array}$$

which is a much stronger base than pyrrol.

Pyrrol has been synthesized in several ways. It has been formed by the interaction of succin-dialdehyde and ammonia:

$$\begin{array}{c}
CH_2 \quad C\!\!<\!\!\begin{array}{c}H\\ \\O\end{array} + NH_3 \quad CH_2.CH\!\!<\!\!\begin{array}{c}OH\\ \\NH_2\end{array} \\
| \\
CH_2 \quad C\!\!<\!\!\begin{array}{c}H\\ \\O\end{array} + NH_3 \quad CH_2.CH\!\!<\!\!\begin{array}{c}NH_2\\ \\OH\end{array}
\end{array}$$

$$\begin{array}{c}
CH = CH \\
| \qquad\qquad >NH + NH_3 + 2H_2O \\
CH = CH
\end{array}$$

Pyrrolidine has also been formed by heating penta-methylene diamine with hydrochloric acid.

$$CH_2\!\!<\!\!\begin{array}{c}CH_2\\ \\CH_2\end{array}\begin{array}{c}CH_2NH\\ \\NH_2\end{array}\begin{array}{c}H\\ \\\end{array} + HCl \rightarrow \begin{array}{c}H_2\\ \searrow\! C\!-\!CH_2 \\ | \qquad | \\ H_2C \qquad CH_2 + NH_4Cl \\ \searrow\ \swarrow \\ NH \end{array}$$

Pictet (Ber. deut. chem. Gesells, 1907, 40, 3771) thinks that alkaloids in plants are formed by the breaking down of complex nitrogenous substances, such as protein and chlorophyll, and by a condensation of these substances with others, as in the syntheses above. He is of the opinion that methylation within the plant can be accomplished by the action of formaldehyde on amino or hydroxyl groups:

$$ROH + CH_2O = RO\ CH_3 + O$$
or
$$RNH_2 + CH_2O = RNHCH_3 + O$$
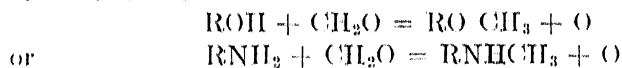
It should be noted that methylation in the animal body is of rare occurrence (see p. 249). Various alkaloids may then be formed by other changes, for example, by heat. The secretion of alkaloids by plants may, according to Pictet, be a means of getting rid of nitrogen which cannot be used in metabolism. It is a curious fact that these alkaloids, though highly toxic to animals, are not toxic to the plants themselves. The theory that alkaloids are necessary compounds in the plant and are secreted to protect the plant from animals does not agree with the fact that plants grow just as well when moved into other latitudes, yet the content of alkaloid is much diminished.

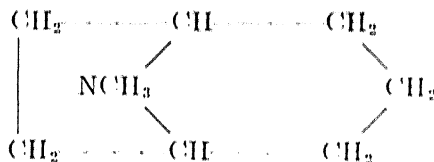Methyl pyrrol can be changed to pyridine by heat:

$$N.CH_3 \qquad\qquad N \qquad Pyridine.$$
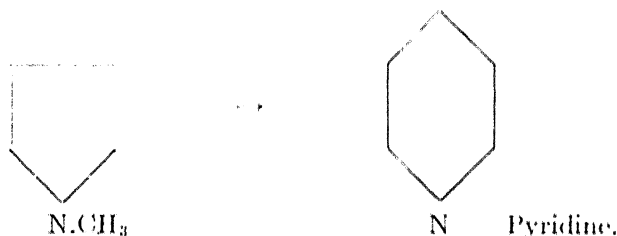
Fate of Pyrrol in the Body

Pyrrol and its derivatives appear to be easily destroyed in the body.

TROPINE ALKALOIDS WITH DIHETERO CYCLIC NUCLEI

Tropane Alkaloid. Tropane has the formula:

$$CH_2 \cdots CH \cdots CH_2$$
$$NCH_3 \qquad\qquad CH_2$$
$$CH_2 \cdots CH \cdots CH_2$$

This substance contains a piperidine ring and a pyrrolidine ring, consequently there may be some duplication in the classification. The tropane alkaloids would include:

I. The atropine group—atropine, hyoscine, hyoscyamine.

II. The cocaine alkaloids—cocaine and tropo cocaine.

III. The pomegranate alkaloids—pelletierine, isopelletierine, etc., from punica granatum.

IV. Cytisine from cytisus laburnum, lupinine from lupinus-luteus and niger, etc.

Tropine differs from tropane in that one of the H. ions of tropane is replaced by hydroxyl:


Tropine　　　　　　　　　　Tropic acid
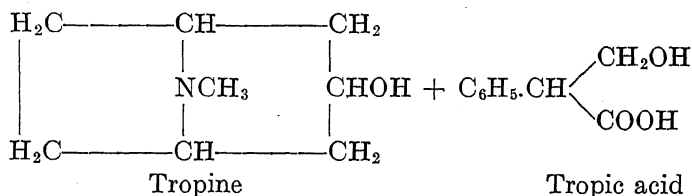
Atropine is a combination of tropic acid and tropine. When other acids are used tropeines are formed.

Atropine:
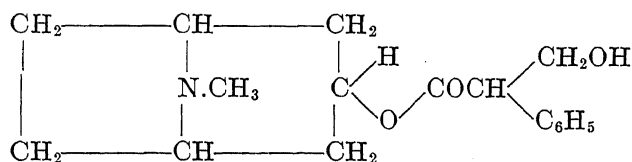
The main actions of atropine are stimulation of the central nervous system and paralysis of the peripheral para sympathetic nerve endings. In these actions the tropine part of the ester is the more important. This is proved by the fact that other acids may be substituted for tropic acid. The only other acid that has yielded an ester of practical importance is mandelic acid, which is

Homatropine, $C_5H_7N(CN_3)C_2H_4O.CO.CHOH.C_6H_5$
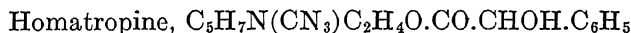
The action of homatropine is practically the same as atropine but it is less toxic. It is used especially in eye work, since the dilation of the pupil caused by it lasts only a few hours, while that caused by atropine may last for days.

The tropines derived from benzoic and cinnamic acids exert no mydriatic action.

The Fate of Atropine in the Body

Atropine is readily absorbed and excreted. After administration it has been found in most all tissues and fluids. It has

been found in the milk and in the fœtal blood. It is decomposed to tropine and oxidized in the body, though some may escape unchanged in the urine. It is very resistant to putrefaction and has been found in bodies after two years.

Tests for Atropine

1. Boil a small amount with dilute H_2SO_4. This gives an orange flower odor which changes to that of bitter almond. The solution gives a green color when a trace of potassium bichromate is added.

2. To a trace of atropine in a test tube add 10 drops of H_2SO_4 and heat until it becomes brown or until white fumes appear. Then add 2 volumes of water. During the heating there will be a sweetish odor resembling tuberose, which is characteristic (Gulichno). The odor is strengthened by adding a little $KMnO_4$ (Reuss). This test is sensitive to 10 milligrams.

3. **Vitali's Test.**—Put 1 or 2 mgms. of atropine in an evaporating dish and dissolve in it a few drops of fuming nitric acid and evaporate to dryness high above the flame or on a water bath; cool and touch the spot with a drop of alcoholic solution of KOH. The color will be violet, changing to cherry red. Veratrine also gives this test, hence it is characteristic only in the absence of veratrine.

4. Atropine dilates the pupil and gives a dry sensation to the mouth and eliminates vagus action on the heart, thus causing a very rapid rate of heart. These tests can be recognized with certainty in presence of veratrine.

Scopolamine or Hyoscine, $C_{17}H_{21}O_4N$, is a tropane alkaloid whose composition is so closely allied to atropine and hyoscyamine that the same reactions are given. With mercuric chloride atropine gives a yellowish red precipitate of mercuric oxide, while hyoscyamine gives a white precipitate.
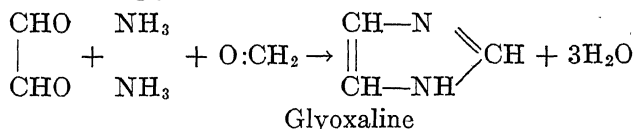
When warmed with barium hydroxide, scopolamine is hydrolyzed yielding tropic acid and a base $C_2H_{13}O_2N$ — named pseudo-atropine, oscine, oxytropine or scopoline.

Hyoscine resembles atropine in its action on the nerve terminals, but has practically no action in stimulating the central nervous system. The main action is a feeling of fatigue and drowsiness. It has been often used to produce "twilight sleep."

THE GLYOXALINE GROUP OF ALKALOIDS

This includes pilocarpine, isopilocarpine and jaborine, which may be a mixture of pilocarpine and isopilocarpine. There are other unimportant members such as pilocarpidine. The only one of interest in medicine is pilocarpine.

Glyoxaline is metameric with pyrazole and may be regarded as a pyrrol nucleus in which one methine radical has been replaced by nitrogen. It is formed when ammonia acts on glyoxal in presence of formaldehyde; sufficient formaldehyde may be formed from the glyoxal without the extra addition of it.

$$\begin{array}{ccc} CHO & NH_3 \\ | & + & + O:CH_2 \to \end{array} \quad \begin{array}{c} CH\!-\!N \\ \| \qquad \searrow CH + 3H_2O \\ CH\!-\!NH \end{array}$$

$$\begin{array}{ccc} CHO & NH_3 \end{array}$$

Glyoxaline

The purine group of alkaloids contain a glyoxaline nucleus and may be regarded as a glyoxaline ring condensed with pyrimidine.
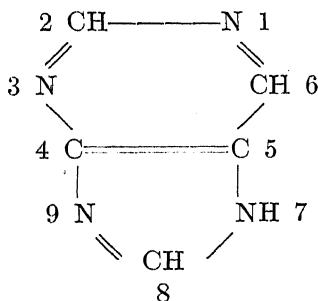
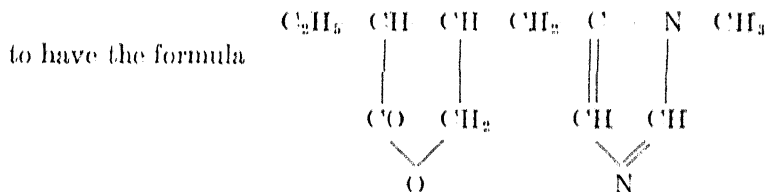Glyoxaline may also be prepared by oxidizing benzimidazole with permanganate.

Glyoxaline dicarboxylic acid

$$\begin{array}{c} H.\ C\!-\!N \\ \| \qquad \searrow CH + 2CO_2 \\ H.\ C\!-\!NH \end{array}$$

Glyoxaline
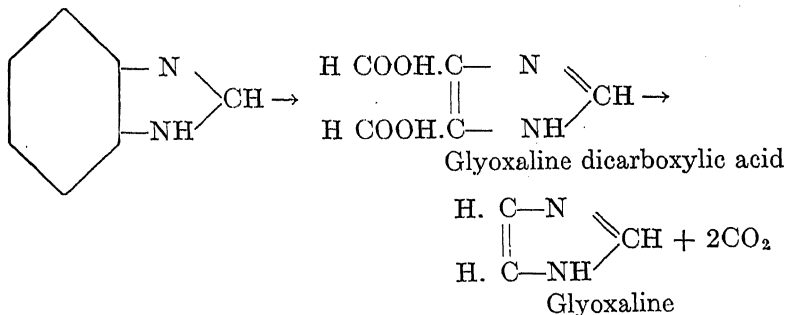
Compare with the given formula for purine, p. 283.

Pilocarpine is a colorless oil, freely soluble in water, alcohol and chloroform and but slightly soluble in ether and light petroleum. It readily forms crystalline salts with acids and the nitrate is the most important. It is readily soluble in water. The alkaloid of commerce is derived from the leaves of pilocarpus jaborandi, a South American plant. It has been prepared synthetically, and based on this synthesis Jowett and Pinner consider pilocarpine

to have the formula

$$C_2H_5 \quad CH \quad CH \quad CH_2 \quad C \quad N \quad CH_3$$
$$| \qquad | \qquad | \qquad \| \qquad |$$
$$CO \quad CH_2 \qquad CH \quad CH$$
$$\diagdown \diagup \qquad \diagdown \diagup$$
$$O \qquad\qquad N$$

Iso-pilocarpine is probably a stereoisomeride.

Action of Pilocarpine

Pilocarpine is a strong stimulant to all glands, especially the sweat, salivary, bronchial, lachrymal, gastric, and intestinal. The smooth muscles of the alimentary tract, the urinary bladder, spleen and bronchi are stimulated . The muscles of the blood vessels are not influenced, but when given intravenously the heart is slowed by an action on the vagus endings. When taken by mouth, the heart rate may be increased. This action has not been satisfactorily explained; it may be secondary. There is some stimulation of the central nervous system, followed by paralysis after large doses. The whole action of pilocarpine resembles that of muscarine, but it is much less poisonous.

Pilocarpine is used in medicine almost totally for its diaphoretic action, especially in cases of dropsy and similar diseases. Iso-pilocarpine and pilocarpine have a similar but weaker action. Pilocarpic acid is inactive. Very large or toxic doses of pilocarpine cause profuse sweating, flow of nasal secretion, tears, pallor, slow heart, and arrythmias, vomiting, diarrhœa, contracted pupil, tremors, cloudiness of the cornea, tracheal râles, and edema of the lungs. The part played by the glyoxaline ring has not been determined.

Atropine is antidotal in all cases and a small dose will neutralize the effects of a large dose of pilocarpine.

Fate in the Body

A large part is excreted unchanged in the urine.   There may be some in combination (Curci).

Tests for Pilocarpine

1. The general alkaloidal reagents especially delicate for pilocarpine are iodo-potassium-iodide, phosphomolybdic acid, and phospho tungstic acid.

2. Pilocarpine nitrate melts at 176° 178°.

3. A solution of pilocarpine in formalin sulphuric acid when warmed becomes yellow-brown-red.

4. In a test tube add a crystal of potassium bichromate to 2 cc. chloroform with pilocarpine and 1 cc. hydrogen peroxide; shake. Depending on the amount of pilocarpine the chloroform is blue violet, dark or indigo blue.

5. Physiological tests: These are constriction of the pupil, slowing of the heart, profuse sweating and an edematous condition of the lungs.

PHENANTHRENE ALKALOIDS

Phenanthrene is an isomer of anthracene and occurs with it in coal tar.

Phenanthrene

Phenanthraquinone
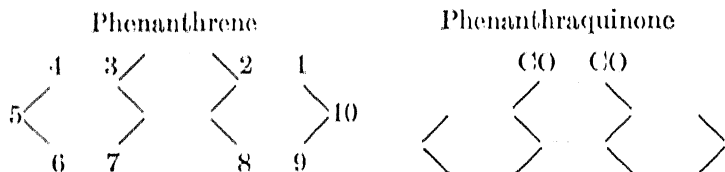
Phenanthrene Group. The most important representatives of the group are morphine, codeine, thebaine, and apomorphine. On distillation with zinc dust these alkaloids yield pyrrol, pyridine, quinoline, and phenanthrene; consequently, they may be placed under either of these headings.
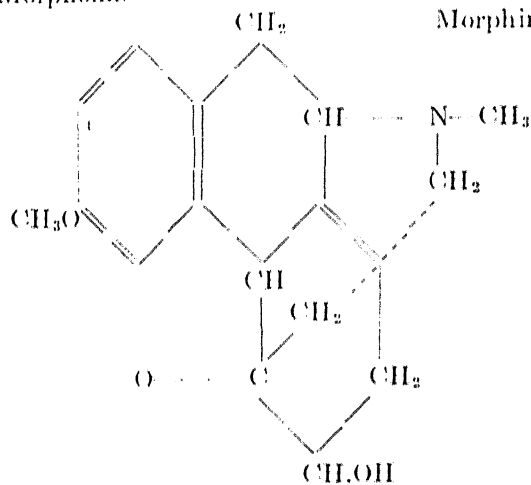
Phenanthraquinone is obtained from phenanthrene by oxidation with glacial acetic and chromic acids.   According to Amoss, morphine is a derivative of tetrahydro-dioxy phenanthrene to which a morpholine is added.   To morpholine he assigned the formula·
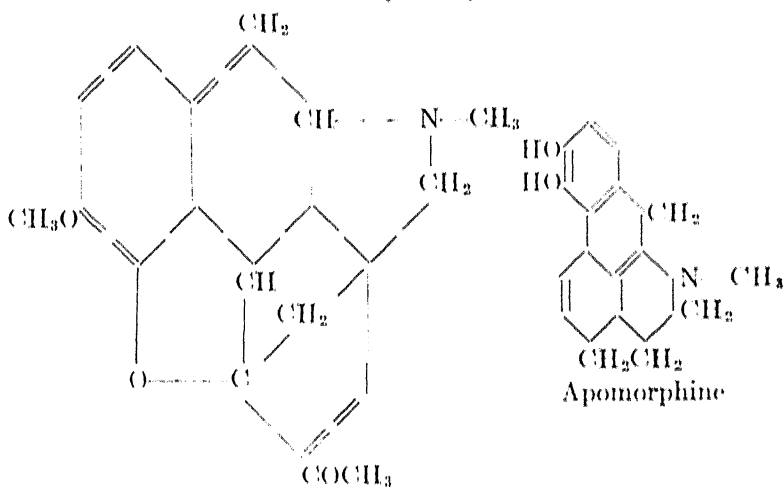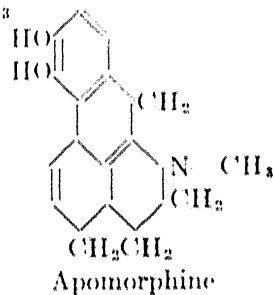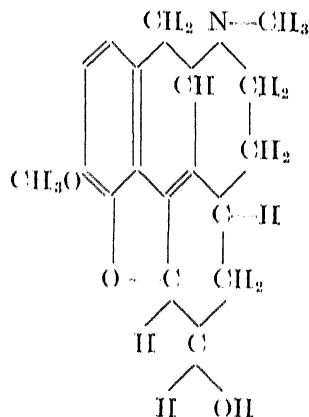
Morpholine

and to morphine

$$\substack{OH \\ OH} C_{14}H_{10}$$
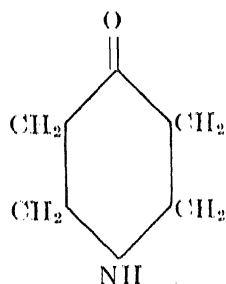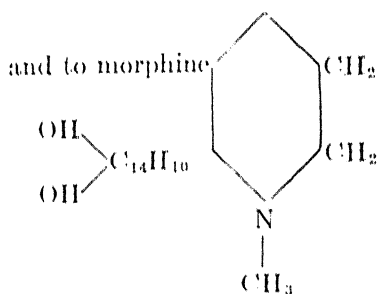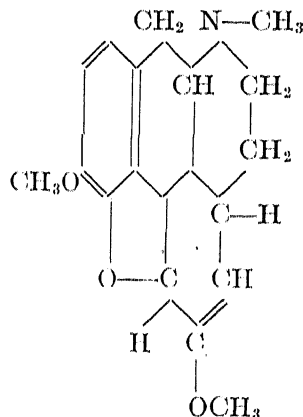
Morphine

Codeine (Knorr)
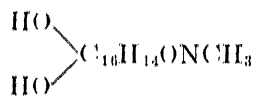
Thebaine (Knorr)

Apomorphine

Codeine (Pschorr)

Thebaine (Pschorr)

Roser and Howard (Berichte, 1886, 19, 1596) think the relationship of morphine, codeine and thebaine may be shown as follows:

$$HO \atop HO \Big> C_{16}H_{14}ONCH_3$$

Morphine

$$CH_3O \atop OH \Big> C_{16}H_{14}ONCH_3$$

Codeine

$$CH_3O \atop CH_3O \Big> C_{16}H_{12}NO.CH_3$$
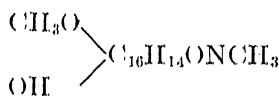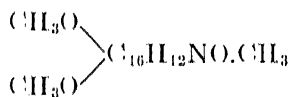
Thebaine

In accordance with this view it has been found that the principal decomposition products of all three are similar. Codeine is methyl morphine. The graphic formulas are now known with certainty, but among others the following have been proposed for morphine:

Knorr's later formula

Pschorr's formula

Bucherer's formula modified by Knorr

The principal pharmacological actions of morphine are:

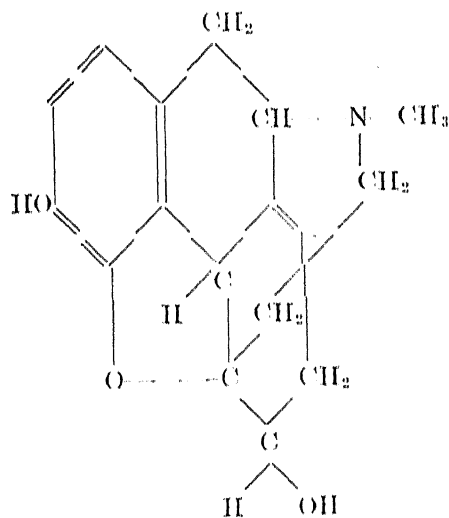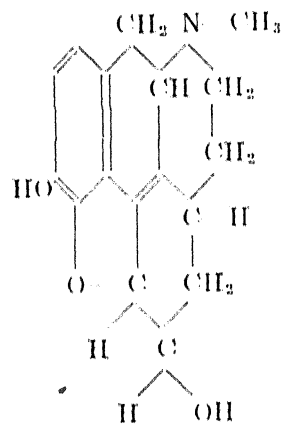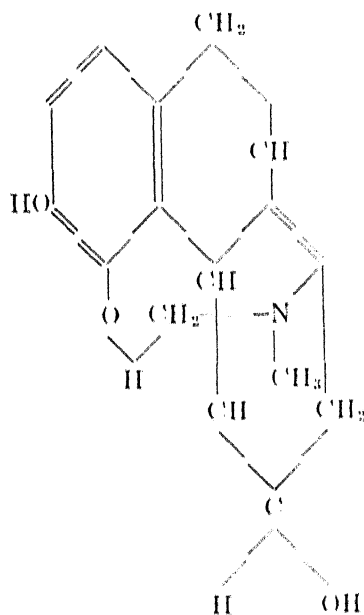1. A marked depression of the central nervous system, commencing above and descending. The perception to pain and the sensitivity of the respiratory center, seem more depressed than other functions.

2. Depression of the blood pressure and slowing of the heart due to an action on the medullary centers.

3. A decrease in the peristalsis of the alimentary canal, preceded in some animals by stimulation.

4. A marked constriction of the pupil, due apparently to the removal of a central action. The constriction disappears in the paralytic stage, and in some animals in which morphine causes stimulation or excitement rather than depression (cat, horse and others) the pupil is dilated at all stages.

5. The cord is stimulated with all these drugs, and the reflexes exaggerated. Morphine applied directly to the cord will cause convulsions, and some of the morphine alkaloids stimulate only. Dixon (Manual of Pharmacology, 1906, p. 137) because of these differences arranges the morphine alkaloids as follows with the percent of these alkaloids in opium

Morphine (most narcotic)................	10.0 per cent.
Papaverine...........................	1.0 per cent.
Codeine..............................	0.5 per cent.
Narcotine............................	6.0 per cent.
Thebaine.............................	0.3 per cent.
Laudanine (most convulsant)...........	trace

Apomorphine.—When morphine is heated in a sealed tube with strong HCl at 140°C. it loses a molecule of water and apomorphine is formed. This change it has also been asserted, occurs when morphine salts or their solutions are exposed to light, but no proof of this has been advanced.

Solutions of apomorphine have a green color and the entire physiological action of morphine is changed by the loss of water from the morphine molecule.

Apocodeine.—$C_{18}H_{19}O_2N$ has been prepared by the action of zinc chloride solution on codeine hydrochloride. It is supposed to bear the same relation to codeine that apomorphine does to

morphine. Dott (Pharm. Journal, 1891, III, XXI, 878, 916, 955, 996) claims that it is not a pure compound, but a mixture of chlorocodeine apomorphine, amorphous bases, and codeine (Knorr and Raabe, *ibid.*, 1908, 41, 3050).

The chief actions of these apo-compounds are:

1. Apomorphine causes vomiting by a strong stimulation of the vomiting center, and

2. Also stimulates: the secretory centers for saliva, perspiration, etc. It has a paralytic action on skeletal and heart muscle.

3. Apocodeine paralyzes all ganglion cells, and is toxic to all forms of motor nerve endings.

The Fate of These Alkaloids in the Body

Morphine is partly oxidized and a part is unchanged and excreted by the alimentary tract. This is a different method of excretion from most alkaloids which are excreted in the urine. Faust found that 70 per cent. of that administered to a non-immunized animal was excreted, but when tolerance is established the oxidizing power of the tissues is increased. The excretion into the alimentary tract begins soon after administration, as shown by the fact that morphine has been found in the vomitus soon after hypodermic administration. Codeine is excreted much in the same way as morphine but tolerance is harder to establish and more is excreted unoxidized. When injected intravenously Marquis found 15 per cent. of the morphine deposited in the liver in 15 minutes and some retained in the central nervous system. A slight amount is excreted in the urine in combination with glycuronic acid. Morphine resists putrefaction and has been found in putrefying material after 15 months.

Tests

Apomorphine.—The solutions have a green color.

1. To a dilute solution add a few drops of HCl or H_2SO_4, then neutralize with Na_2CO_3 and add a drop of an alcoholic solution of iodine. The emerald green color which is produced becomes violet when shaken with ether.

2. Dissolve a trace of apomorphine hydrochloride in water and shake. A green color appears. Add a trace of ferrous sulphate and shake. The solution gradually turns blue and finally black.

On the addition of alcohol the blue color returns (different from codeine and morphine).

3. Dissolve a trace of apomorphine in concentrated H_2SO_4 and add a drop of concentrated HNO_3; a violet color changing quickly to red and yellowish red is formed.

4. Physiologic test: 0.01 gram apomorphine hydrochloride hypodermically in a dog causes vomiting in a few minutes.

Codeine. 1. To a little of the dry alkaloid in a crucible add a few drops of concentrated H_2SO_4 and heat. A greenish color which changes to violet-red results. Morphine gives none, or only a slightly yellow color, except when heated, then it is brown. HNO_3 changes the reddish violet color of codeine to yellow and purple.

2. Codeine with H_2SO_4 heated, with a drop of nitric acid added, gives a blood red color.

3. Codeine with H_2SO_4 gives no color; add a drop of formalin and a violet color is produced. Morphine gives an intense purple.

4. Codeine with H_2SO_4 with a trace of ferric chloride added gives a violet blue color.

Tests for Morphine

1. 1 gram of morphine is soluble in 3340 cc. of water, 210 of alcohol, 6250 of ether, or 1220 of chloroform.

2. A saturated aqueous solution of morphine is alkaline to litmus.

3. Concentrated sulphuric acid produces either no color or only a red or yellow tint when added to a morphine solution. On heating a brown color is developed. Concentrated sulphuric acid containing 0.1 per cent. formalin gives a purple color.

4. Concentrated nitric acid with morphine produces an orange red color fading to yellow.

5. Ferric chloride added to a neutral solution of morphine, made by adding dilute H_2SO_4 to morphine, produces a blue color.

6. Iodic acid test: When morphine in dilute sulphuric, is shaken with a few drops of iodic acid and chloroform, iodine is liberated and dissolves in the chloroform producing a violet color. Other reducing substances may give this test.

7. Prussian blue test: When morphine is added to a dilute

mixture of ferric chloride and potassium ferricyanide, a deep blue color appears. When considerable morphine is added a precipitate may be produced.

8. When morphine is added to silver nitrate with an excess of ammonium hydroxide a gray precipitate of metallic silver is formed.

Thebaine.—1. Thebaine gives a blood red coloration which gradually becomes yellowish red with concentrated sulphuric acid.

2. With nitric acid thebaine gives a yellow color.

3. Chlorine water dissolves thebaine. If ammonia be added to the solution it becomes red-brown.

Papaverine occurs in opium to the extent of 0.5–1 per cent.

Papaverine
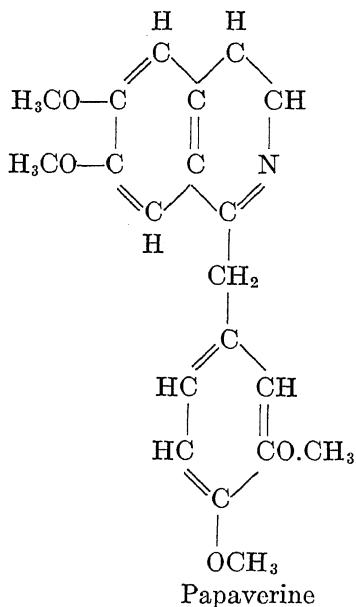
It crystallizes in colorless poisons which melt at 147°C. It is insoluble in water, soluble in ether 1 to 260 and freely soluble in chloroform. Ether partially extracts it from tartaric acid solution, and completely extracts it from alkaline solutions. Chloroform extracts it easily from either acid or alkaline reaction.

Tests

1. When pure, cold sulphuric acid does not color papaverine, it becomes violet when heated. Impure solutions may be violet without heating.

2. Concentrated nitric acid dissolves papaverine with a dark red color.

3. Papaverine gives a purple color, changing to black and green, when dissolved in sulphuric acid containing iodic acid.

4. With iodine in alcohol, papaverine yields a characteristic crystalline periodide.

THE CAFFEINE GROUP

Caffeine and related drugs are important from the standpoints of biochemistry, pharmacology, and as foods. They occur especially in tea, coffee, cocoa, kola, gurana maté and in numerous other plants in small amounts. The most important drugs of this group are:

Purine, or the nucleus of the group.

Caffeine, or 1.3.7—trimethyl xanthine.

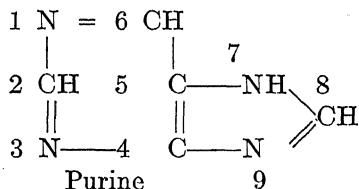Theobromine, 3.7—dimethyl xanthine.

Theophylline, 1.3—dimethyl xanthine.

Xanthine, 2.6—dioxy purine.

Hypoxanthine 6— oxy purine.

Guanine 2—amino. 6 oxy purine.

Adenine 6 amino purine.

Uric acid 8—hydroxy xanthine, or 2, 6, 8 trioxy purine.

```
 1 N  =  6 CH
    |        |      7
 2 CH   5   C——NH  8
    ||       ||      >CH
 3 N——4    C——N  /
        Purine       9
```

The word purine is a portmanteau word, a combination of purum uricum.

```
N(CH3)—CO              NH———CO
   |        |             |       |
  CO      C—N(CH3)       CO      C——N(CH3)
   |       ||    >CH      |       ||    >CH
N(CH3)— C———N /        N(CH3)— N ———N /
     Caffeine              Theobromine
```

$$\begin{array}{c} \text{CH---N---CO} \\ |\qquad| \\ \text{CO} \quad \text{C---NH} \\ |\qquad| \qquad\diagdown\text{CH} \\ \text{CH}_3\text{---N---C----N}\diagup \end{array}$$

Theophylline

$$\begin{array}{c} \text{NH--- CO} \\ |\qquad| \\ \text{CO} \quad \text{C---NH} \\ |\qquad\| \qquad\diagdown\text{CH} \\ \text{NH---C--- N}\diagup \end{array}$$

Xanthine

$$\begin{array}{c} \text{NH---CO} \\ |\qquad| \\ \text{HC} \quad \text{C---NH} \\ \|\qquad\| \qquad\diagdown\text{CH} \\ \text{N--- C--- N}\diagup \end{array}$$

Hypoxanthine

$$\begin{array}{c} \text{NH---CO} \\ |\qquad| \\ \text{H}_2\text{N---C} \quad \text{C---NH} \\ \|\qquad\| \qquad\diagdown\text{CH} \\ \text{N---C--- N}\diagup \end{array}$$

Guanine

$$\begin{array}{c} \text{N}{=}\text{C---NH}_2 \\ |\qquad| \\ \text{HC} \quad \text{C---NH} \\ \|\qquad\| \qquad\diagdown\text{CH} \\ \text{N---C---N}\diagup \end{array}$$

Adenine

$$\begin{array}{c} \text{NH---CO} \\ |\qquad| \\ \text{CO} \quad \text{C---NH} \\ |\qquad\| \qquad\diagdown\text{CO} \\ \text{NH---C---NH}\diagup \end{array}$$
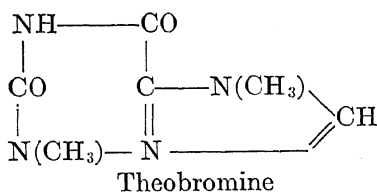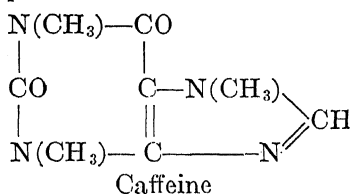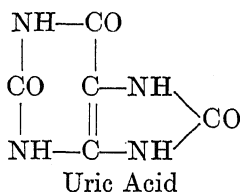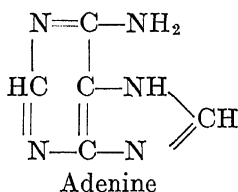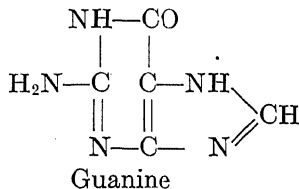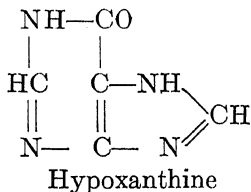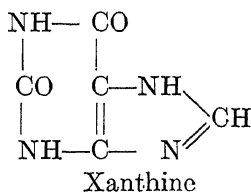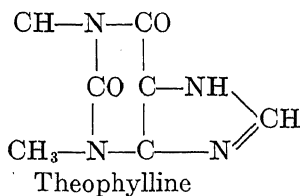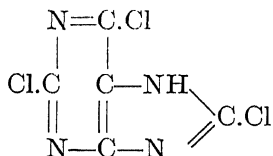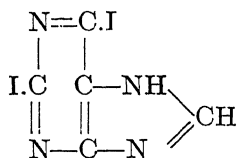
Uric Acid

Purine or the nucleus of the group is of interest only in showing the chemical relationship of the whole group to uric acid. Purine has been prepared from uric acid, and this in turn from simpler well known compounds. The sodium salt of uric acid when treated with phosphorus oxychloride, yields hydroxy di chlor purine.

$$\begin{array}{c} \text{N}{=}\text{C---Cl} \\ |\qquad| \\ \text{Cl.C} \quad \text{C---NH} \\ \|\qquad\| \qquad\diagdown\text{C.OH} \\ \text{N---C---N}\diagup \end{array}$$
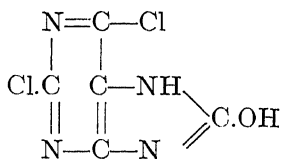
When this is acted on by phosphorus trichloride, it gives trichlor-purine

$$\begin{array}{c} \text{N}{=}\text{C.Cl} \\ |\qquad| \\ \text{Cl.C} \quad \text{C---NH} \\ \|\qquad\| \qquad\diagdown\text{C.Cl} \\ \text{N---C---N}\diagup \end{array}$$

ınd when this is treated with hydriodic acid, diodo-purine is

$$
\begin{array}{c}
N = C.I \\
| \quad | \\
I.C \quad C—NH \\
|| \quad || \qquad CH \\
N—C—N
\end{array}
$$

ormed, which when reduced by zinc dust and water gives purine (p. 283).

According to Fischer purine may occur in the body, but cannot be detected on account of its ease of decomposition in the body.

The establishment of the formulæ of uric acid and related substances has been a slow growth. The suggestions for the synthesis came principally from a study of the products of hydrolysis of uric acid. Among these products were urea, parabanic acid, alloxan, allantoine, etc., depending on the oxidatizing agent. After numerous attempts, the following steps were successful in establishing the synthesis and formula of these bodies.
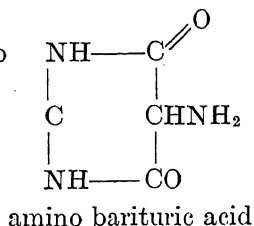
(I)
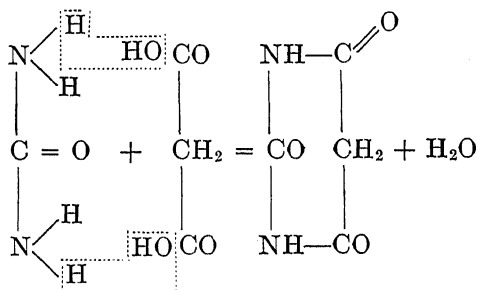
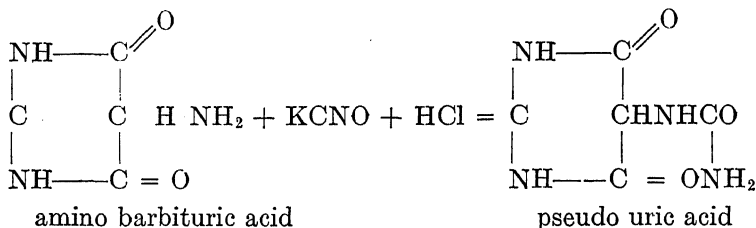urea + malonic acid = malonyl urea or barbituric acid.

(II)
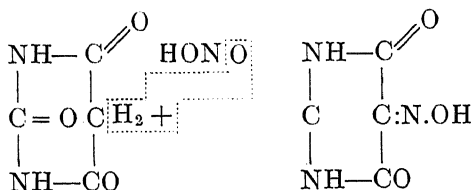
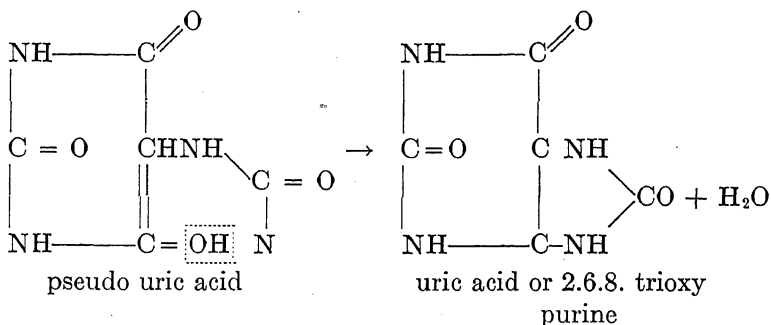Barbituric acid + Nitrous acid = iso-nitroso-malonyl urea

(III) Reduction of iso-nitroso
malonyl urea gives:

$$
\begin{array}{ll}
NH\!\!-\!\!C\!\!\diagup^{O} & \\
| \qquad | & \\
C \qquad CHNH_2 & \\
| \qquad | & \\
NH\!\!-\!\!CO &
\end{array}
$$

amino barituric acid

(IV)

$$
\begin{array}{ll}
NH\!\!-\!\!C\!\!\diagup^{O} & \\
| \qquad | & \\
C \qquad C\ H\ NH_2 + KCNO + HCl = \\
| \qquad | & \\
NH\!\!-\!\!C = O &
\end{array}
\qquad
\begin{array}{ll}
NH\!\!-\!\!C\!\!\diagup^{O} & \\
| \qquad | & \\
C \qquad CHNHCO \\
| \qquad | & \\
NH\!\!-\!\!C = ONH_2 &
\end{array}
$$

amino barbituric acid   pseudo uric acid

(V) Pseudo uric acid loses water on treatment with dilute
mineral acids and gives uric acid.

$$
\begin{array}{ll}
NH\!\!-\!\!-\!\!C\!\!\diagup^{O} & \\
| & \\
C = O \qquad CHNH \\
| \qquad\qquad \| \quad C = O \\
NH\!\!-\!\!-\!\!C = \boxed{OH}\ N \\
\end{array}
\rightarrow
\begin{array}{ll}
NH\!\!-\!\!-\!\!C\!\!\diagup^{O} & \\
| \qquad\qquad | & \\
C = O \qquad C\ NH \\
| \qquad\qquad | \quad\diagdown CO + H_2O \\
NH\!\!-\!\!-\!\!C\!\!-\!\!NH \\
\end{array}
$$

pseudo uric acid   uric acid or 2.6.8. trioxy
                              purine

By reduction, the purin base has been prepared from uric acid,
as shown above.

Caffeine occurs especially in tea and coffee and similar stimu-
lant food' stuffs, in the following amounts:

Tea....... 1–4.8 per cent. Kola nuts..... 2.5–3.6 per cent.
Coffee.... 1–1.5 per cent. Mate......... 1.2–2.0 per cent.
                 Gurana.......... 3.0–5 per cent

It occurs partly free and partly combined as caffeine chlorogenate.
Caffeine has also been prepared synthetically by the action of

methyliodide on theophylline. It crystallizes in slender silky needles which melt at 234°. It is soluble in water 1 : 46, alcohol 1 : 66, and in chloroform 1 : 8. Its solubility in water is increased by heat, citric acid, benzoates and salicylates, bromides, antipyrine and a number of other substances. Combinations, such as caffeine sodiosalicylate and caffeine sodiobenzoate, prepared by mixing caffeine with such solutions and evaporating the mixture, are used in medicine. The object is to increase solubility and to make the preparations available for hypodermic use.

Theobromine is the chief alkaloid of cocoa beans and is found in small quantities in Kola nuts and leaves and in tea leaves. It has also been synthesized. Caffeine may be separated fairly well from theobromine by extraction with cold benzine in which theobromine is insoluble.

Hypoxanthine, and guanine (6 oxy 2 amino purine) occur together in a number of plants, especially, curcubita pepo, hordeum sativum. Hypoxanthine occurs free to some extent in animal tissues, especially muscles, more is found in the combined state.
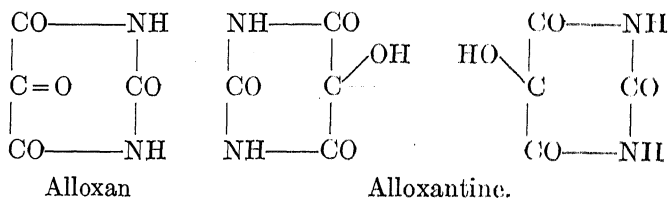
Xanthine is found in tea leaves, and the juice of beet root; theobromine, in theobroma cocoa; caffeine, in tea and coffee. Uric acid is not found in plants. The murexide test makes the recognition of the purine base an easy matter, but the identification of the individual members is a difficult task. Hypoxanthine and xanthine when administered to man increase the uric acid to about 55 per cent. of the theoretical amount.

Guanine is uually prepared from guano—hence the name. It occurs commonly in animal organisms and has been found in small quantities in yeast, sugar cane, and beet root. It has also been synthesized. Its main interest in pharmacology is its relation to the more important caffeine drugs. In the urine of pigs xanthine, hypoxanthine, with smaller amounts of adenine and guanine preponderate in amount over uric acid. The tissues of these animals are deficient in guanase, and the pig sometimes suffers from "guanine gout". Nitrous acid converts guanine into xanthine. This may also be accomplished by boiling it with hydrochloric acid.
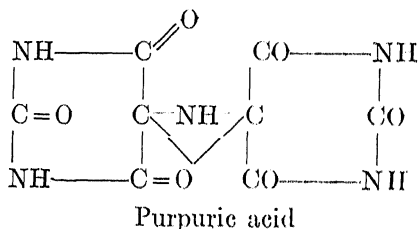
Adenine occurs in beet root, yeast, tea, and other plants and in the animal organism especially in the pancreas. Adenase converts it into hypoxanthine $C_5H_3N_4NH_2 + H_2O = C_5H_5N_5O + NH_3$.

Murexide Test

Put 3 or 4 milligrams of caffeine in a white evaporating dish. Add a few cc. of saturated chlorine or bromine water and evaporate to dryness on a water bath. To the yellow residue add a drop of NH_4OH. A bright purple color is produced. Nitric acid may be used to oxidize the caffeine instead of the chlorine water, but it is not so efficient. HCl with a crystal of $KClO_3$ may also be used. This decomposes the purine bases to alloxan which, on reduction yields alloxantine:

```
CO———NH      NH——CO              CO——NH
|        |     |      |   OH   HO   |      |
C=O      CO    CO     C          C      CO
|        |     |      |          |      |
CO———NH      NH——CO              CO——NH
   Alloxan              Alloxantine.
```

Alloxantine in presence of ammonia forms ammonium purpurate or murexide.—$NH_4.C_8H_4N_5O_6 + H_2O$

```
         O
NH———C          CO———NH
|        |        |      |
C=O      C–NH   C      CO
|        |        |      |
NH———C=O      CO———NH
       Purpuric acid
```

2. Caffeine is also precipitated by the alkaloid reagents.
These tests are not characteristic.

3. The melting point is 235–237°. It is soluble in 46 parts of water, 5.5 of chloroform, and in 530 parts of ether.

Action of Caffeine Compounds

Caffeine is used mainly as (1) a diuretic, and (2) as a stimulant to respiration and circulation, (3) for its influences on muscle, and (4) for its action on the nervous system. Theophylline has less action than caffeine on the central nervous system and heart, but is a stronger diuretic, this diuretic action is said not to last as long as that produced by theobromine, which is a less powerful diuretic. Theobromine also acts less on the central nervous

system than caffeine. The other compounds have varying actions, but these are not important in medicine.

1. **The Diuretic Action of Caffeine.**—Caffeine compounds are the diuretic drugs par excellence. Many laboratory exercises on this point fail because they do not consider the fundamentals of urine secretion or the condition in which caffeine acts best as a diuretic. First, the kidneys cannot secrete water unless water is present. While the blood normally contains over 90 per cent. water, this water is apparently in combination with colloid material and only free water can be secreted. In those clinical cases where caffeine compounds act to the best advantage, the tissues are water logged either because of inadequacy on the part of the heart, or change in the proteins, or salt retention. Caffeine under these conditions causes a diuresis either by causing a greater elimination of the free water or by liberating some of the combined water. In normal animals the change caused by caffeine on diuresis is so small that, as a class experiment, it is unsatisfactory. Only as much water as is taken in can be poured out, and in normal conditions this pouring out or urination proceeds at a constant rate and is hastened but little by diuretics. To make a laboratory experiment show the real action of caffeine on the kidneys, the animal should be given a large volume of liquid a short time before the caffeine is administered.

The action of caffeine is direct on the kidney because:

1. There are no secreting nerves to the kidney. Diuresis occurs after section of all nerves and on the isolated kidney, and after degeneration of the nerves.

2. The fluids in the tissues are not changed.

3. The kidney increases in volume, when secreting:

(a) The action therefore is local but may be either on the vessels—a circulatory action, or

(b) It may be an action on the secreting cell. Opinion at present favors a direct action on the secreting cell:

4. Rost[1] has found that the flow of urine is increased only when considerable caffeine passes into the urine.

5. Richards and Plant[2] have shown that diuresis may occur with caffeine even when there is no change in kidney volume.

[1] Schmidebergs Archiv., 1895, vol. 36.
[2] Jour. of Pharmacology, 1915, p. 485.

19

Fate of Caffeine in the Body

In the body caffeine loses its methyl groups—first becoming dimethyl—then monomethyl xanthine. Then xanthine is formed and this may be broken down into urea. Of the monomethyl xanthines, 7 monomethyl is formed in greatest quantity. Of the dimethyl xanthines, paraxanthine—1, 7 dimethylxanthine is found. Both of these may be found in the urine after the ingestion of caffeine. While this is true for man there is some difference in the order in which the methyl groups are lost, in different animals. In the dog all three dimethylxanthines appear in the urine after larger doses of caffeine, although theophylline 1.3 dimethylxanthine predominates; while in the rabbit under the same conditions and in man, paraxanthine or 1.7 dimethylxanthine predominates. The monomethyl xanthines are also excreted in different proportions in the various species of animal, but in man and the rabbit heteroxanthine—7 methyl xanthine prevails.

Only about 10 per cent. of the ingested caffeine appears in the urine in the form of the above decomposition products. The rest is oxidized in the body to urea and other end products, carbon dioxide and water. After the ingestion of 1 to 1.5 grams caffeine daily uric acid elimination is increased (Benedict). This is apparently due to a conversion of caffeine to uric acid, though it might also be due to a stimulation of the kidney to secrete the normal uric acid of the blood.

The tolerance that is acquired from the prolonged uses of tea and coffee, is in great part due to the body acquiring the ability to oxidize these alkaloids more rapidly than at the beginning. This is not the only explanation, however, for large quantities may still be obtained from the tissues.

Purin metabolism is especially interesting in relation to gout, in which an apparent deficiency of the oxidation of uric acid or an increased formation, or a change in combination exists. It has been found that when dogs, pigs or rabbits are fed nucleic acid, 90–95 per cent. of it can be recovered as allantoine, 3 to 6 per cent. as uric acid and 1 to 2 per cent. as purin bases. It may be that in perverted metabolism more than the usual amount of purin bases is converted into uric acid. There is no increase in the uric acid content of the blood after the ingestion of foods

rich in purines except in cases of renal insufficiency, for this reason gout is looked upon as a beginning nephritis (Denis).

In normal cases the oxidation of purin bases takes place as follows — hypoxanthine → xanthine → uric acid → allantoine. It has been taught that allantoine was oxidized to CO_2 and urea, but at present it is believed by many that allantoine is the end product of purine oxidation. The human organism cannot oxidize allantoine, since allantoine injected hypodermically in man has been completely recovered.

It has been also found that 60 to 90 per cent. of uric acid administered hypodermically can be recovered in the urine. Some have found as much as 99 per cent. of that administered. Uric acid is oxidized with much greater difficulty in man than in monkeys, dogs, cats, rabbits or pigs. In fact no adequate evidence exists that the tissues of man can oxidize uric acid. Urea is formed from uric acid in vitro by a variety of oxidizing agents and allantoine is hydrolysed by boiling water into allanturic acid and urea, so that its resistance to oxidation in the body is difficult to understand.

Economic Use of Caffeine

Owing to the daily use of caffeine compounds in the form of tea and coffee, frequent cases of chronic poisoning are seen. The symptoms, mainly those of dyspepsia, are: epigastric uneasiness, depression, succeeded by nervousness, restlessness and excitement, tremors, disturbed sleep, anorexia, headache, vertigo, confusion, palpitation, constipation and hysterical disturbances. These symptoms are relieved by the gradual removal of the drug. No acute fatal case of caffeine poisoning is recorded and the fatal dose is not known, but it is over 10 grams. To avoid the symptoms of chronic poisoning and to allow the use of tea and coffee in susceptible individuals, numerous attempts to remove the caffeine from tea and coffee have been made. Some manufacturers have placed the blame for the nervous symptoms on the volatile oil content—the so-called caffeol—but this is insufficient to cause the symptoms, and the caffeine content is quite sufficient to explain all the untoward symptoms.

TO ILLUSTRATE IN GENERAL THE ISOLATION OF ALKALOIDS

POWER AND CHESTNUT'S METHOD OF ASSAYING CAFFEINE IN VEGETABLE MATERIAL[1]

Ten grams of the finely ground material, previously moistened with a little alcohol, are extracted for about 8 hours in a Soxhlet apparatus with hot alcohol. The alcoholic extract is then added to a suspension of 10 grams of heavy magnesium oxide in 100 cc. of water, contained in a porcelain dish, the flask being rinsed with a little hot water, and this liquid added to the mixture. The mixture is allowed to evaporate slowly on a steam-bath or water-bath, with frequent stirring, until all the alcohol is removed and a nearly dry, powdery mass is obtained. This is mixed with sufficient hot water to enable it to be brought on a filter, which preferably should be smooth, and, after thoroughly cleaning the dish by means of a glass rod, to which a piece of rubber tubing is attached, the contents of the filter are washed with successive portions of hot water until about 250 cc. of filtrate is obtained. To the filtrate, contained in a flask of one-liter capacity, is added 10 cc. of a 10 per cent. solution of sulfuric acid, which causes the liquid to become much lighter in color, and with some kinds of material, such as Ilex leaves, a considerable precipitate is produced. In some cases, as with tea and guarana, it was found necessary to use 20 cc. of the above-mentioned acid in order to prevent the formation of an emulsion on subsequently extracting with chloroform. After the addition of the acid, a small funnel is placed in the neck of the flask, and the liquid, which is at first gently heated until any frothing ceases, is kept in a state of active ebullition for half an hour. This treatment is for the purpose of hydrolyzing any saponin that may be present. After being allowed to cool, the liquid is passed through a double moistened filter into a separatory funnel, the flask and filter being washed with small portions of about 0.5 per cent. sulfuric The clear acid filtrate is then shaken with 6 successive ʹ of chloroform of 25 cc. each, which usually separates d quickly, but, if not, can be made to do so by gently

rotating the separatory funnel, or, if necessary, by the use of somewhat larger portions of chloroform. The united chloroform extracts are brought into another dry separatory funnel and shaken with 5 cc. of a 1 per cent. solution of potassium hydroxide, which serves to remove coloring matter. After complete subsidence of the chloroform solution it is passed through a small, dry filter into an Erlenmeyer flask, the alkaline liquid remaining in the separatory funnel being subsequently washed with two successive portions of chloroform of 10 cc. each. These washings of the alkali are passed through the previously mentioned filter, and, after washing the latter with a little chloroform, they are added to the first chloroform solution. The chloroform is finally removed by distillation from a water-bath the residual caffeine brought by means of a little chloroform into a tared beaker, and, after the solvent has been allowed to evaporate spontaneously, the caffeine is dried for half an hour in a water-oven and weighed. On heating for another half an hour there is usually a further slight diminution of weight, and this second weighing may be considered to represent the correct amount of caffeine, which, when multiplied by ten, denotes the percentage. As so obtained the caffeine is nearly colorless, and possesses a quite satisfactory degree of purity.

ISOLATION OF CAFFEINE

The most important source of caffeine is tea and coffee. To separate and estimate the amount of caffeine in tea and coffee:

Keller's Method. Take 6 grams of tea leaves and place them in a separatory funnel. Add 120 grams of chloroform. Shake and in a few minutes add 6 cc. 10 per cent. solution of NH_3. Shake repeatedly during a period of 30 minutes. Let stand for 3 to 6 hours or until the solution is clear and the leaves have absorbed all of the water. Filter through a paper moistened with $CHCl_3$ and collect 100 grams in a small weighed flask. This represents 5 grams of the tea. Evaporate the chloroform over a water bath. Pour 3-4 cc. of absolute alcohol on the residue and heat on the water bath to drive off the alcohol. The residue represents chlorophyll, fat, caffeine, etc., or $CHCl_3$ extract. To purify this add 10 cc. 30 per cent. alcohol, heat on a water bath. The caffeine passes into solution. The coloring

matter forms in lumps and can be filtered off. Pass the solution through a filter and wash the filter with 10 cc. of water. Evaporate the filtrate on a small weighed evaporating dish to dryness on a water bath. The residue is nearly pure caffeine. Calculate the per cent. in the original tea. The tea is thus assayed.

High heat decomposes organic substances, hence a water bath is used in this assay. The ammonia liberates the free alkaloid which is readily soluble in the chloroform. The ammonia also combines with tannic acid, the amount of which depends on the variety of the tea.

This method may also be used for coffee and cola preparations. There are other much more refined and elaborate methods for estimating caffeine, than this one.

UNCLASSIFIED ALKALOIDS

Veratrine is a mixture of alkaloids of unknown composition. The effects of veratrine resemble closely those of aconite (qv). In addition the muscles are stimulated and relaxation greatly prolonged. The chief tests are:

1. Concentrated sulphuric acid added to veratrine gives an intense yellow color, which changes to orange and finally cherry red.

2. Concentrated hydrochloric acid gives a cherry red color only after heating 10–15 minutes on a water bath.

3. Vitali's test: Dissolve veratrine in a few drops of fuming nitric acid and evaporate to dryness on a water bath, a yellow residue remains which when moistened with alcoholic potash gives an orange red or red violet color.

Atropine, hyoscyamine, scopolamine and strychnine also give this test.

4. Physiological test: When 0.5 cc. of 0.1 per cent. veratrine is injected into the lymph sac of a frog, a muscle preparation prepared after 30 minutes shows an enormously increased relaxation period.

Physostigmine or Eserine. $C_{15}H_{21}O_2N_3$ is an alkaloid found in calabar bean. Its composition is unknown. It has a considerable use in medicine and resembles muscarine and pilocarpine in action but has a greater effect on parenchymal tissue. Its chief actions are:

1. Marked constriction of the pupil and spasm of the ciliary muscle, seen as a rule only when applied locally.

2. A powerful stimulation of the muscular mechanism of all muscles innervated by the parasympathetic system especially the gastro-intestinal system.

3. A stimulation of the vagus endings to the heart.

4. Some initial stimulation followed by depression, of the medullary centers and spinal cord.

TESTS

1. Light and heat cause solutions to turn red on standing.

2. If a physostigmine salt is evaporated to dryness and ammonium hydroxide added a bluish green residue remains.

3. Nitric acid dissolves physostigmine forming a yellow solution.

4. If a solution of physostigmine is shaken with an excess of NaOH solution, a red coloring matter rubroserine is formed. Crystals separate on standing which become greenish blue.

5. A solution of eserine dropped in the eye of a rabbit or cat causes constriction of the pupil. Atropine will remove the constriction.

Colchicine.—This is an alkaloid of unknown composition. It is found in all parts of meadow saffron, and is used in the treatment of gout. When hydrolysed with H_2SO_4 it yields colchicein and methyl alcohol

$$C_{22}H_{25}NO_6 + H_2O = C_{21}H_{23}NO_6 + CH_3OH$$
$$\text{colchicine} \qquad \qquad \text{Colchiceine}$$
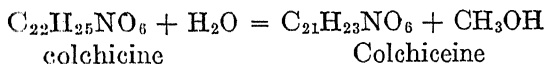
In toxic doses it causes acute intestinal pain with nausea vomiting and diarrhœa. The lethal dose is about .0012 gram per kilo of body weight. Death is due to vasomotor paralysis.

Tests

Unless the aqueous solutions have a yellow color colchicine is absent. It may be confused with dilute sols. of picric acid.

1. Precipitation occurs by the general alkaloidal reagents.

2. Concentrated nitric acid dissolves colchicine with a dirty yellow color changing to red and finally yellow. Addition of NaOH produces an orange red or orange yellow color.
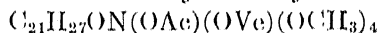
3. Concentrated sulphuric acid dissolves colchicine with an intense yellow color. A drop of concentrated nitric added to this produces a green, blue, violet and finally yellow color, an excess of KOH will now produce a red color.

Unclassified or Alkaloids of Unknown Composition.—The most important are the aconite alkaloids:
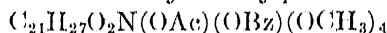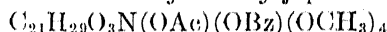
Aconitine: Acetylbenzoylaconine
$$C_{21}H_{27}O_3N(OAc)(OBz)(OCH_3)_4$$
Bikhaconitine: Acetylveratroylbikhaconine
$$C_{21}H_{27}ON(OAc)(OVe)(OCH_3)_4$$
Indaconitine: Acetylbenzoylpseudaconine
$$C_{21}H_{27}O_2N(OAc)(OBz)(OCH_3)_4$$
Japaconitine: Acetylbenzoyljapaconine
$$C_{21}H_{29}O_3N(OAc)(OBz)(OCH_3)_4$$
Pseudaconitine: Acetylveratroylpseudaconine
$$C_{21}H_{27}O_2N(OAc)(OVe)(OCH_3)_4$$
Ac = acetyl; Bz = benzoyl; Ve = veratroyl.
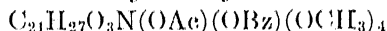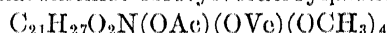
The Quebracho Alkaloids.

Aspidosamine,................	$C_{22}H_{28}O_2N_2$.
Aspidospermatine,..	$C_{22}H_{28}O_2N_2$.
Aspidospermine,.............	$C_{22}H_{30}ON_2$.
Hypoquebrachine,...........	$C_{21}H_{26}O_2N_2$.
Quebrachamine	
Quebrachine,................	$C_{21}H_{26}O_3N_2$.

Ergotoxine.

Ergotoxine,..................	$C_{35}H_{41}O_2N_5$.
Ergotinine,..................	$C_{35}H_{39}O_5N_5$.

The Colchicine Alkaloids.

Colchicine,..................	$C_{22}H_{25}O_2N$
Colchiceine,.................	$C_{21}H_{23}O_6N.\frac{1}{2}H_2O$.
Yohimbinine,................	$C_{35}H_{45}O_6N_3$
Yohimbine,.................	$C_{22}H_{30}O_6N_2$
Cytisine,...................	$C_{11}H_{14}ON_2$.

The amount of any known alkaloid can be determined by dissolving it in an excess of normal acid and titrating the excess

of the acid, just as ammonia is titrated.   We know that 1 cc. of
each normal solution is equivalent to 1 cc. of every other normal
solution.   If we titrate NH_4OH with H_2SO_4 the reaction is as
follows:

$$H_2SO_4 + 2NH_4OH = (NH_4)_2SO_4 + 2H_2O$$

   1cc. of normal H_2SO_4 = therefore   .014 grams N or
   1 cc. of N/10 H_2SO_4 =   .0014 grams N or
                                            .0017 grams NH_3

   The factors for the various alkaloids differ depending on the
molecular weight of the alkaloid, but 1 cc. n/10 H_2SO_4 always
represents .0014 N in the alkaloid just as it does in ammonia, but
while the molecular weight of NH_3 is 17, that of atropine is 289.19.
Hence, the amount of atropine equivalent to 1 cc. n/10 H_2SO_4
is 17 : 289.19 :: .0017 : X = .029 = .
   The amount of each alkaloid represented by 1 cc. n/10 H_2SO_4
is as follows:

Aconitine	0.0645
Atropine	0.0289
Brucine	0.0394
Cocaine	0.0303
Coniine	0.0127
Morphine + H_2O	0.0303
Physostigmine	0.0273
Pilocarpine	0.0208
Quinine	0.0324
Strychnine	0.0334
Combined alkaloids of Cinchona	0.0309
Combined alkaloids of Ipecac	0.0240

THE PHYSIOLOGICAL SIGNIFICANCE OF NITROGEN BASES

   Since many of these bases are exceedingly reactive in animals
one wonders what role they play in the life of the plant.   Three
views are held regarding this:
   1. They are the end product of plant metabolism rendered
harmless to the plant and correspond to the urea and uric acid
of animals.   This view is generally accepted.

2. They are protective materials, against the attack by animals and parasitic fungi.

3. They are nutritive or plastic material used by the plant in metabolism.

In favor of the first view is the fact that the purine bases generally are formed in places of great cellular activity, and their disappearance is never accompanied by a simultaneous increase in albuminous substances. Again Kerbosch has presented evidence to show that narcotine is formed from protein during the germination of poppy seeds. Caffeine and theobromine are generally held to be decompositive products of protein. The difference in plants and animals in this regard is that animals have a mechanism for the elimination of these waste products while in plants there is no such elimination.

The view that they are protective against animals and fungi has little to recommend it since plants grow just as well in latitudes where no alkaloid or much less is formed.

There is little evidence to show that they are nutritive since it has been shown that in the germination and early growth of potatoes, nux vomica, thorn apple, and other seeds there is no change in the alkaloid content. Certain lower forms of plant life, that do not contain alkaloids, can utilize atropine, cocaine, morphine in their growth. Strychnine is toxic to some, quinine to others.

XXVII. PROTEINS

The name protein comes from the Greek word Protos, first, and in the animal body they are of the first importance. In plants, carbohydrates constitute the greater part, with some protein, while in the animal, the greater part of the living matter is made up of protein with some carbohydrate always associated.

Proteins, fats and carbohydrates, are organic materials, and are always associated with life. Some authors hold that the protein molecule in life is in a labile form, probably due to the presence of aldehyde and nitril groups. When life ceases, there is an intramolecular rearrangement, to the stable or dead form. The vibration or movement of the protein molecule is life. Whether this movement ever can be analysed or imitated the
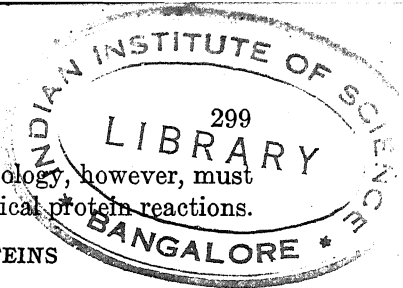
future only can tell. Progress in pharmacology, however, must consist to a great degree in a study of chemical protein reactions.

CLASSIFICATION OF PROTEINS

Owing to the complexity of the proteins, and to the fact that their chemistry is still to a great extent unknown, and still the subject of research, the nomenclature is continually changing. The American Society of Biochemists and the American Physiological Society, have agreed on the following classification:

I. Simple proteins.

II. Conjugated or compound proteins.

III. Derived proteins.

THE SIMPLE PROTEINS

These on hydrolysis yield only monoamino acids. They are subdivided into:

A. Albumins.—These are soluble in water and dilute saline solutions. They are coagulable by heat in neutral or acid solution. They are not precipitated by saturation with NaCl, or $MgSO_4$. Unless the reaction be acid they are precipitated by saturation with ammonium sulphate. They are rich in sulphur and yield no glycocoll on hydrolysis.

The typical albumins are egg white, serum albumin, lact albumin, legumelin of the pea and leucosin of the wheat and other cereals. Traces of albumin are found in all seeds.

B. Globulins.—These are insoluble in water but soluble in dilute saline. In neutral solution they are precipitated by saturation with magnesium sulphate or half saturation with ammonium sulphate. They can be separated from the albumins by dialysis. They are found associated with albumins. The albumins and globulins are the only proteins that are coagulated by heat; but many vegetable globulins differ from those of animal origin in that they are coagulated by heat with difficulty. Serum globulin and edestin are the chief representatives. They are the commonest form of the reserve protein of plants.

C. Glutelins.—These are insoluble in water and neutral saline, but dissolve in dilute acid or alkali. Only two are known, glutenin found in wheat and oryzenin in rice. They are hard to prepare pure and have been but little investigated.

D. Prolamines or Gliadins.—These are vegetable proteins found in cereal grains only. They are insoluble in water or saline, soluble in 70–90 per cent. alcohol, soluble in dilute acids or alkalies. On hydrolysis they yield a considerable amount of proline—hence the name prolamine. Gliadin, hordein, zein are the chief representatives.

E. Albuminoids.—These are insoluble in water, or in dilute acid, alkali, or saline. Elastin, keratin, and collagen are the chief members. They are found on connective tissue, skeletal tissue, hair epidermis especially. On hydrolysis these are lacking in certain amino acids such as cystein, tyrosin and tryptophane.

F. Histones.—These are strongly basic, soluble in water and dilute acid, and insoluble in ammonia. They are characterized by being precipitated by ammonia. They are related to the protamines, but are more complex than these. They have been prepared mainly from bird's blood corpuscles and the thymus gland.

G. Protamines.—These are strongly basic. They are the simplest proteins known, and usually associated with nucleic acid. They are soluble in ammonia and yield large amounts of diamino acids sturin, salmin, clupein, etc., on hydrolysis.

No compounds of this kind have been isolated from plants.

CONJUGATED PROTEINS

These are combinations of simple proteins with a non-protein group, which is usually acid in character. This group is sometimes called the prosthetic group (prosthesos—additional). The group is subdivided as follows:

A. Hemoglobins or Chromoproteins.—In these the prosthetic group is colored. The representatives are hemoglobin, hemocyanin, phycoerythrin, and phyocyan.

B. Glyco or glucoproteins, represented by mucin, ichthulin, mucoids. The prosthetic group is a carbohydrate.

C. Phosphoproteins.—Compounds of a simple protein with an unidentified phosphorus containing prosthetic group—casein and vitellin are types.

D. Nucleoproteins.—These are perhaps the most important conjugated protein. They are combinations of protein with

nucleic acid, and are found in the nucleus and chromatin. Nuclein and nucleolustone.

E. Lecitho proteins, the prosthetic group is lecithin or a phospholipin. English chemists do not recognize this group. They probably exist, though none has been isolated.

F. Lipoproteins.—The existence of this group is also doubtful. They are supposed to be combinations of proteins and a higher fatty acid.

DERIVED PROTEINS

This group includes products formed from the simple proteins by hydrolysis.

A. Primary Products

(*a*) **Proteans.**—These are the incipient or first products formed on digestion. Edestan, myosan.

(*b*) **Meta-proteins.**—These are products of the further action of acids and alkalies on proteins. They are soluble in weak acids and alkalies but precipitated on neutralization. Acid and alkali albumins are examples.

(*c*) **Coagulated Proteins.**—These are insoluble proteins formed by the action of heat, alcohol, etc.

B. Secondary or Intermediate Protein Derivatives

(*a*) **Proteoses.**—These are hydrolytic cleavage products of proteins that are soluble in water, and not coagulated on heating. They are completely precipitated by saturation with ammonium sulphate.

(*b*) **Peptones.**—These hydrolytic products are not precipitated by ammonium sulphate. They give the biuret reaction and are diffusible.

(*c*) **Peptides or Polypeptides.**—These are compounds of amino acids of known composition, such as leucyl glutamic acid. Many are synthetic. They are called di, tri, tetra—etc. according to the number of amino acids in the molecule. They are not coagulable by heat, are diffusible, and may or may not give the biuret reaction.

The English Biochemists classify proteins as follows:

I. Simple Proteins
1. Protamines
2. Histones
3. Globulins
4. Albumins
5. Glutelins
6. Gliadins. (Prolamins) (Soluble 70–90 per cent. alcohol; insoluble in water).
7. Sclero-proteins. (Forming the skeletal structure of animals).
8. Phosphoproteins. Caseinogen.

II. Conjugated Proteins
1. Chromoproteins
2. Nucleoproteins
3. Glucoproteins.

III. Hydrolyzed Proteins
1. Metaproteins
2. Albumoses or proteoses
3. Peptones
4. Polypeptides

COMPARISON OF ANIMAL AND VEGETABLE PROTEINS

The general properties of these are the same, but there are some striking individual differences: With the exception of diamino trihydroxy-dodecanic acid, a hydrolytic product of casein, all the products of hydrolysis of animal protein have been found in plant protein.

Vegetable proteins as a rule yield more glutaminic acid, proline, arginine, and ammonia than animal proteins.

Prolamins or alcohol soluble proteins are found only in plants. None have so far been found in animals.

AMINO ACIDS FOUND IN PLANTS

Leucine has been found in the sprouts and buds of the horse chestnut.

Iso-leucine in the residue of molasses.

Arginine in etiolated pumpkin seeds, in conifer seed, and in lupin seed.

Phenyl-alanin in germinating lupin seeds.

Tyrosine has been isolated from a number of growing shoots.

Tryptophane in the seedlings of several species of legumes.

Proline is obtained on the hydrolysis of a number of vegetable proteins, but has not been found free in any plant.

GENERAL PROPERTIES OF PROTEINS

The following are some of the more prominent properties of the group:

I. Proteins are colloids (some have been prepared in crystalline form). They will not diffuse through a membrane.

II. The ultimate elements are present in a certain proportion varying only within narrow limits.

C...................... 50.6-54.5 per cent.
H...................... 6.5- 7.3 per cent.
N...................... 15.0-17.6 per cent.
S...................... 0.3- 2.2 per cent.
P...................... 0.4- 0.85 per cent.
O...................... 21.4-23.5 per cent.

III. Proteins give precipitation and color reactions. The color depends upon certain chemical groups or complexes within the protein molecule, while the precipitate is due to a new compound formed with the reagent. Heavy metals and the alkaloidal reagents precipitate the proteins.

Color Reactions

1. Millon's reaction depends upon the presence of a monohydroxy benzene nucleus group.

2. The xantho-proteic (xanthos-yellow) reaction is given by all proteins containing the benzene nuclei in the molecule.

3. Adamkiewicz's reaction is given only by bodies which contain the indol groups.

4. The biuret reaction has some relation to the amine group linked to carbon.

$$CONH_2 \quad CSNH_2 \quad C(NH)NH_2 \quad CH_2NH_2 \quad \text{etc.}$$

Precipitation Reactions

The following reagents cause precipitation of most proteins. Exceptions may be seen under the classification of proteins:

1. Alcohol.
2. Boiling or heat.
3. Mineral acids.
4. Solutions of salts of heavy metals.
5. Excess of the salts of the alkalies.
6. Potassium ferro-cyanide *in acid reaction* with acetic acid.
7. Tannic acid *in acid reaction* with acetic acid.
8. A solution of phosphotungstic or phosphomolybdic acid, after acidification with a mineral acid.
9. Iodine in potassium iodide (Lugol's solution).
10. Picric acid.
11. Precipitins.

Hydrolytic Products

(IV) When hydrolysed proteins split into definite complexes, albuminoses, peptones, polypeptids, amino acids, etc., which are constant for the same, but vary for each protein.

Twenty-one amino acids have been prepared from protein. They are as follows:

A—Mono-amino—mono-carboxylic fatty acids:

H	H	H
$\|$	$\|$	$\|$
H—C—NH$_2$	H—C—H	H—C—H
$\|$	$\|$	$\|$
O—C—OH	H—C—NH$_2$	H—C—H
	$\|$	$\|$
	O—C—OH	H—C—NH$_2$
		$\|$
		O—C—OH
$C_2H_5NO_2$	$C_3H_7NO_2$	$C_4H_9NO_2$
Glycocoll	Alanine	(a-amino
(a-amino acetic	(a-amino	butyric
acid)	propionic	acid)

$$
\begin{array}{c}
H \\
| \\
H-C-H \\
| \\
H-C-H \\
| \\
H-C-H \\
| \\
H-C-NH_2 \\
| \\
O=C-OH
\end{array}
$$

$C_5H_{11}NO_2$
(a-amino
valerianic
acid)

$$
\begin{array}{c}
CH_3 \quad CH_3 \\
\diagdown \diagup \\
C-H \\
| \\
H-C-NH_2 \\
| \\
O=C-OH
\end{array}
$$

$C_5H_{11}NO_2$
Valine
Iso-propyl
acetic acid)

$$
\begin{array}{c}
H \\
| \\
H-C-H \\
| \\
H-C-H \\
| \\
H-C-H \\
| \\
H-C-H \\
| \\
H-C-NH_2 \\
| \\
O=C-OH
\end{array}
$$

$C_6H_{13}NO_2$

(a-amino normal
caproic acid)

$$
\begin{array}{c}
CH_3 \quad CH_3 \\
\diagdown \diagup \\
C-H \\
| \\
H-C-H \\
| \\
H-C-NH_2 \\
| \\
O=C-OH
\end{array}
$$

$C_6H_{13}NO_2$

Leucine
(a-iso
butyl
a-amino
acetic
acid)

$$
\begin{array}{c}
CH_3 \\
| \\
H-C-H \quad CH_3 \\
\diagdown \diagup \\
C-H \\
| \\
H-C-NH_2 \\
| \\
O=C-OH
\end{array}
$$

$C_6H_{13}NO_2$

Iso-leucine
(ethyl, methyl
a-amino propionic
acid)

20

$$
\begin{array}{c}
\text{H} \\
| \\
\text{H—C—OH} \\
| \\
\text{H—C—NH}_2 \\
| \\
\text{O=C—OH}
\end{array}
\qquad
\begin{array}{c}
\text{H} \\
| \\
\text{H—C—SH} \\
| \\
\text{H—C—NH}_2 \\
| \\
\text{O=C—OH}
\end{array}
$$

$C_3H_7NO_3$ $C_3H_7NSO_2$

Serine   Cysteine

(B-hydroxy   (B-thio, a-amino

a-amino   propionic acid)

propionic

acid)

$$
\begin{array}{cc}
\text{H} & \text{H} \\
| & | \\
\text{H—C—S —} & \text{S—C—H} \\
| & | \\
\text{NH}_2\text{—C—H} & \text{H—C—NH}_2 \\
| & | \\
\text{O=C—OH} & \text{O=C—OH}
\end{array}
$$

$C_6H_{12}N_2S_2O_4$

(Cystine)

B. Mono-amino dicarboxylic acids

$$
\begin{array}{c}
\text{O=C—OH} \\
| \\
\text{H—C—H} \\
| \\
\text{H—C—NH}_2 \\
| \\
\text{O=C—OH}
\end{array}
\qquad
\begin{array}{c}
\text{O=C—OH} \\
| \\
\text{H—C—H} \\
| \\
\text{H—C—H} \\
| \\
\text{H—C—NH}_2 \\
| \\
\text{O=C—OH}
\end{array}
$$

$C_4H_7NO_2$ $C_5H_9NO_2$

Aspartic acid   Glutamic acid

(a-amino   (a-amino glutaric

succinic acid)   acid)

C. Isocyclic amino acids

$$\begin{array}{cc}
& \text{C—OH} \\
\text{HC} & \text{CH} \\
\text{HC} & \text{CH} \\
& \text{C} \\
\text{H—C—H} \\
\text{H—C—NH}_2 \\
\text{O}=\text{C—OH} \\
\text{C}_9\text{H}_{11}\text{NO}_3
\end{array}
\qquad
\begin{array}{cc}
& \text{CH} \\
\text{HC} & \text{CH} \\
\text{HC} & \text{CH} \\
& \text{C} \\
\text{H—C—H} \\
\text{H—C—NH}_2 \\
\text{O}=\text{C—OH} \\
\text{C}_9\text{H}_{11}\text{NO}_2
\end{array}$$

Tyrosine
(β-para-hydroxy-
phenyl, a-amino
propionic acid)

Penyl alanine (β-phenyl
a-amino-, propionic acid)

D. Heterocylic amino acids

$$\begin{array}{c}
\text{CH} \qquad \text{H NH}_2 \text{ O} \\
\text{HC} \quad \text{C—C—C—C—C—OH} \\
\text{HC} \quad \text{C} \quad \text{C H H} \\
\text{CH} \quad \text{NH} \quad \text{H}
\end{array}
\qquad
\begin{array}{c}
\text{H}_2\text{C———CH}_2 \text{ O} \\
\text{H}_2\text{C} \quad \text{C— C—OH} \\
\text{NH} \quad \text{H}
\end{array}$$

$C_{11}H_{12}N_2O_2$ (Tryptophane)
(a-amino, β-indole
propionic acid)

$C_5H_9NO_2$ (Proline)
(a-pyrrolidine carbox-
ylic acid)

$$HC-N$$
$$\|\quad\ \ \diagdown CH$$
$$C-NH$$
$$|$$
$$HC-H$$
$$|$$
$$H-C-NH_2$$
$$|$$
$$O=C-OH$$

$C_6H_9N_3O_2$

Histidine

(a-amino, β-imidazole
propionic acid)

$$H_2C\ \ \quad CHOH$$
$$\qquad\qquad O$$
$$\qquad\qquad \|$$
$$H_2C\quad\ C-C-OH$$
$$\diagdown\ \diagup\ \ |$$
$$NH\quad H$$

$C_5H_9NO_3$
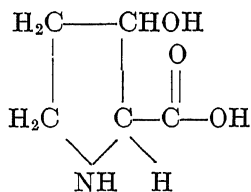
Oxy-proline

(The position of the hydroxyl
is uncertain)

E. Mono-carboxylic, diamino acids

$$NH_2$$
$$|$$
$$C=NH$$
$$|$$
$$N-H$$
$$|$$
$$H-C-H$$
$$|$$
$$H-C-H$$
$$|$$
$$H-C-H$$
$$|$$
$$H-C-NH_2$$
$$|$$
$$O=C-OH$$

$C_6H_{14}N_4O_2$
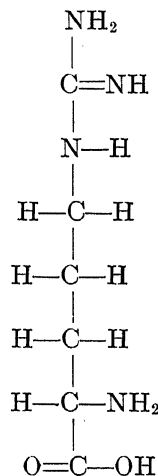
Arginine

(a-amino, d-guanidine
valerianic acid)

$$NH_2$$
$$|$$
$$H-C-H$$
$$|$$
$$H-C-H$$
$$|$$
$$H-C-H$$
$$|$$
$$H-C-H$$
$$|$$
$$H-C-NH_2$$
$$|$$
$$O=C-OH$$

$C_6H_{14}N_2O_2$
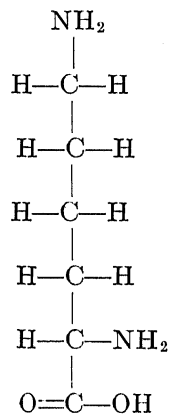
Lysine

(α, ϵ, amino, caproic
acid)

GENERAL CHARACTERS OF AMINO ACIDS

I. **Reaction.**—The mono-carboxylic mono-amino acids are amphoteric to litmus. The diamino acids, and arginine and

histidine are alkaline, and in solution absorb CO_2. The mono-amino dicarboxylic acids are acid to litmus.

II. **Solubility.**—As a rule they are soluble in water. Tyrosine is but slightly soluble in cold but is soluble in hot water. They are soluble in dilute acids and alkalies. They are insoluble in ether.

III. **Combinations.**—Since amino-acids contain both NH_2 and $COOH$ group they will unite with both acids and bases. The NH_2 group unites with acids as does ammonia. The $COOH$ group unites with NaOH etc. to form salts of the amino acid. Through the amino group they unite with salts of the heavy metals, such as Cu, Pt, Ag, Hg etc. to form such combinations as $—CH_3.CH_2.CH.NH_2CuCl_2.COOH$. These salts are insoluble in water.

IV. **Condensation.**—Amino acids may condense or unite with each other to form polypeptides. The amino group of one uniting with the carboxyl group of another. Such combinations are two molecules of glycocoll or glycyl-glycine:

$$NH_2CH_2CO.NHCH_2COOH \text{ and}$$

Leucyl—asparagine:

$$\underset{CH_3}{\overset{CH_3}{>}}CH.CH_2.CH(NH_2)CO.NH.\underset{\underset{CONH_2}{|}}{\underset{CH_2}{|}}\overset{\overset{COOH}{|}}{CH}$$
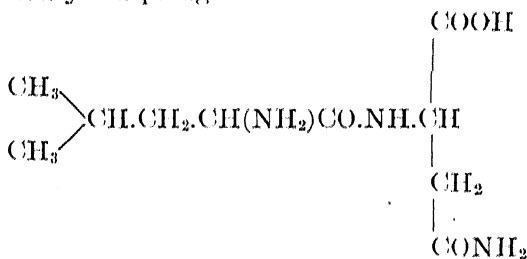
A great number of such polypeptides have been prepared and are named di, tri, penta, etc. according to the number of amino acids in the combination. The most complex of these so far synthesized contained 18 amino acids, and contained three leucine and 15 glycocoll groups. It was l-leucyl-triglycyl-l-leucyl-triglycyl-l-leucyloctoglycylglycine. $NH_2CH(C_4H_9)CO.$ $(NHCH_2CO)_3.NHCH(C_4H_9)CO.(NHCH_2CO)_3.NHCH(C_4H_9)$ $CO.(NHCH_2CO)_8NHCH_2COOH.$

CONDENSATION PRODUCTS

The alpha amino acids readily condense by the elimination of water from the $COOH$ groups:

$$\begin{array}{ccccccc} CH_2 & NH|H & HO|OC & & CH_2 & NH & OC \\ | & & & & | & & | \\ CO|OH & H|HN & CH_2 \rightarrow & & CO & HN & CH_2 \end{array} \quad + 2H_2O$$
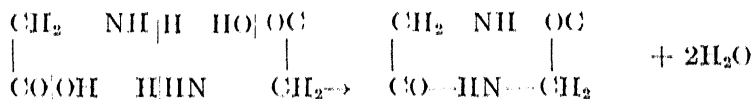
Beta amino acids condense through loss of ammonia with the formation of unsaturated acids:

$$|NH_2|CH_2 \ CH|H \ COOH = NH_3 + CH_2 : CH.COOH$$

B. amino propionic acid   ·   acrylic acid

Amino acids through the loss of water yield inner anhydrides which, because of the similarity to lactones, are called lactams:

$$\begin{array}{cccc} CH_2 & CH_2 & CH_2 & CO \\ | & & & \\ NH(H & & & OH) \end{array} \qquad \begin{array}{cccc} CH_2 & CH_2 & CH_2 & CO \\ | & & & \\ HN & \rule{3cm}{0.4pt} & & \end{array}$$
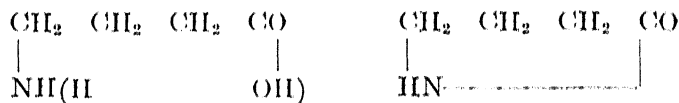
Amino butyric acid $\longrightarrow$ lactam of aminobutyric acid

Lactones are the inner anhydrides of gamma and delta hydroxy acids, *i.e.*, instead of the amino group in amino acids a hydroxyl group may be substituted. Such condensations as these *may* explain the formation of alkaloids in plants. Thus when solutions of leucine are evaporated diketo condensation imides are formed:

$$\begin{array}{c} \quad\quad\quad\quad\quad\quad\quad\quad O \\ \quad\quad\quad\quad\quad\quad\quad\quad || \\ (CH_3)_2 \ CH-CH_2 \ CH.NH-C \\ \quad\quad\quad\quad\quad\quad\quad\quad\quad | \\ O \ C-NH-CH-CH_2-CH-(CH_3)_2. \end{array}$$
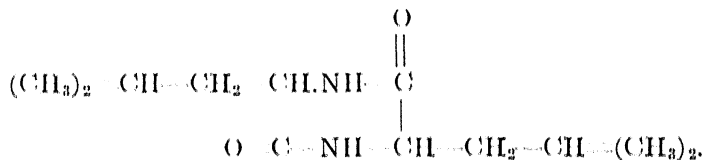
Leucinimide (Diisobutyl-diketopiperazine)

This gives rise to diketo piperazine from which piperazine may be prepared:
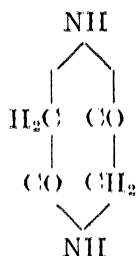
Diketo piperazine
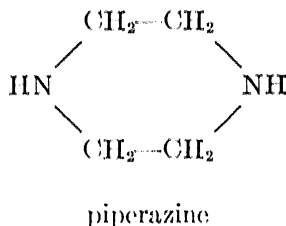
piperazine

From the pharmacological point of view, lactams are interesting
preparations producing strychnine like convulsions in animals.
This is a common characteristic of ring compounds.   The amino
acids themselves are devoid of visible action.   Such molecular
rearrangements may be the cause of many obscure reactions in
indigestion, uremias, gout, etc.

 The precipitation of urates in gout according to some (Gudzent)
is due to uric acid changing from the lactam to the lactim form.
The lactim form of uric acid is:

$$
\begin{array}{ll}
N\!=\!C\!-\!OH & \\
| \quad\; | & \\
HOC \quad C\!-\!NH & \\
\| \quad\;\; \| & \searrow \\
 & \quad COH \\
\| \quad\;\; \| & \nearrow \\
N \quad\; C\!-\!-\!N &
\end{array}
$$
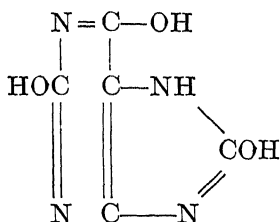
Cf. formula p. 284.

Piperazine has been advocated in the treatment of gout, but
it is without influence.

Condensation with Formaldehyde

Ammonia condenses with formaldehyde to form hexamethylene
tetramine.   The product formed in this case is $N_4(CH_2)_6$.

The amino acids also condense with formaldehyde according
to the formula.

$$
\begin{array}{ccc}
NH_2 & & N\!=\!CH_2 \\
| \quad\; O & & | \quad\; O \\
| \quad\; \| & & | \quad\; \| \\
R\!-\!C\!-\!C\!-\!OH + HC\!=\!O & = & R\!-\!C\!-\!C\!-\!OH + H_2O \\
| \qquad\quad\; | & & | \\
H \qquad\quad\; H & & H
\end{array}
$$
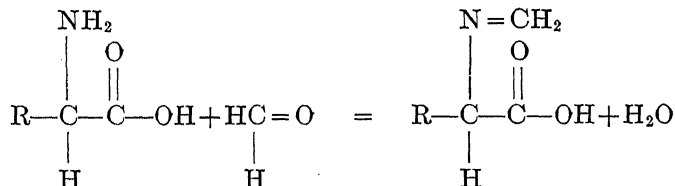
<div align="right">Methylene amino acid</div>

This methylene derivative has no basic properties and can be
sharply titrated with alkali.   This is the basis for the Sorensen
titration method for the titration of amino acids in a mixture.
This is perhaps one of the mechanisms in the formation of
amino acids in plants and animals.   Erlenmeyer and Kunlin[1]

[1] Ber. deut. chem. Gesells. 1902-35-2438.

were able to synthesize formyl derivatives of alanine and glycine by the interaction of ammonia and glyoxylic acid, and since both of these occur in plants, the probability of such formation in the plant is suggested.

$$2 \quad \begin{array}{c} CHO \\ | \\ COOH \end{array} \quad +NH_3 \quad = \quad \begin{array}{c} CH_2NH\ CHO \\ | \\ COOH \end{array} +H_2O+CO_2$$

Glyoxylic acid   Formyl-glycine

$$\begin{array}{c} CH_2\ NH\ CHO \\ | \\ COOH \end{array} \quad +H_2O \quad \rightarrow \quad \begin{array}{c} CH_2NH_2 \\ | \\ COOH \end{array} +HCOOH$$

Formyl-glycine   Glycine
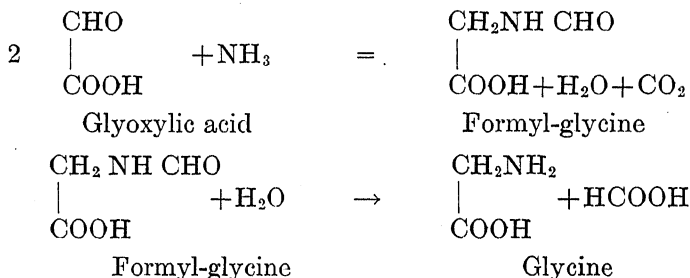
THE DEAMINIZATION OF AMINO ACIDS

In the preparation of amino acids from protein, the usual method is to boil the protein with acid for hours. This fact shows the stability of the amino groups in acid solution. The slight amount of nitrogen that is evolved is in the amide condition, that is, in the form of $R.CONH_2$. Amino acids are also quite stable in alkaline solution. Arginine decomposes to ornithin and urea, and cystine and cysteine lose considerable of their sulphur, but as a rule little decomposition occurs.

Oxidation may cause deaminization through splitting off ammonia. Various oxidizing agents like hydrogen peroxide, and potassium permanganate, cause, *in vitro*, the deaminization as follows:

$$\begin{array}{c} CH_3 \\ | \\ H{-}C{-}NH_2 \\ | \\ O{=}C{-}OH \end{array} + O \leftrightarrows \begin{array}{c} CH_3 \\ | \\ C{=}O \\ | \\ O{=}C{-}OH \end{array} + NH_3$$

Alanine   Pyruvic acid
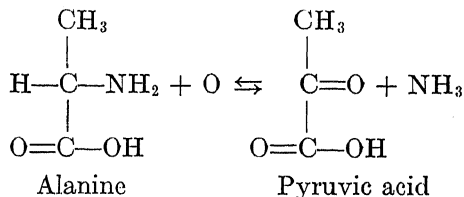
Where deaminization takes place in the body is not known. It seems that all tissues, perhaps due to a ferment, have deaminizing properties. It is thought by some that since no amino acids, or only a trace, can be demonstrated in the blood, that deaminization takes place in the intestine. There is no direct proof that

the intestine possesses this property to a greater extent than any other tissue.

URETHANE FORMATION OR THE CARBAMINO REACTION OF AMINO ACIDS

Chloroformic ester reacts with ammonia to form urethane or amino ethyl-formate—or the ethyl ester of carbamic acid.

$$CO\begin{smallmatrix}Cl\\ \\OC_2H_5\end{smallmatrix} + NH_3 = CO\begin{smallmatrix}NH_2\\ \\OC_2H_5\end{smallmatrix} + HCl$$
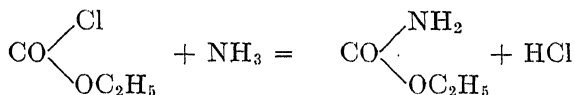
Ammonium carbamate is formed as follows:

$$\overset{O}{\overset{\|}{HO-C-OH}} + 2NH_3 \rightarrow \overset{O}{\overset{\|}{NH_4-C-O-NH_2}} + H_2O$$
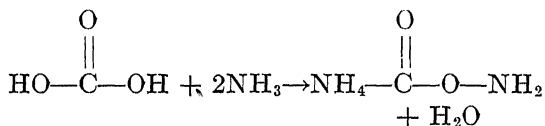
Carbonic acid

Urethane is the ethyl ester of ammonium carbamate, and a reaction of this kind is known as the carbamino reaction.

Ammonium carbamate is the intermediary compound in the formation of urea in the body.

$$NH_2 - COONH_4 = CO\begin{smallmatrix}NH_2\\ \\NH_2\end{smallmatrix} + H_2O$$
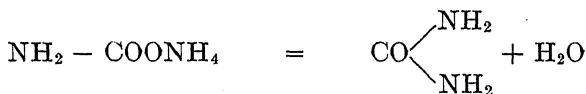
Ammonium carbamate,   *urea* or carbamide.

Carbamate salts, differ from carbonates in their solubilities,

$$2CO\begin{smallmatrix}OCa\\ \\NH_2\end{smallmatrix}$$ or calcium carbamate being soluble in water.
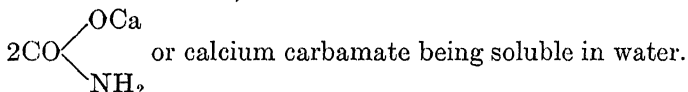
When boiled however calcium carbonate is formed and NH_3 is driven off. This difference in the solubilities is used to advantage in determining the composition of mixtures of amino acids. If in a solution containing amino acids the CO_2 formed is equivalent to the N, or $\frac{CO_2}{N} = 1$ the relation is that of mono-amino acids. If diamino acids or polypeptids are present the ratio is less than 1.

The Taste of Amino Acids

There is nothing distinctive in the taste of amino acids. Glyco-coll as the name indicates is sweet. Alanine and glycoleucine are also sweet. Leucine is tasteless and iso-leucine is bitter. Taste in relation to chemical structure is not well understood. See p. 205.

OPTICAL PROPERTIES OF AMINO ACIDS

The alpha atom of amino acids is asymmetric, consequently the acids are optically active. The presence of the asymmetric C atom does not necessarily confer optical activity, but no optically active organic substance is known without the asymmetric C atom. Like most natural products many amino acids are levoro-tatory; proteins also are levorotatory and on hydrolysis the rotation increases, so that the rate of digestion can be measured by increase of optical activity.

Knowing the formula of a compound it is impossible to tell what direction the rotation may be, and when one group is substituted for another prediction of the change can not be made.

It is possible by substituting one group for another to transform an optically active compound into its optical antipode. This is known as Walden's inversion. In several cases it has been possible to start with a substance and by a reaction cycle obtain the optical antipode and again the original substance Walden treated l. Chlorsuccinic acid with moist silver oxide and obtained l. malic acid. This on treatment with phosphorus pentachloride was converted into d. chlorsuccinic acid, which was converted into d. malic acid which on treatment with phosphorus pentach-loride yielded l. chlorsuccinic acid.

These transformations are diagrammed in the following scheme:

$$\begin{array}{ccc}
 & \text{AgOH} & \\
\text{l-Chlorosuccinic acid} & \xrightarrow{\hspace{2cm}} & \text{l-Malic acid} \\
\uparrow \,|\, \text{PCl}_5 & & \Big\downarrow \text{PCl}_5 \\
 & \text{AgOH} & \\
\text{d-Malic acid} & \longleftarrow & \text{d-Chlorosuccinic acid}
\end{array}$$
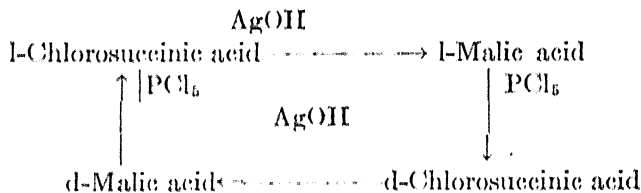
With alanine, and nitrosyl bromide—Emil Fisher worked out the following reaction cycle:

$$\text{d-Alanine} \xrightarrow{\quad\text{NOBr}\quad} \text{l-Bromopropionic acid}$$

d-Alanine $\xuparrow{} NH_3$ l-Bromopropionic acid $\xdownarrow{} NH_3$

$$\text{d-Bromopropionic acid} \xleftarrow{\qquad} \text{l-Alanine}$$
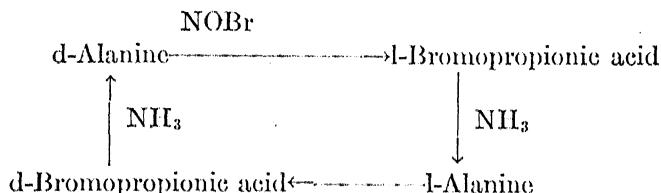
The significance of optical activity in so far as amino acids are concerned, and in general, is little understood. A knowledge of the cause of these facts would do much to advance the understanding of drug action.

The facts that certain moulds can ferment dextrotartaric acid and not levo; that yeast will ferment such sugars as d-mannose d-glucose, or d-fructose, but will not ferment l-fructose, l-glucose, l-mannose, or l-galactose; and that dextrohyoscyamine, dextro-epinephrine, etc. are so much more potent than the levo forms, are full of suggestions and when understood may do much to clarify vital activities.

Regarding the formation of optical bodies little is known, but in plants photo chemical reactions seem to play an important role. Cotton (Am. Chem. Phys., 1896, VII, 8, 373) found that the dextro and levo forms of tartaric acid absorb d. circularly polarized light at different rates, which suggest a method of their formation.

The Action of Amino Acids in the Body

The amino acids are utilized in the body as foods. This use may be in the building up of protein in the body, and repair of used protein. Amino acids may also be to some extent converted into carbohydrate and consequently into fat and will exert the action of these food stuffs. The following formulas show the possibility of carbohydrate formation from amino acids:

$$2\begin{array}{l} COOH \\ | \\ CH_2 \\ | \\ CHNH_2 \\ | \\ COOH \end{array} + H_2O \rightarrow 2\begin{array}{l} COOH \\ | \\ CH_2 \\ | \\ CH_2OH \\ \hline 2CO_2 \end{array} \rightarrow C_6H_{12}O_6$$

Aspartic acid β. lactic acid   Dextrose

$$
\begin{array}{lll}
COOH & & COOH \\
| & & | \\
CH_2 & \longrightarrow & CH_3 \\
| & & \overline{} \\
CH_2 & + \ HOH & CH_2OH \\
| & & | \\
CHNH_2 & + \ HOH \rightarrow & CHOH \\
| & & | \\
COOH & & COOH \\
\text{Glutamic acid} & & \text{Glyceric acid}
\end{array}
$$
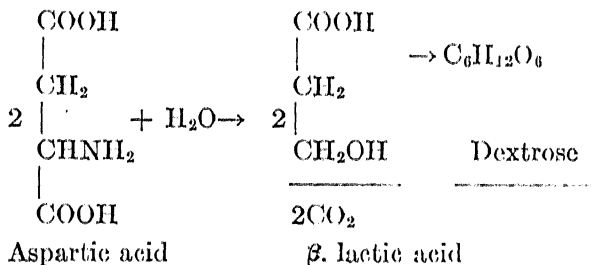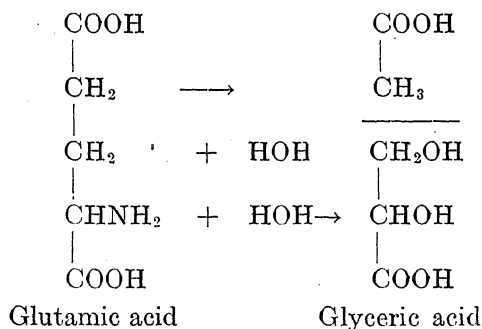
Two molecules of glyceric acid forms glucose on reduction:—
Glyceric acid→glyceric aldehyde→glucose

When fed to glycosuric dogs, many amino acids, like protein, increase sugar excretion, and are converted into sugar. It is probable that carbohydrates may be used to some extent in the formation of amino acids, though this is not definitely proven. The only nitrogen containing carbohydrate of the body is glucosamine. This is found especially in chitin which forms the external skeleton of orthopods. It can also be prepared from cartilage and ovalbumin.

Besides their function in metabolism, amino acids exert a specific stimulating action on metabolism. A similar action however is exerted by all food stuffs and is known as the specific dynamic action. When for example, an animal is starving and the energy metabolism is represented by 100 calories and we wish to keep the animal at this level by feeding protein, it will be necessary to feed 140 calories, or fat 114 calories or carbohydrate 106 calories. The excess of heat generated above the 100 per cent. is the specific dynamic action. Lusk (1912) thinks that in the case of proteins this is due to the mass action of the amino acids on the cell protoplasm which they stimulate.

The Fate of Amino Acids in the Body

The amino acids derived from protein hydrolysis are readily oxidized in the body and ultimately excreted as urea, CO_2 and H_2O. Stolte found that when injected intravenously into rabbits, the nitrogen of glycine and leucine is almost totally excreted as urea, while that of alanine, cystine, aspartic acid and glutamic

acid are less readily catabolized, and phenyalanine and tyrosine led to no immediate urea excretion.

Traces of unchanged amino acids may be found in the normal urine.   The presence of glycine has been definitely established, and it may reach as high as 1 per cent. of the total nitrogen output.

Tyrosine, leucine, and glycocoll are regularily found in the urine in cases of acute yellow atrophy of phosphorus poisoning and in other conditions.   Cystine is found in cases of cystinuria, a disease of metabolism not well understood.· In these cases, the diamines, putrescine and cadaverine, formed by putrefaction in the intestine may also be found.

In the normal catabolism of the amino acids, the first step in the formation of urea is thought to begin with the alpha position:

$$R.CH_2CHNH_2COOH + O_2 = RCH_2COOH + CO_2 + NH_3$$
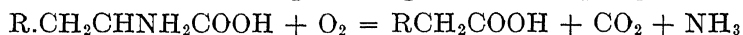
Many examples of this kind of reaction are known, *e.g.*, leucin on oxidation gives iso-valeric acid

$$\begin{array}{c} CH_3 \\ \diagdown \\ \diagup \\ CH_3 \end{array} CH.CH_2CHNH_2COOH + O_2 =$$

$$\begin{array}{c} CH_3 \\ \diagdown \\ \diagup \\ CH_3 \end{array} CH.CH_2COOH + CO_2 + H_2O$$

Iso-valeric acid
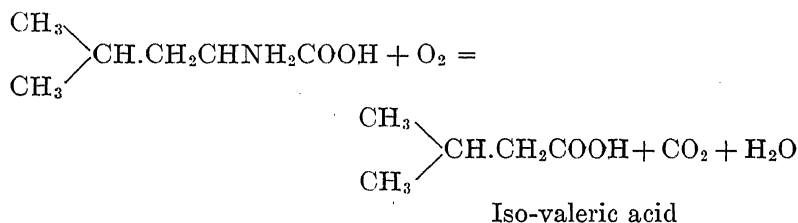
In cases of alkaptonuria tyrosin undergoes a similar change to form homogentisic acid

$$\begin{array}{cc} \text{Tyrosin} & \text{homogentisic acid} \end{array}$$
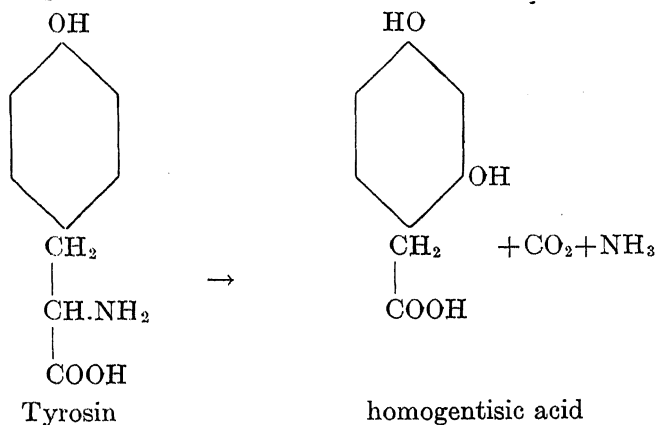
Homogentisic acid in turn is oxidized by the normal organism, and this may be the usual mechanism of tyrosin catabolism. In alkaptonuric cases homogentisic acid is either not oxidized or at a much slower rate than in the normal.

Alanine is oxidized in the body as follows,

$$CH_3CH.NH_2.COOH + O \rightarrow CH_3CHO + CO_2 + NH_3$$
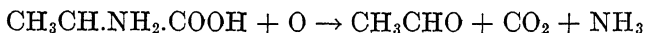
When oxidized in vitro by hydrogen peroxide or potassium permanaganate the amino group is replaced by oxygen and a ketonic acid is formed:

$$
\begin{array}{cc}
CH_3 & CH_3 \\
| & | \\
H\!-\!C\!-\!NH_2 \quad O \rightleftharpoons & C\!=\!O+NH_3 \\
| \quad\quad + & | \\
COOH & COOH
\end{array}
$$
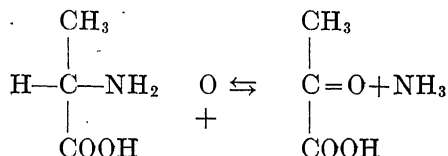
This reaction may be reversed by reducing agents. By reduction of the alpha ketonic acids hydroxy acids may be formed, in this case lactic acid

$$
\begin{array}{c}
CH_3 \\
| \\
CH.OH \\
| \\
COOH
\end{array}
$$
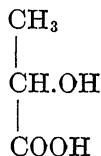
is formed, and this indirect method may explain the production of lactic acid in the body. Lactic acid is found chiefly in cases of tissue asphyxia due to excessive exercise, or deficient supply of oxygen.

The reversibility of the alanine—lactic acid reaction, and the relation of lactic acid to carbohydrates, suggests the possibility of a synthesis of amino acids from carbohydrates and ammonia in the body. Embden obtained evidence of this synthesis by perfusing a liver with glycogen and found that alanine was formed. Many other examples of alpha ketonic acids being formed from alpha amino acids. It is assumed that alpha ketonic acids are essential products in the oxidation of alpha amino acids, and hydroxy acids are formed from these by reduc-

tion and are not directly derived from the amino acids (see Dakin, Oxidations and reductions in the animal body).

The ultimate fate of alpha amino acids and alpha ketonic acids in the body is the same but, in the process of catabolism the ketonic acid may undergo three types of change:

1. It may be oxidized to a lower fatty acid:

$$R.CH_2CO.COOH + O = R.CH_2COOH + CO_2$$
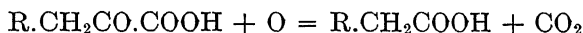
2. It may be reduced with formation of an hydroxy acid:

$$R.CH_2.CO.COOH + H_2 = R.CH_2CHOH.COOH$$
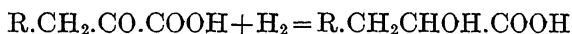
3. Its ammonium salt may be reduced to the corresponding amino acid:

$$R.CH_2CO.COONH_4 + H_2 = R.CH_2.CH.NH_2COOH + H_2O$$
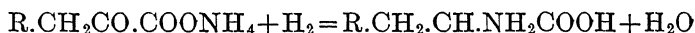
These three types have been imitated in vitro.

The Fate of Alpha Amino Acids in Abnormal Conditions

In cases of diabetes, in which there is a reduction of the ability of the tissues to oxidize carbohydrates, and perhaps some other bodies, amino acids may give rise to sugar and aceto acetic acid.

The following table from Dakin (oxidations and reductions in the animal body) shows this:

Substance	Increased glucose excretion when given to diabetic animal	Acetoacetic acid formation when perfused through surviving liver
Glycine................	+	−
Alanine...............	+	−
Valine................	?	−
Leucine...............	−	+
Aspartic acid...........	+	−
Glutamic acid...........	+	−
Phenylalanine..........	?	+
Tyrosine...............	−	+
Histidine..............	+	+(?)
Lactic acid............	+	−

Since carbohydrates can be formed from amino acids, it follows that alcohols may also be formed. Their actions in the formations of alcohols appears to be as follows:

$$R.CH_2.CH.NH_2.COOH \quad \xrightarrow{\text{oxidation}} \quad R.CH_2.CO.COOH \rightarrow$$
$$\text{a, Ketonic acid}$$

$$CO_2 + R.CH_2CHO \quad \xrightarrow{\text{reduction}} \quad R.CH_2.CH_2 OH$$
$$\text{Aldehyde} \qquad\qquad\qquad \text{Alcohol.}$$
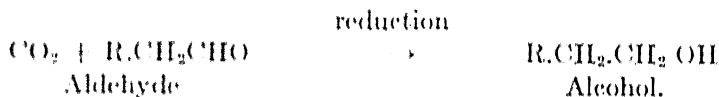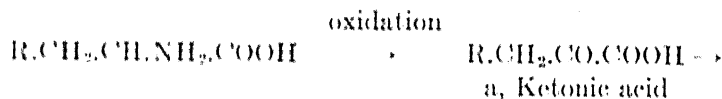
The fate of cystine, the only sulphur containing amino acid is of interest since sulphur is important in pharmacology. In normal conditions this acid is completely oxidized and the sulphur eliminated in the form of sulphate. In certain individuals the ability to oxidize cystine is lacking and it appears in the urine. Such persons appear normal, and do not suffer from the condition. It is an inherited condition and is more frequent in males than females. The cause of this anomaly of metabolism is not known.

Taurine, $CH_2.NH_2.CH_2SO_3H$, which is found in the bile combined with cholic acid, as taurocholic acid, appears to be a derivative of cystine or cysteine:

$$
\begin{array}{ccc}
COOH & COOH & CH_2.NH_2 \\
| & | & | \\
CHNH_2 \rightarrow & CH.NH_2 \rightarrow & CH_2(SO_3H) \\
| & | & \text{Taurine.} \\
CH_2(SH) & CH_2(SO_3H) & \\
\text{Cysteine} & \text{Cysteic acid} &
\end{array}
$$
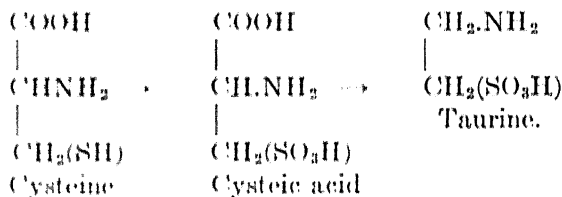
Because of the relation to the active principles of ergot, adrenalin etc. the fate of tyrosine, phenylalanine and tryptophane are of especial interest. These are normally completely oxidized in the organism. This is contrary to the fact that most aromatic bodies are not readily oxidized. In cases of alkaptonuria tyrosin and phenylalanine may be converted into homogentisic

$$
\begin{array}{ccc}
\text{COOH} & \text{COOH} & \text{COOH} \\
| & | & | \\
\text{CHNH}_2 & \text{CH}_2 & \text{CH.NH}_2 \\
| & | & | \\
\text{CH}_2 & \text{CH}_2 & \text{CH}_2
\end{array}
$$
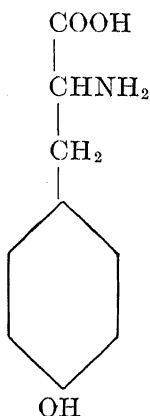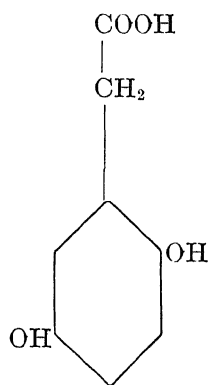
Tyrosine   Homogentisic acid   Phenyl-alanine
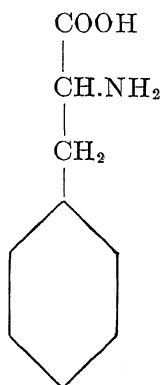
The normal organism oxidizes homogentisic acid readily, but but alkaptonurics have not this power.

Tryptophane.—Little is known of the mechanism of the fate of this body in the human organism. It apparently undergoes complete oxidation. When fed to dogs, it causes an increase in the excretion of kynurenic acid.
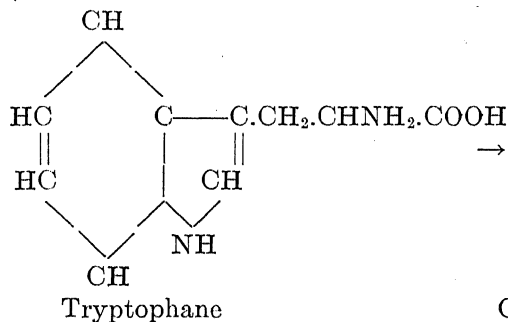
Tryptophane
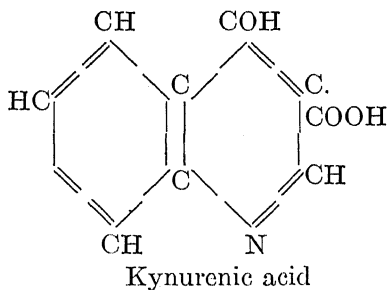
Kynurenic acid

In this reaction an additional C atom has entered the indole ring.

The fate of histidin in the body is of especial interest because of its relation to the active principles of ergot. When CO_2 is split off from histidin, histamine or β imido azole ethyl amine, or ergamine is formed.

$$
\begin{array}{ccc}
\text{C—NH} & & \text{C—NH} \\
\| \quad \diagdown \text{CH} & & \| \quad \diagdown \text{CH} \\
\text{C—N} \diagup & & \text{C—N} \diagup \quad\quad + CO_2 \\
| & & | \\
\text{CH}_2 \quad \rightarrow & & \text{CH}_2 \\
| & & | \\
\text{CH.NH}_2 & & \text{CH}_2\text{NH}_2 \\
| & & \\
\text{COOH} & & \\
\text{Histidin} & & \beta\text{-imino azole ethyl amine} \\
& & \text{(histamine or ergamine)}
\end{array}
$$
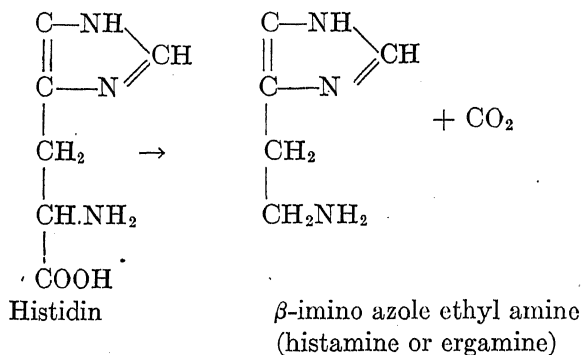
The effects of ergamine differ in different animals. In dogs and cats it causes a condition resembling anaphylactic shock due to dilation of the peripheral vessels. While in the rabbit it tends to constrict the vessels. It acts directly on the vessel wall and may have some action on the neuro-muscular junction. According to some authors, histamine is the same as vasodilatin. Such substances as histamine, epinephrine, and perhaps many unknown hormones may be intermediate products in the catabolism of amino acids.

POISONOUS PROTEINS

These are protein substances, and have been termed vegetable agglutinins; they coagulate milk and blood. They resemble bacterial toxins and have been found in a number of higher plants, and are therefore called phytotoxins. The most important are Ricin—from the castor bean (Ricinus communis). Abrin, from the seeds of abrus precatorius—Crotin, from the seeds of croton tiglium. Robin from the leaves and bark of the locust, Robinia pseudoacacia, and Curcin from the seeds of Jastropha curcus. The general properties and actions of these substances are similar. Ricin is found in ricinus communis along with castor

oil, but the oil itself does not contain ricin. It is the most powerful of the phytotoxins. One thousandth of a milligram per kilo is fatal to a rabbit when given hypodermically. The ricin agglutinates the corpuscles and also precipitates serum. Death occurs several days after a subcutaneous injection, with but few symptoms other than loss of appetite, and towards the end diarrhœa and vomiting. Post mortem examination shows congestion and inflammation of the gastro-intestinal tract with ecchymoses; blood in the serous cavities; punctiform hemorrhages beneath the serous surfaces and extravasations in various organs. Microscopical examination shows foci of necrosed tissue in the spleen, liver, intestine stomach and other organs. The whole picture is much the same as that caused by diphtheria toxin. The poisons are eliminated through the intestinal mucosoa, which accounts for the great amount of gastro-intestinal injury. An immunity can be developed against these toxins, and antitoxins can be prepared.

Abrin contains two poisons, a globulin and an albumose, of which the former is more powerful. Crotin is less powerful than ricin or abrin, but the action is similar. Robin and curcin are less known than the others. Curcin differs from all the others in having no hemagglutinative action.

XXVIII. ENZYMES OR ORGANIC FERMENTS

Nothing definite is known of the chemistry of enzymes. The word means literally "in yeast" (from the Greek "en", in; and "zyme", leaven. They are complex organic substances, capable of rendering food available for the cell. Because of their colloidal nature and the difficulty of obtaining enzymes in a pure condition, their chemical nature is unknown. They are formed within the living cells, although in certain cases, the cells do not secrete the complete enzyme, pro-ferments or zymogens, which are transformed into active enzymes outside of the cell, being first formed.

Enzymes differ from catalysts in their sensitivity to heat and light. All enzymes are destroyed at 100°C. and most of them at 60°C. Each enzyme acts best at a definite temperature which is the optimum temperature. For the digestive enzymes this is about 40°C. The destructive action of heat is perhaps due to a coagulation of the proteins of the enzyme.

Regarding light, there seems to be two kinds of action:

(*a*) Those produced by ordinary light in presence of oxygen. This is greatly accelerated by the presence of fluorescent substances such as eosin, quinoline red etc., which though not understood yet offers hope of therapeutic value in many diseases.

(*b*) Ultra-violet light independent of oxygen destroys diastase and other enzymes. In this connection we might add that various rays of light and emanations are now used with considerable effect in cancer and other diseases the causes of which are unknown.

The colloidal nature of enzymes is shown by lack of diffusibility and by their precipitation by other colloids. Enzymes are adsorped readily by many finely divided inert particles such as charcoal, infusorial earth, etc. This adsorption is a phase of precipitation, and in this case is electrical.

The addition of salts, drugs, etc. influence enzyme action; those substances hastening it being called accelerators, those depressing it being called depressants or paralysers.

If enzymes are injected subcutaneously into an animal, an antienzyme may be formed, which neutralizes the activity of an enzyme in a manner similar to toxin and antitoxin.

ENZYMES USED AS MEDICINES

The digestive ferments diastase, pepsin, and trypsin have been used to some extent in medicine. The value of these in most cases is questionable, for the reason that it is doubtful if deficiency of the natural digestive enzymes ever occurs. The term "Amylaceous dyspepsia" has been used to indicate cases of dyspepsia supposedly due to incomplete digestion of starches. However, for all practical purposes, starches are digested in the intestine, and it has never been shown that there is any deficiency of the diastatic intestinal ferments. Diastase preparations as medicines would therefore seem superfluous. The pepsin of the stomach is almost always capable of digesting proteins, providing the reaction is acid, and the deficiency is not in pepsin but a lack of acid. The treatment therefore, except in rare cases, is acid medication not the administration of pepsin. However, while pepsin in the majority of cases is superfluous it is not injurious.

Pancreatic Ferments. The value of these in medicine is even more problematical than pepsin. When given they are adminis-

tered in a capsule or in a salol coated pill, to avoid digestion in the stomach. To get such preparations through the stomach without digestion, and at the same time, have them in a form that will be liberated in the intestine is very difficult. It is doubtful if any of the preparations that pass through the stomach undigested are liberated in the intestine. If they are not liberated they are useless, and if liberated, superfluous.

THE FATE OF ENZYMES IN THE BODY

Since the chemistry of the enzymes is unknown, the exact fate cannot be determined. The protein part, or impurity, suffers the fate of all protein in the body. The enzymes may be used over again in the body to some extent. They are also excreted in the urine and fæces.

Under hydrolytic enzymes, we find a group of fat-splitting enzymes called lipases or steapsins. This group was found by Green (1890) and subsequently confirmed by Connstein, Hoyer, and Wartenberg, who found that castor-oil seeds contain an enzyme that hydrolyses the fats present. In the tissues of the body, this fat-splitting rôle of lipase which brings about the separation of neutral fat in the presence of an excess of water is reversible and builds up fat, when allowed to act upon a mixture of fatty acids and glycerol in a medium poor in water. Diastase, which hydrolyses starch to maltose and dextrose, is one of the commonest of enzymes, and occurs in practically all living matter.

Under fermenting enzymes may be mentioned the alcoholic fermentation of glucose, levulose, mannose, etc., by zymase, which probably occurs also in animal tissues, this supposition, however, requires more evidence than has yet been shown. It is thought that traces of alcohol found in the blood may have been formed in the intestine by bacterial action.

Coagulating enzymes, are represented by rennin, which curdles milk; thrombin, which coagulates blood; and pectase, which coagulates soluble pectic bodies.

The oxidizing enzymes are divided into (a) those which oxidize alcohols to acids, and (b) those which set free oxygen from hydrogen peroxide or other peroxides. These are the peroxidases or catalases.

Life processes of all kinds are accompanied by enzyme action.

Growth, repair, ripening of fruit, decomposition, etc., have been explained by enzyme activity.   Enzymes are not held to originate an action, but simply to accelerate those already in progress. Whether the facts justify this opinion remains to be determined.

Enzymes are classified according to the substance acted on as follows:

Coagulating enzymes (thrombin rennet).

Pepsin, trypsins, erepsins, amidases, catalases, etc.

The most important are arranged in tabular form as follows:

FERMENTS ACTING ON CARBOHYDRATES

Name of Enzyme	Substances on which Enzyme acts.	Products of the reaction
Invertin or sucrase	Cane sugar	Dextrose and levulose
Amylase or diastase	Starch and dextrins	Maltose
Glucase or maltase	Dextrins and maltose	Dextrose
Lactase	Lactose mycose or	Dextrose and galactose
Trehalase	Trehalose	Glucose
Cytase	Hemi-cellulose	Mannose and galactose
Pectase	Pectin	Pectates and sugars, arabinose
Caroubinase	Caroubin	Caroubinose
Invertase which hydrolyses	Raffinose to	Levulose and melibiose
Maltase which hydrolyses	Maltose (malt sugar)	Dextrose
Inulase which hydrolyses	Inulin to	Levulose

FERMENTS ACTING ON FATTY SUBSTANCES

Steapsin or lipase	Fatty substances	Glycerin and fatty acids

FERMENTS ACTING ON GLUCOSIDES

Emulsin	Amygdalin and other glucosides	Glucose, oil of bitter almonds, and hydrocyanic acid
Myrosin	Potassium myronate	Glucose and allyl isosulphocyanate
Betulase	Gaultherin	Oil of wintergreen Glucose
Phytase	Phytin	Inosite and phosphoric acid

FERMENTS ACTING ON PROTEINS.—*Continued*

Name of Enzyme	Substance on which Enzyme acts	Products of the reaction
	FERMENTS ACTING ON PROTEINS	
Rennet	Caseinogen (Casein, Hammarsten)	Casein (Para casein)
Plasmase	Fibrinogen	Fibrin
Pepsin	Albuminoid substances	Proteoses, peptones
Trypsin	Albuminoid substances	Proteoses, peptones
Trypsin	Albuminoid substances	Polypeptides and amido acids
Papain	Albuminoid substances	Polypeptides and amido acids

Erepsin contained in the intestine which hydrolyses

	Proteins to	Polypeptides and amino acids

Bromelin contained in the pineapple juice which hydrolyses

	Proteins to	Polypeptides and amino acids

FERMENTS CAUSING—MOLECULAR DECOMPOSITION

Zymase or alcoholic diastase		Starches. Alcohol and carbonic acid. Various sugars CO_2 lactic acid etc.
Lactic acid bacteria	Lactose	
Butyric bacteria, etc.	Lactose	Butyric acid

FERMENTS ACTING ON PROTEINS TO CAUSE CLOTTING

Rennin (Chymosin)	which curdles milk	
Thrombin	which coagulates blood	
Pectase	which coagulates soluble pectic bodies	
Laccase	Uruschic acid	Oxyuruschic acid
Oxidin	Tannin, anilin, etc. Coloring matters of cereals	Unknown products of oxidation
Malase	Coloring matters of fruits	Unknown products of oxidation
Tyrosinase	Tyrosine	CO_2 parahydroxy ethylamine, NH_3 etc.
Oenoxidase	Coloring matter of wine	CO_2 parahydroxy ethylamine NH_3 etc.
Oxidases which oxidize	alcohols to	acids *e.g.*, action of Mycoderma aceti, etc.

FERMENTS ACTING ON PROTEINS.—*Continued*

Name of Enzyme	Substance on which Enzyme acts	Products of the reaction
	FERMENTS ACTING ON UREA	
Urease	Urea	Ammonia and CO_2
	DEAMIDIZING ENZYMES	
Nuclease	Splits nucleic acid	Purin bases, etc.
Guanase	Converts guanine	Xanthine
Adenase	Converts adenine	Hypoxanthine
	OXIDIZING FERMENTS	
Oxidases	Causes oxidation of organic substances	
Catalase	Decomposes hydrogen peroxide	Water, oxygen

XXIX. CHLOROPHYLL

Chlorophyll (Gr. chloros, green—phyllon, leaf). Plant colors have no physiological action and if used in medicine, it is for their esthetic or psychic effect. But the relation between chlorophyll and hemoglobin is of great biological significance.

The name chlorophyll was first applied by Pelletier and Caventou to the green coloring matter of plants. By the use of the spectroscope it has been found that chlorophyll of the green leaf instead of being one simple color, contains at least seven different pigments.

The reactions in the formation of chlorophyll are not well understood. Light is essential. The presence of iron and magnesium is necessary. Starch and sugar may or may not be essential. This point is still under investigation; as is also the chemistry of the substances which immediately precede chlorophyll and from which it is formed. Lecithins and proteins seem to take part in its formation. The chemistry is complex and not definitely known, but is sufficiently understood to show a definite chemical relationship between chlorophyll and hemoglobin.

RELATIONSHIP OF CHLOROPHYLLS AND HEMOGLOBINS

There are several different chlorophylls, just as there are different hemoglobins. The hemoglobin of different animals varies slightly in composition but all are closely related chemically.

By the action of glacial phosphoric acid containing HI on hematin or hemochromogen, hæmopyrrol, $C_8H_{13}N$, a colorless oil which in air gradually changes to urobilin is formed. Urobilin is also produced by the action of the same reducing agents on the chlorophyll derivative, phyllocyanin. This shows a close relationship between chlorophyll and hæmoglobin.

There are two well known chlorophylls:

$$\text{Chlorophyll } (a) \quad C_{32}H_{29}N_3Mg \begin{cases} \diagup COOCH_3 \\ -COOC_{20}H_{39} \\ \diagdown CO \\ NH \diagup \end{cases}$$

and chlorophyll (b) $C_{32}H_{28}O_2N_4Mg \diagup^{COOCH_3}_{COOC_{20}H_{39}}$
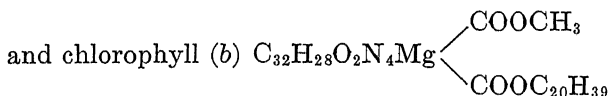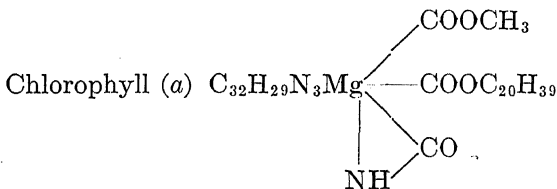
(Willstätter and Isler)

When these are treated with alkalies, two groups of products are formed:

1. Phyllins, which contains magnesium and
2. Porphyrins, which are free from magnesium.

On oxidation with chromic and sulphuric acid, Marchlewski, also Willstätter and Asahina, think the pyrrol group $\begin{matrix} C\!-\!\!-\!C \\ | \qquad \diagdown N \\ C\!-\!\!-\!C \diagup \end{matrix}$ exists in the chlorophyll molecule since the pyridine derivatives

$$\begin{matrix} CH_3.C\!-\!\!-\!CO \\ \quad \| \qquad \qquad \diagdown NH \\ COOH.CH_2.CH_2C\!-\!\!-\!CO \diagup \end{matrix}$$ Hæmatinic acid imide, and

$$\begin{matrix} CH_3.C\!-\!\!-\!CO \\ \quad \| \qquad \qquad \diagdown NH \\ CH_3.CH_2C\!-\!\!-\!CO \diagup \end{matrix}$$ Methylethylamalcinimide are formed.

Haematinic acid $\begin{matrix} CH_3.C.COOH \\ \| \\ COOH.CH_2.CH_2.C\;COOH \end{matrix}$ has been obtained
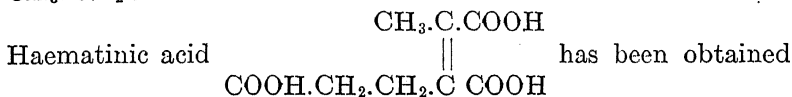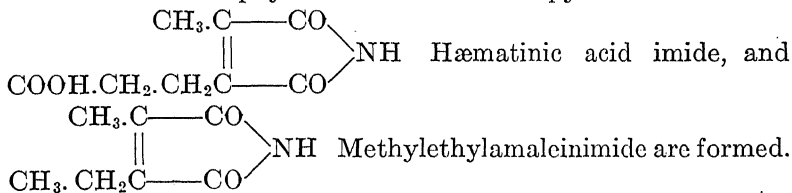
from hemoglobin and the imide of this obtained from chlorophyll again establishes a relationship between chlorophyll and hemoglobin. Hematin and hæmatoporphyrin also yield hæmatinic acid imide.

Pyrrol is an important nucleus in many biological compounds, being found in alkaloids, nicotine, cocaine, and others, and in proteins. In fact, proteins may be looked upon as containing an alkaloidal nucleus.

The structure of the pyrrol derivatives is indicated as follows:

$$\beta) \quad \overset{HC——C}{\underset{\|\quad\|}{}} H \quad (\beta$$
$$\alpha) \quad HC \qquad C\, H \quad (\alpha$$
$$\diagdown\diagup$$
$$NH$$
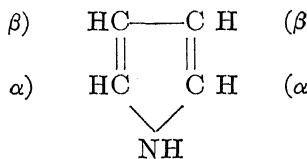
Besides these mentioned, the following derivatives of hæmatin are of biological importance.

(I)
$$CH_3. \quad \overset{C——C}{\underset{\|\quad\|}{}} C_2H_5$$
$$CH_3. \quad C \quad CH$$
$$\diagdown\diagup$$
$$NH$$
Isohemopyrrol
β-ethyl α' β' dimethyl pyrrol

(II)
$$CH_3—\overset{C———C}{\underset{\|\quad\|}{}}—C_2H_5$$
$$C \quad C\ CH_3$$
$$\diagdown\diagup$$
$$NH$$
Kryptopyrrol or α methyl β ethyl β-methyl pyrrol

(III)
$$CH_3. \quad \overset{C——C}{\underset{\|\quad\|}{}} C_2H_5$$
$$CH_3 \quad C \quad C\ CH_3$$
$$\diagdown\diagup$$
$$NH$$
Phyllo pyrrol or α methyl β-ethyl α' β' dimethyl pyrrol

(IV)
$$CH_3. \quad \overset{C——C}{\underset{\|\quad\|}{}} CH_2.CH_2.COOH$$
$$C \quad C$$
$$\diagdown\diagup$$
$$NH$$
Isophonopyrrol carboxylic acid or β-propionic acid α' β' dimethyl pyrrol.
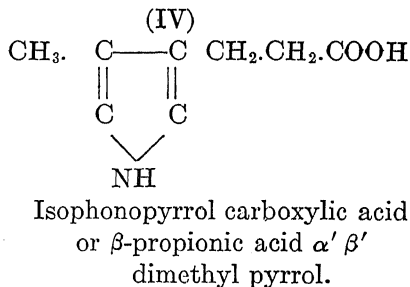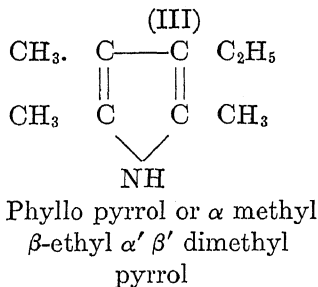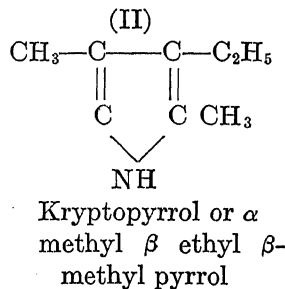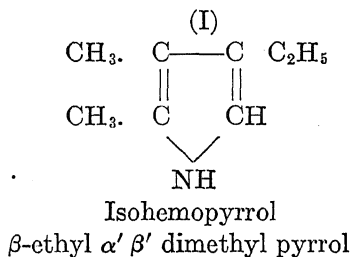
The bile acids are derivatives of hemoglobin and also contain pyrrol nuclei which are derived from the hematin of blood. When blood is dropped into acetic acid containing some NaCl and the solution heated to 95°C. the hydrochloride of hæmatin, hæmin

$C_{33}H_{32}O_4N_4FeCl$, crystallizes out. When haemin is treated with HBr, a dibrom compound is formed and iron is lost. When the dibrom compound is hydrolysed hæmato porphyrin is formed which is a dibasic acid of the formula:

$$C_{31}H_{34}N_4 \diagup\begin{matrix}OH\\OH\\COOH\\COOH\end{matrix}$$
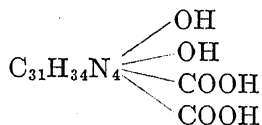
Hematoporphyrin

The intermediate reaction is not known. When hematophyrin is reduced by heating with methyl alcoholic potassium hydroxide in pyridine solution, hemoporphyrin $C_{33}H_{36}O_4N_4$ is formed, which on heating with soda lime forms aetioporphyrin $C_{31}H_{36}N_4$. Willstätter thinks this is the mother substance from which both chlorophyll and hematin are derived.
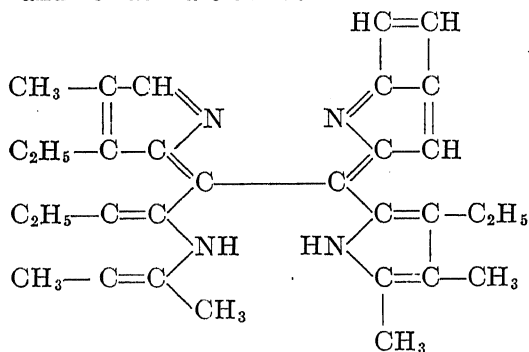
Aetioporphyrin.
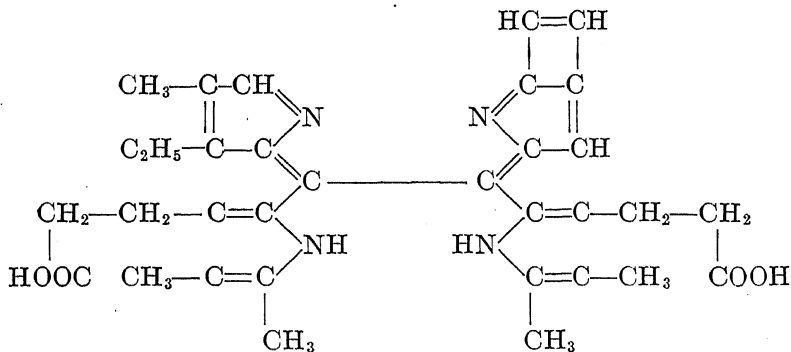
Hæmoporphyrin.

The following skeleton formulæ has been suggested by Werner to show the relationship between chlorophyll and hæmatin.

Chlorophyll   Hæmatin
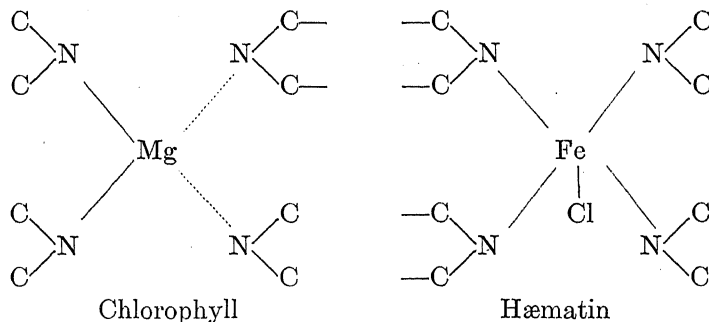
In addition to chlorophyll plants contain many other related pigments such as carotin, the yellowish red pigment of carrots, which is found with chlorophyll in many plants. It has the molecular formula $C_{40}H_{56}$. Xanthophyll $C_{40}H_{56}O_2$ and carotin, both neutral substances, are closely related and on reduction xanthophyll can be converted into carotin. Tucoxanthin $C_{40}H_{54}O_6$ isolated from brown algæ has basic properties and forms blue salts with HCl and H_2SO_4.

Besides the colors mentioned, there are yellow colors known as flavones and xanthones as well as anthocyanin, which give blue, red, and violet tints; and many others, which have as yet only a remote interest in the chemistry of drugs. Chlorophyll is the only one that has been investigated in detail.

While chlorophyll and hemoglobin are related chemically, their functions are quite dissimilar. The chief function of hemoglobin is as a carrier of oxygen, while chlorophyll participates in both metabolism and assimilation. Chlorophyll contains no iron, while the main function of hemoglobin depends on this element.

The following diagram shows the relationship of chlorophyll, hemoglobin and bile pigment (after Mathews, p. 423):

The great difference between plants and animals is that in the plant, reduction and synthesis are the predominant chemical processes, while in the animal, oxidation and hydrolysis predomi-

I.	II.	III.
Hemoglobin		Chlorophyll

Globin ← Hematin
$C_{32}H_{32}N_4O_3Fe(?)$ ↓

Hematoporphyrin   Bilirubin   Phylloporphyrin
$C_{32}H_{36}N_4O_6(?)$ $C_{32}H_{36}N_4O_6(?)$ $C_{32}H_{36}N_4O_2$

Chlorophyll → Phyllocyanin

Biliverdin
$C_{32}H_{36}N_4O_8$

Urobilin
$C_{32}H_{40}N_4O_7(?)$

Hemopyrrols   Hemopyrrols   Hemopyrrols
$C_8H_{13}N$ (etc.) $C_8H_{13}N$ (etc.) $C_8H_{13}N$ (etc.)

Hematic acids
$C_8H_8O_5 \ C_7H_9NO_2 \ C_8H_9NO_4$
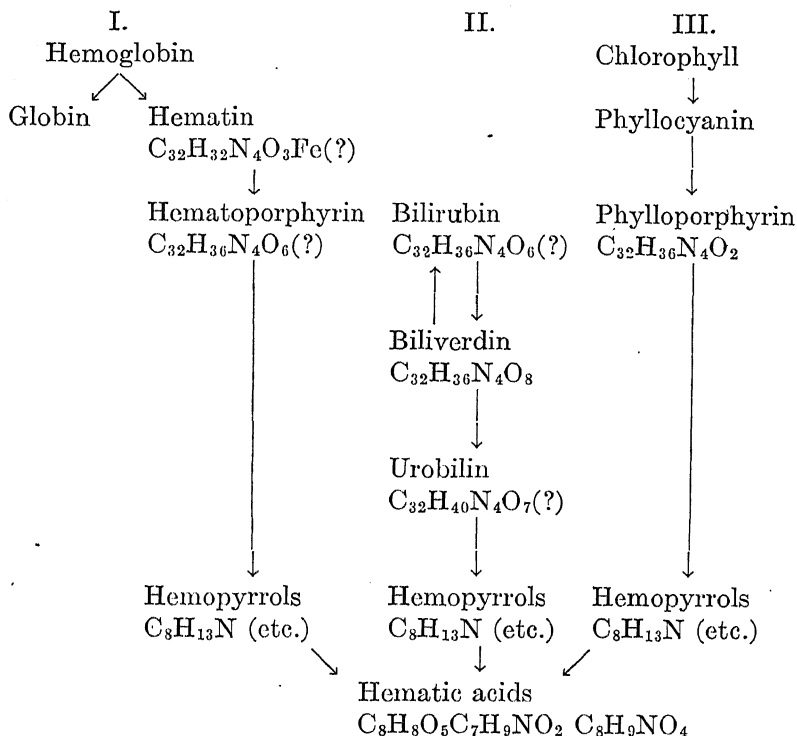
The Fate of Chlorophyll in the Body

We known nothing definitely about the transformations of chlorophyll in the alimentary tract. Neither chlorophyll nor hæmatin are absolutely essential in the diet, since the animal body is apparently able to construct respiratory pigments from the split products of protein. Those containing the pyrrol ring are probably used in this synthesis.

Other Plant Colors

Litmus results from the fermentation of the lichens Rocella and Lecanora. These lichens contain orcinol, partly free and partly as orsellic acid and combinations. By special treatment with ammonia and potassium carbonate, litmus is formed. The concentrated salt mixed with

CH_3

OH ⬡ OH

Orcinol
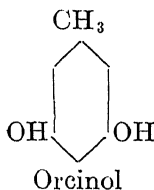
chalk or gypsum, constitutes commercial litmus.   Little is known of the chemistry of this substance, which contains several colors, azolitmin, erythrolitmin, and erythrolein.   The first named is the most important and is soluble in water, but insoluble in alcohol. The others are insoluble in water and soluble in alcohol.   When orcinol is exposed to the air and ammonia it changes to orcein, $C_{28}H_{24}N_2O_7$, which is a reddish brown amorphous powder, the chief constituent of archil, which is also known as cudbear or persio.   It is sometimes used to color medicines.

Curcumin, curcuma, $C_{14}H_{14}O_4$ or tumeric is the coloring principle in the root of curcuma longa.   It dissolves in alkalies to form brownish red salts.

Hemotoxylin $C_{16}H_{14}O_6 + 3\ H_2O$ is the coloring matter of logwood, sometimes used in medicine for its astringent effects. It reduces Fehling's solution, dissolves in alkalies with a violet color (and therefore may be used as an indicator).   When fused with KOH it yields pyrogallic acid and resorcinol.

Red saunders is the heart wood of pterocarpus santalinus. When extracted with alcohol, it gives a red solution and is used to color the compound tincture of lavender.

Coccus (cochineal) is the coloring matter of the cochineal bug. Besides its use in pharmacy, it is particularly valuable in chemistry as an indicator and is employed especially in the titration of ammonia and the carbonates.

Carmine is prepared by extracting the cochineal with water and precipitating with alum and lime or cream of tartar.

Crocus or saffron is made of the stigmas of crocus sativa.

Caramel is partly burnt sugar.

Annato is the pulp surrounding the seeds of Bixa Orallana, a South American Plant.   Annato and saffron are also used to color butter and oleomargarin.

Alkanet is the root of alkanna tinctoria.   This is red with acids and blue with alkalies.

Indicane $C_7H_6NCOC_6H_{11}O_5$ is a glucoside found in a number of plants, as indigo fera anil

    I. arrecta
    I. tinctoria
    I. summatrana and many other plants.   When boiled with a mineral acid, indicane breaks up into glucose and indoxyl.

$$C_7H_6NCOC_6H_{11}O_5 = C_6H_{12}O_6 + C_6H_4 \overset{COH}{\underset{NH}{\diagup}} CH$$
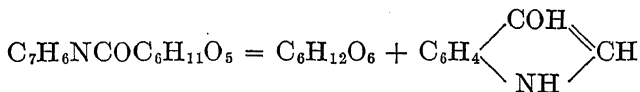
Indican   Indoxyl

When indoxyl is exposed to the air it is oxidized and gives a deep blue coloring matter indigo

$$C_6H_4 \overset{CO}{\underset{NH}{\diagup\!\diagdown}} C : C \overset{CO}{\underset{NH}{\diagdown\!\diagup}} C_6H_4$$
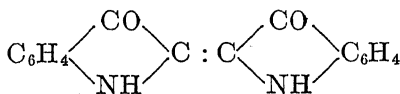
Indigo blue

It was formerly supposed that plant indican was identical with urine indican the latter being so named, because of this supposed identity. The two are not identical, however, although both may give rise to indoxyl; plant indican through hydrolysis, and urinary indican by oxidation of indol.

Indol $C_6H_4 \overset{CH}{\underset{NH}{\diagup\!\diagdown}} CH$ is also formed in the intestine as the

result of putrefaction. It is oxidized most probably in the liver to indoxyl and this is eliminated as the potassium sulphuric ester.

$$C_6H_4 \overset{C(OSO_2OK)}{\underset{NH}{\diagup\!\diagdown}} CH.$$ This ester is known as urine indican and on oxidation gives indigo blue and acid potassium sulphate.
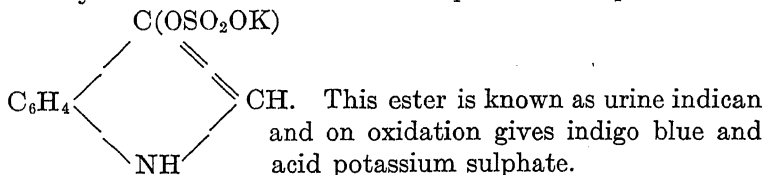
XXX. COLLOIDS

In all reactions of chemical pharmacology, one of the reacting bodies is a colloid. The word colloid was first applied to bodies that had the properties of glue (Gr. kolla, glue; eidos, appearance). More recent study has widened the original scope of this word. Graham, in 1861, divided substances into crystalloids and colloids, classifying them on the following basis; those substances that would diffuse through an animal membrane or parchment paper he called crystalloids, and those that would not do so, colloids. Sodium chloride, sugar, alka-

loidal salts and the like are crystalloids, while gums, starches, resins and proteins are colloids.

Besides the property of non-diffusion through membranes, colloids are amorphous, viscous, and when sufficiently concentrated, form gels. The pseudo solution of the colloid to distinguish it from a true solution is called a *sol*. According to the liquid in which the colloid is suspended (water, alcohol, etc.) the sol is called hydrosol, alcosol, and the gel, hydrogel, alcogel.

Graham also found that under some conditions, non-colloidal matter might become colloidal. He discovered that by adding an excess of dilute hydrochloric acid to a dilute solution of sodium silicate he obtained a clear solution instead of a precipitate of silicic acid. When such a solution was dialyzed, the sodium chloride was washed out and the ordinarily insoluble silicic acid remained in a colloidal condition. A similar method is used at present to prepare colloidal iron.

Colloidal matter under some conditions can also be crystallized; hemoglobin and egg albumen have been obtained in crystalline form. At the present time, therefore, the opinion is that the colloidal condition is not entirely due to the kind of matter, but also to the condition under which the matter is found, and the size of the particles. In proper solvents, perhaps any form of matter may be amorphous or crystalline. Even such a typical crystalloid as sodium chloride in benzene may be colloidal, while under other conditions the typical colloid, albumen, may be crystalline. These extreme cases, however, should not minimize the difference between crystalloids and colloids as they are found in nature.

CHARACTER, OR NATURE, OF COLLOIDS

Enzymes are colloids, and the study of artificial enzymes has done much to explain the nature of colloids. Bredig found that if an electric spark produced by a current of 8–12 amperes at 30 to 40 volts is passed through pure water between two platinum wire electrodes, the metal disintegrates and the water becomes first, yellow, and then a brown or black color. The liquid filters easily, no particles are visible under the microscope, and apparently the platinum has gone into solution. The physical constants, however, do not show a true solution. The freezing

point, boiling point, or osmotic pressure is but little changed, whereas if an equivalent quantity of a salt is added, these constants are definitely changed. Instead of being in true solution, the platinum is in a pseudo solution or a state of extreme division (dispersion) that may be seen by the aid of the ultra microscope. The size of these particles has been estimated at 0.00001 millimetre. These particles in colloidal solutions are known as the disperse phase of the colloidal solution. The water is the continuous phase. Gold, silver, copper, and other metals have been prepared in pseudo solution. These solutions, when allowed to stand, do not respond to the laws of gravitation; the solution is rather permanent, due to the fact that the particles carry an electric charge. The evidence to support the theory that the particles are changed electrically is:

1. The method of preparation. The current that causes the disintegration of the metal, and carries it into solution, would probably remain on it.

2. The particles will wander in the stream if a current of electricity is led through the solution.

3. Electrolytes will precipitate colloids. This is well shown by the action of Na_2SO_4 or $MgSO_4$ on the colloidal iron, or by the action of HCl on colloidal arsenic sulphide and by the fact that colloidal platinum can not be kept for any length of time if electrolytes are present in the water.

4. Colloids of opposite electrical sign precipitate each other. Practical application is made of this in the use of aluminum cream $Al(OH)_3$ and colloidal iron, $Fe(OH)_3$ to precipitate the proteins of blood, in blood sugar determinations.

5. Non-electrolytes such as sugar will not precipitate colloids in water solution. Alcohol, however, which is also a non-electrolyte will cause precipitation but this is due to a changed solvent.

The chief electro-negative colloids are arsenious sulphide, antimony sulphide, gold, copper, and nearly all metals, as well as most proteins, in neutral or slightly alkaline solution, lecithin and phosphatides, the carbohydrates, gum, starch and glycogen, and nucleic acid and soaps.

The electro-positive colloids are ferric hydrate, aluminum hydrate, basic proteins, histones and protamines, proteins in acid solution, and oxyhemoglobin.

Classification.—The colloidal solution of a metal like platinum is vastly different in viscosity from a solution of gum or protein. The classification of colloids, which is based mainly on this difference of viscosity of their solutions, is as follows:

1. Suspensoids, or inorganic.
2. Emulsoids, or organic.

As the names indicate, suspensoid colloids resemble a suspension of solid matter in a liquid, while emulsoids resemble emulsions. Colloids differ from simple suspensions or emulsions in being charged electrically. The particles of colloid all bear the same kind of electricity, hence repel each other. This keeps them in solution. The electrical charge also acts against the force of gravity, and there is but little tendency to form a deposit or precipitate until the charge is neutralized. Only inorganic colloids belong to the suspensoid class. They may be prepared first, by the use of an appropriate electric current under water, or, second, by the reduction of dilute solution of metals by reducing agents such as formaldehyde, third, when hydrogen sulphide is passed through a solution of arsenious acid, arsenic trisulphide may remain in colloidal solution. Some other metals act in the same way. Some of the suspensoid colloids are used in medicine.

Colloidal preparations of silver are used in medicine especially in the treatment or prevention of gonococcus infections of the eye and mucous membranes. Colloidal gold is employed as a diagnostic aid in syphilis, tuberculosis, etc. Copper has been advocated in the treatment of carcinoma, etc. Platinum, in the form of platinum black, has been used to a considerable extent by laboratory workers. The chief suspensoid colloids are:

$$\text{colloidal metals}\begin{cases} \text{Fe.Ag.} \\ \text{Cu.Au.} \\ \text{Pt.Al.} \end{cases}$$

kaolin, antimony sulphide, arsenious sulphide.

DIFFERENCES BETWEEN THE SUSPENSOID AND EMULSOID COLLOIDS

The emulsoid colloids make up the greater part of living material. They are solutions of a liquid in a liquid; in other words, the disperse phase as well as the solution is liquid. This ac-

counts for their having a greater viscosity than suspensoids. Solutions of liquids in liquids have no sharp boundary lines as might be expected between solids and liquids, and they have little, if any, electrical properties. When free from electrolytes, they do not travel with the electric current, and are not as susceptible to electrolytes as suspensoids, which are precipitated by traces of electrolytes. Emulsoids are precipitated only after the addition of considerable quantities of electrolytes. Traces of electrolytes seem to aid fluid solution, presumably by adding their charge to the colloid.

Emulsoids are precipitated by suspensoids. Colloidal iron has been used for this purpose to remove the blood proteins in blood sugar analysis. The excess of the suspensoid is removed at the same time by the addition of an electrolyte like $MgSO_4$ or Na_2SO_4. However, where there are large amounts of emulsoid present, it forms a coating on the suspensoid particles and prevents their complete precipitation by the electrolytes. This is the chief objection to this method for blood-sugar work.

The difference between emulsoid and suspensoid colloids is probably due to a difference in the affinity of the two substances for the solvent. Suspensoids have practically no affinity for the solvent, and readily fall out of solution when their electric charges are removed. Emulsoid colloids which are hydrophylic require an excess of the neutralizing salt to overcome the union of the colloid and the water. Such colloids are called hydrophyl because they have an affinity for water. This is strikingly illustrated in the change of viscosity in water caused by a small amount of colloid. A 1 per cent gelatine increases the viscosity of water 29 per cent.

GEL FORMATION

In an ordinary solution of an emulsoid colloid, the solvent or water is the continuous phase. It is possible to think of a small body going through the solution, passing around the isolated or dispersed particles as a ship would sail around small islands. When these colloids gel, a molecular arrangement of the disperse phase takes place, and a network is formed. The water now appears to be the disperse phase, as it is enmeshed in a cellular network of colloid. One could think of a body being able to pass along the network from any portion of it to any other over

a continuous route. This netlike structure can be substantiated by the use of the microscope.

When gelling occurs, the colloid acts more like a solid than a liquid. Gelatin and agar-agar form gels readily, but on heating they will liquefy, and again, on cooling, set or gel. Such substances are called reversible gels. Protoplasm, on heating, forms an irreversible gel. If a gelatin or agar gel is allowed to stand for some time, it contracts and some water is liberated. This process of contraction with the liberation of liquid is called *syneresis*. Blood, on clotting, may show the same phenomenon, which is well known in the preparation of bacterial media also. This phenomenon may be of great importance in pharmacology. The water holding capacity of protoplasm is changed in a similar way, and the diuresis following the administration of alkalies and salts has been explained on such a basis. It is well known that the water holding capacity of gelatin and fibrin is modified enormously by the presence of salts.

LYOTROPE SERIES

Colloids, according to the affinity of the disperse phase for the dispersing medium may be classified as lyophile, where there is a marked affinity of the disperse phase and the medium and lyophobe, where no such affinity is shown. When water is the dispersing medium, the terms hydrophile and hydrophobe are also used.

In the lyophobe series, which is synonymous with suspensoid, the physical properties of the sol are very little different from those of the dispersing medium, while the physical properties of the lyophile markedly change those of the medium. Much greater concentrations of electrolytes are necessary to precipitate the lyophile series of colloids. According to Pauli, both ions of an electrolyte play a rôle in the precipitation of colloids. While one ion precipitates, the other may have a solvent effect. Cations as a rule act as precipitants, while anions are solvents, the total action being the algebraic sum of these actions. From a series of experiments, the relative efficiency of the ions in causing precipitation, etc., has been arranged from the least to the most effective. This series is known as the *lyotropic series*. The following table shows the relative action of the various ions.

Kations ———————————	Mg	NH$_4$	K	Na	Li
Anions					
Fluoride......................		+	+	+	
Sulphate....................	+	+	+	+	+
Phosphate..................			+	+	+
Citrate......................			+	+	+
Tartrate....................			+	+	+
Acetate.....................		−	−	+	+
Chloride....................	−	−	+	+	+
Nitrate.....................	−	−	−	+	+

The action of the ions in this series is so nearly the same sequence in many other reactions in which they can react only indirectly that their action in most cases is thought to be on the solvent or dispersing medium rather than on the colloid. The sequence does not follow any chemical order as valence, atomic weight, or the like; for example,

1. In the hydrolyses of esters by acids,

anions $\quad SO_4 < (H_2O) < Cl < Br$

kations $\quad H_2O < Li < Na < K < Rb < Cs$

In this case, SO_4 retards action, in all others the ions accelerate.

2. In the hydrolyses of esters by bases,

anions $\quad I > NO_3 > Br > Cl > H_2O < SO_4$

kations $\quad Cs > Rb > K > Li \quad H_2O$

It is seen here that the ions that accelerated the acid hydrolysis retard basic hydrolysis.

3. The surface tension of aqueous solutions,

$$H_2O < I < NO_3 < Cl < SO_4 < CO_3$$

All these ions increase surface tension. A similar influence is exerted on viscosity.

ELECTRIC CONDITIONS OF COLLOIDS

As we have seen, there are various reasons for believing that colloids are electrically charged: (1) they migrate in an electric current; (2) oppositely charged colloids precipitate each other.

The proteins are amphoteric, but are more acid than basic. The isoelectric point, *i.e.*, the reaction in which they will not migrate in the electric current, is:

	PH
Serum albumin	4.7
serum globulin	5.4
casein	4.7
oxyhemoglobin	6.74

It may be that all colloids to some degree at least are amphoteric.

PROTECTIVE POWER OF COLLOIDS

The presence of colloids in a solution greatly lessens the action of electrolytes. Suspensoid colloids are also protected by the presence of emulsoid colloids of the same sign; suspensoids mixed with emulsoids can be evaporated to dryness and the residue redissolved in water. Without the emulsoid, the colloidal nature of the suspensoid would be destroyed. Colloidal mercury and silver can be made more stable by admixture with emulsoid colloids. This protective power is used in medicine to disguise or lessen the taste of acid and bitter medicines. Solutions of glycyrrhizæ, acacia, etc., are used as vehicles because of this protective action on the nerves of taste.

CHANGE IN COLLOIDS IN GEL FORMATION AND PRECIPITATION

Just as there is no sharp line between crystalloids and colloids so there is no sharp line between pharmaceutical emulsions and emulsoid colloids. The emulsions of the pharmacist are, perhaps, electrically charged to some extent, and this helps to hold them in solution. The emulsifying agents used are usually gum acacia or tragacanth which produce very viscous solutions which settle very slowly. The magma of magnesia which is mainly magnesium hydroxide resembles colloidal iron or iron hydrate. Under a variety of conditions, all emulsions or emulsoid colloids "crack" or precipitate. The cause of these changes may be: (1) spontaneous; (2) heat or cold; (3) changes in the volume or composition of the solvent; (4) the action of enzymes; (5) other colloids; (6) electrolytes.

1. Spontaneous change. Just as any electrically charged body may lose its charge and become neutral, so a colloidal solution after a time may crystallize, precipitate, or otherwise lose its colloidal character.

2. Cold is especially liable to destroy pharmaceutical emulsions. Emulsoid colloids are also less stable on freezing. Heat above the coagulative point of an emulsoid coagulates it. Heat will also demagnetize iron.

3. The effect of changes in the volume of a solvent is well illustrated when a dilute solution of gelatin or agar is evaporated to a small volume. It gels. If the solution is changed by adding alcohol, the gelatin or agar is precipitated, in the first instance there is no intramolecular change other than the abstraction of water and when this is again added, the emulsoid character is restored. In such a case, the change is reversible. In the second there is an intramolecular change aside from the changes in the solvent and this change is irreversible.

4. The action of enzymes. The clotting of blood and the curdling of milk are types of irreversible gel formation. The mechanisms of these actions are not well understood, but are due to an electrical neutralization of the colloids, in all probability.

5. Suspensoid colloids are especially susceptible to the action of electrolytes. The action here is due to the neutralization of the charges on the suspensoid by the electrolyte. Emulsoids are but little influenced by small amounts of electrolytes, due to their characteristics being less well defined, but are precipitated by larger amounts of the salts. That the electrical charge of the emulsoid plays some part in the precipitation is seen in the series of effectiveness of the anions in the salting out of non-electrolytes.

SURFACE TENSION

A substance in a gaseous state tends to increase its volume, while substances in the liquid state tend to contract into the smallest volume, or volume with the least surface area. The surface in this condition, in all liquids behaves as if stretched. This stretch or pull on the surface film is the result of unbalanced molecular forces. In any liquid the molecules have a definite attraction for each other. This attraction has been estimated at 10,000 to 25,000 atmospheres. A molecule in the center is subject to the same force from all sides, and consequently there is no movement one way or the other. Below the surface layer, the molecules exert an attraction for those above them in the surface layer, while those on the top are not attracted by the

atmospheric gases, and bend or curve in the direction of the pull from within, hence tend to assume the spherical form. The thickness of this film, or the range of the molecular attraction has been estimated at about 6×10^{-8} millimetres.

This stretch or pull on the surface layer interferes with the movements of the molecules, and for this reason confers on the liquid some of the properties of a solid, since in the solid state, freedom of movement in the molecules is limited. Various methods have been devised to measure surface tension, the most practical being the following. The average weight of a drop of the fluid falling from a standardized pipette or stalagmometer is taken. The surface tension of water is considered as unity, and that of any other fluid, like blood or serum, is calculated by dividing the weight of the liquid by the number of drops, and comparing this with water under the same conditions.

Surface tension of liquid = sp. gravity of solution multiplied

by $$\frac{\text{number of drops of water}}{\text{number of drops of solution}}$$

There are other methods, more accurate and correspondingly more complicated than this one. The above formula gives the surface tension in relation to water. Since water has a tension of 73 ergs. per square centimeter, the formula, to read in ergs., should be:

$$\frac{\text{no. of drops of water} \times \text{density of liquid}}{\text{number of drops of liquid}} \times 73 \text{ dynes}$$

The surface tension of liquids in dynes per centimeter is

water...................... 73
alcohol.................... 22
ether...................... 16

Surface tension undoubtedly plays an important rôle in many biological reactions. In phagocytosis or the taking up of bacteria by cells, substances (toxins?) which change the surface tension modify the phagocytic power. *The clumping of bacteria* and *opsonic index*, shows a change in the surface tension of bacteria; similarly anesthesia may in the last analysis be due to changes in surface tension.

The following experiment by Rhumbler (Arch. Entwichlungs-mech, 1898 (VII), 249) is interesting in this regard:

If one tries to pierce a drop of chloroform under water with a fine glass rod, it is very difficult or impossible. If now the rod be coated with shellac it is sucked into the chloroform. The shellac in this case changes the surface tension in a manner similar to the changes that may occur in bacteria by toxins or between nervous and muscular tissue by an anesthetic.

VISCOSITY AND SURFACE TENSION

The distinctive character of solids is that the relative position of the molecules is fixed and can not be changed except by the expenditure of a relatively great force. The characteristic of a liquid is its tendency to flow. The molecules can be moved with relative ease; in gases, the fluidity is much greater than in liquids. In liquids, although the particles move relatively easily, the fluidity is not perfect. The particles adhere to each other so that when a thread of the liquid moves, it drags some of the other particles with it, and is in turn held back by them. There is thus a movement of the different layers past each other in the direction of the flow. This shearing, or internal friction, or property of the particles to adhere to each other, is viscosity. It is exerted only during movement. Ether, water, oils, balsams and waxes are examples of fluids possessing progressively greater viscosity.

The suspensoid colloids, which are solid particles suspended in a liquid, have little intimate relation with the liquid in which they are suspended, and hence have little viscosity, while the emulsoid colloids, which are liquids in liquids, have the properties of liquids, and thus a greater viscosity than the suspensoids.

Surface tension is a surface phenomenon only. It is due to the attraction or pull of the molecules on each other; it is exerted at all times, but is only manifest at the boundary surfaces of liquids, because here the balance of force is upset. The force of attraction of the molecules of a fluid for each other is exerted at a very short range only—about 6×10^{-8} millimetre. All molecules in a liquid this distance below the surface will be attracted with an equal force in all directions but the layers of molecules in the surface fluid will be attracted only by those

below, without a balanced pull from above. Hence they will tend to pack together and assume the spherical form, since potential energy always tends to become a minimum. The surface, therefore, contracts as much as the conditions will allow. The strength of the pull of the molecules on each other will depend entirely on the kind or chemistry of the molecule. In the case of viscosity, this depends more on the physical state of the molecules.

The tendency of liquids to assume this spherical form can be shown:

1. In Hammerschlag's method of determining the specific gravity of the blood; mix benzene and chloroform until it is of the same specific gravity as the blood. Then place a drop of blood in the mixture and the blood will assume a spherical form.

2. Alcohol and water is made to the same density as olive oil. Drops of olive oil in this will neither rise nor sink, but will assume a globular form.

3. If conditions are imposed so that the liquid can not assume the spherical form, it will assume the smallest surface area that conditions will permit, as Van der Mensbrugge's experiment shows: "A loop of fine silk is taken and tied to a wire ring. If the whole be dipped into soap solution, so as to produce a film, the loop floats in the film; the silk thread forming its boundary is quite loose, and can be readily moved into any shape by means of
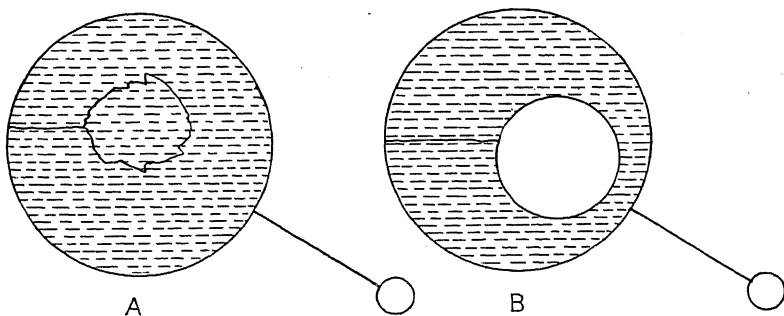
FIG. 2.—Mensbrugge's Experiment.

a fine needle wetted with the soap solution. (A) The film inside the loop is now broken by touching it with a bit of filter paper cut

to a fine point. The loop is immediately drawn to a circular form by the tension of the film surrounding it, and can be felt to resist attempts to change its shape by the needle. (B) The soap solution should be prepared by the method of Boys (1912, p. 170), from pure sodium oleate, with the addition of about 25 per cent. of glycerol."

Substances that lower the surface tension always collect on the surface. They are never uniformly distributed through the liquid; float two small pieces of wood parallel to each other and a few millimetres apart. Now let a drop of alcohol fall between them. They will suddenly fly apart. The reason for this is that the surface tension of alcohol is less than that of water, and the drop of alcohol weakens the surface tension film between the small pieces of wood so that it breaks and they fly apart. In the same way, a film of water on a glass slide breaks when a drop of alcohol or ether is added. Camphor placed on water darts about over the surface, because it lowers the surface tension unequally at different points and the rupture of the surface film causes it to move.

Superficial Viscosity.—This is different from, and independent of surface tension, which, as we have said, is a constant stress at the boundary of liquids. Surface viscosity is a sort of surface friction which is manifest only when there is something to disturb or rupture the film. If a liquid assumes a globular form, it is due to surface tension, independent of viscosity. Pure water has a large surface tension, but no viscosity. It will not foam on shaking. A solution of saponin has a marked superficial viscosity, but no marked surface tension above that of water. A magnetic needle placed on the surface of the saponin solution, because of the viscosity is not changed in position by the earth's magnetic directive force, while it will be changed in a water solution. A saponin solution foams on shaking superficial viscosity holding the bubble together while the surface tension is tending to break it. Oil has a small surface tension but a large surface viscosity.

RELATION OF COMPOSITION TO SURFACE TENSION

The surface tension of a liquid decreases with the rise of temperature; hence comparisons should only be made of liquids at

the same temperature. As might be expected, the surface tension varies enormously with composition, but no definite rule can be made, nor from chemical composition can predictions of surface tension be made with certainty. In a homologous series like the paraffin series, increase in CH_2 does not appreciably change surface tension. Water has a surface tension of 73 dynes, alcohol = 22, and ether = 16. Here it would seem that the introduction of C_2H_5 decreases surface tension. Isomeric compounds have the same surface tension only when they have similar constitutions.

Salts increase the surface tension of water, as do gum arabic, starch and plum gum. On the other hand, gelatin glue, egg albumen, dextrin, cherry gum, and traces of fatty acids, soaps, bile acids, tannic acid and resins lower it.

Since the same chemical substance may be a suspensoid in one dispersion medium and an emulsoid in another, we find that the same substance may lower surface tension in water and raise it in alcohol, and vice versa. Thus the dye, Night Blue, lowers the surface tension of water and raises it for alcohol.

RELATION OF COMPOSITION TO VISCOSITY

As a rule, viscosity or internal friction increases with molecular weight. An iso compound always has a larger coefficient of viscosity than the normal compound. In many cases, the molecular viscosity can be calculated from known viscosity constants. Thus the viscosity constant of

H   = 44.5
C   = 31.0
hydroxyl O   = 166.0
carbonyl O   = 198.0
Cl in monochlorides = 256.0
I in monoiodides   = 374.0
Double linkage   = 48.0
Ring grouping   = 244.0

There is a relation between chemical constitution and viscosity, although water and alcohol present exceptions to any relation yet discovered. In suspensoids the viscosity is little different from the water-dispersing medium. There is also little chemical union here, it being merely a physical suspension. Colloids, however,

low a marked viscosity, which depends upon the amount of the
colloid.   One per cent. gelatine increases the viscosity of water
9 per cent.

ADSORPTION

Adsorption is the term applied to surface absorption.   This
process has long been used by chemists to clarify liquids, especi-
ally for polariscopic work.   If a solution contains color, or is
otherwise opaque, it has been the custom to add powdered char-
coal, shake, and filter the solution.   The coloring material in
most cases adheres to the surface of the particles of charcoal.

Filter paper also adsorbs certain colloids.   If a piece of filter
paper is dipped into a solution of Congo red, it soon accumulates
enough of the dye on the surface so that the solution becomes
visibly lighter in color.   Fuller's earth and kaolin also absorb
coloring matter and alkaloids in the same way.   Bunsen recom-
mended freshly precipitated ferric hydroxide as an antidote in
arsenic poisoning.   He thought that a compound of basic ferric
arsenite was formed; $4Fe_2O_3$, As_2O_3, $5H_2O$.   Recent work shows
that this is an adsorption compound.

Charcoal condenses and absorbs gases, and for this reason has
been used in treatment of gas accumulation in the stomach and
intestines.   The gas is adsorbed.   Similarly, palladium and
platinum adsorbs hydrogen.   In the gas chain method of deter-
mining hydrogen ion concentration, spongy platinum holds so
much hydrogen that it acts as an hydrogen electrode.

Selective Adsorption.—Colloidal materials in many cases, for
unknown reasons, exert a selective adsorption.   Sea weeds, for
example, select iodine from the sea water out of all proportion to
the amount present.   In the same way, plants take up potassium
as compared with sodium.   Adsorption in all these cases may be
preliminary to chemical combination or chemical action; similar
to the adsorption of pepsin by fibrin.   If a thread of fibrin is
introduced into a solution of pepsin, most of the ferment is soon
adsorbed by the fibrin.

Influence of Salts on Absorption.—Salts seem to have a marked
influence in some cases.   Bone black does not absorb diptheria
toxin in water, but it is readily absorbed from saline or Ringer's
solution.   Bone black adsorbs sugar in neutral solution, but not
when acidified with acetic acid.

The explanation of adsorption is not easy. It is a surface phenomenon, and is increased by increase of surface. In colloidal solutions, the surface is enormous. It has been calculated that in a red colloidal solution of gold containing 0.5 grams of gold in a liter, the surface amounts to 8 square meters. Although colloidal solutions of the same sign may adsorb each other as in the case of Congo red and filter paper, the kind of electric charge on the solid does influence adsorption. When colloids of the same sign are adsorbed, it may be that they are amphoteric.

Acid dyes are in general adsorbed by electro positive colloids like clay and colloidal iron, while basic dyes are adsorbed by electronegative colloids like kaolin, sulphur, charcoal, silk, cotton, etc.

XXXI. THE REACTION OF LIVING MATTER

Living matter is alkaline in reaction, but becomes acid after death. To determine the reaction during life therefore, it is necessary to use an indicator that will act in the living body without killing it. Such indicators are neutral red and cyanamine, the former being an orange red color in alkaline reaction and pink in acids. Cyanamine is red in alkaline and blue in acids. Acid fuchsin does not stain alkaline protoplasm, but stains it red when the protein reacts acid. When the circulation stops, protoplasm becomes acid. This may be shown in the following experiment: Inject a frog with a solution of acid fuchsin. After it has penetrated all the tissues, tie off the circulation of one leg, and stimulate the muscles of this leg. On removal of the skin from the muscles on the ligated side, it will be found that they have become red due to acid formation. It is known that lactic acid develops during muscular contraction, in the absence of sufficient oxygen.

In order to determine the reaction of tissues by the use of a stain, several conditions must be fulfilled: (1) The stain must penetrate the tissue fluids. (2) It must not kill the tissues, since the reaction changes after death. (3) Since the tissues have oxidation and reduction properties, the stain must not be influenced by the oxidation and reduction processes of the body.

The alkaline reaction of the body is due to excess of OH ions. Acid reaction is due to H ions. The concentration of

these ions present in the body fluids may be determined by a number of methods.

1. **The Colorimetric Method.**—Solutions of acids of known strength in which complete ionization has taken place, or where the degree of ionization is known, in terms of a normal solution, are colored by some indicators in intensity directly as the concentration of the ions. This being the case, one may determine the hydrogen ion concentration of a solution by comparing it, when treated with an indicator, with the color solutions produced by the same indicator in solutions of known hydrogen ion concentration. This is most easily done by using tubes of the same bore, and containing the same amount of fluid as the control and the same amount of indicator by using a series of tubes of known but varying PH concentrations as controls the unknown concentration can be found by matching its color with a control tube. Such control tubes sealed and with different PH values can be obtained, sealed from Hynson Westcott and Co., Baltimore.

2. **Electro Potential Method or Gas Chain Method.**—When a metal is dipped in a solution of one of its salts an electromotive force is set up at the surface of contact. The voltage developed depends on the strength of the salt solution. These electrode potentials are susceptible of direct measurement, consequently, two solutions of different concentration having the same ions in common have different electrical potentials. When such solutions are connected by a conductor, a current flows from the stronger toward the weaker. The strength of this current depends upon the relative concentration of the two solutions. In the case of an acid it is in direct ratio of the hydrogen ions. It has been found that a ten fold difference in the ionic concentration of solutions with common ions is equal to a voltage of 58 millivolts. Since the logarithm of 10 is 1, the factor obtained by dividing the voltage by .058 will give the logarithm of the dilution. To determine the hydrogen ion concentration of blood or other fluid by this method therefore the difference in the concentration of a known solution as compared with the concentration of H ions in the blood may be represented by the formula;

$$e = K \log \text{Conc. } H_1 / \text{Conc. } H_2$$

Where e = the difference in the potential determined by

measurement. $K = .058$ volts when common logarithms are used, consequently $\dfrac{\text{E.M.F.}}{.058}$ is equal the number of ten-fold dilutions or PH.

In an actual determination of PH there are many technical difficulties to be observed and overcome. While every ten-fold dilution makes a difference in potential of 58 millivolts an actual determination if made in a chain consisting of —

$H|HCl \; n/10|HCl \; n/100|H$ would show only 0.019 volts. This is due to a contact potential at the junction of the acid solutions developed by the difference in speed of H. and Cl ions and which acts in opposition to the electrode potentials. To obviate this error, a neutral conducting solution is placed between the acid solutions. Such a solution is KCl. The ions of this solution have about the same speed, but in opposite directions, consequently neutralize the effect of each other. When such a chain is connected we get a voltage of 0.058 at 20°C.

$$H|HCl \; n/10|KCl|HCl \; n/100|H$$
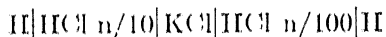
Again in actual practice instead of using two hydrogen electrodes, as in the above, a standard calomel electrode is used for the known solution. The normal calomel electrode has a voltage of 280 millivolts above the normal hydrogen electrode. Consequently the electromotive force E, developed by this when assembled with an unknown hydrogen cell (C) would be:

$$E = 0.280 - .058 \log C \text{ or}$$
$$\frac{E - 0.280}{0.058} = -\log C = \log \frac{1}{C} = P_H.$$

If a normal tenth normal calomel electrode be used it has a voltage of .337 above the normal hydrogen electrode, consequently 0.337 is used instead of 0.280 in the above formula.

METHOD OF EXPRESSING HYDROGEN ION CONCENTRATION

The hydrogen ion concentration of body fluids is very close to that of water. It would be cumbersome to express frequently a dilution of one molecule of dissociated H. in ten million litres of water by 0.000,000.1. In biologic work we have to deal mainly with such dilutions. The adoption of a more convenient method of expression is therefore advisable.

Since the ionization constant of water is H times OH = 10^{-14} or H = 10^{-7} and OH = 10^{-7}, and since the factor 10^{-14} is always constant, when H increases, OH decreases.

Thus if H = 10^{-1}, OH = 10^{-13}, and theoretically if H = 10^0 OH = 10^{-14} = 1 gram molecule OH in 10.000.000.000.000 litres. The older methods of expressing H ion concentration retained the constant 10^{-7} and until recently the acidity or alkalinity of body fluids was expressed:

$$2 \text{ times} \ldots \ldots \ldots \ldots \ldots 10^{-7}$$
$$1 \text{ times} \ldots \ldots \ldots \ldots \ldots 10^{-7}$$
$$\text{or } 0.5 \text{ times} \ldots \ldots \ldots \ldots \ldots 10^{-7} \quad \text{etc.}$$

Following the suggestion of Sorensen it is customary to express the reaction by the reciprocal or cologarithm of the number. In reality this is the logarithm of the dilution in terms of normal solution. Thus potential of H when H = 10^{-7} is expressed PH = 7, and H = 10^{-10}, PH = 10. This method of expression is brief but confusing until one gets accustomed to translating the numbers, and knowing that the greater the value of PH the lesser the acidity, and thinking in terms of logarithms and remembering that PH_1 PH_2 PH_3 etc. differ by powers of 10. Thus:

$$PH_1 \ = n/10 \text{ acid or} \qquad PH = \ 1$$
$$PH_2 \ = n/100 \text{ acid} \qquad PH = \ 2$$
$$PH_3 \ = n/1000 \text{ acid} \qquad PH = \ 3$$
$$PH_6 \ = n/1{,}000{,}000 \text{ acid} \qquad PH = \ 6$$
$$PH_8 \ = n/1{,}000{,}000 \text{ alkali} \qquad PH = \ 8$$
$$PH_{11} = n/1000 \text{ alkali} \qquad PH = 11$$
$$PH_{12} = n/100 \text{ alkali} \qquad PH = 12$$
$$PH_{13} = n/10 \text{ alkali} \qquad PH = 13$$
$$PH_{14} = n/1 \text{ alkali} \qquad PH = 14$$

Since the numbers refer to negative logarithms the higher the number the fewer H ions in a given volume, while the OH ions increase. This is quite comprehensible when we recall that H times OH is always 14 or 10^{-14}. If PH is 14, it follows that OH must be O and if PH_1 is N/10 acid $P(OH)_1$ must be N/10 alkali.

Some confusion may also raise in translating such expressions as PH = 2×10^{-6} into the more modern figures. One readily sees that in terms of normal solution 2×10^{-6} is twice as strong

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as 10^{-6} but that PH = 5.70 (Log. 2 = $-$ 0.3 hence 6 $-$ 0.3 = 5.70) = n/500.000, is not so obvious.
Similarily:

$$0.35 \times 10^{-7} = \text{n}/28.580.000 \text{ or PH} = 7.45$$
$$0.91 \times 10^{-1} = \qquad\qquad\qquad \text{PH} = 1.04$$
$$0.98 \times 10^{-3} = \qquad\qquad\qquad \text{PH} = 3.01$$

Since normal metabolism and therefore, normal health, depend on the maintenance of the normal alkalinity, pharmacology is concerned with the regulating mechanisms and the changes in the alkalinity that may be produced by drugs.

REGULATING MECHANISM

The blood always contains a mixture of CO_2, $NaHCO_3$, NaH_2PO_4 and Na_2HPO_4. All of these dissociate so weakly and normally occur in such quantities that the reaction is constantly kept close to PH = 7.2. The normal ratio of NaH_2PO_4 : Na_2HPO_4 is stated by Michaelis and Garmendia to be 1 : 5.1 molecules. If these were the only salts present in a solution of water in the proportion of 1cc. n/10 NaH_2PO_4 and 2.5 cc. n/10 Na_2HPO_4 we would have a PH of 7.0. The carbonates modify this to the PH found in the blood. While the salts which maintain the normal PH are fairly well known the reason why these salts are found in the necessary concentrations is not known. It should be emphasized that there is a wide margin of safety within which they may vary without materially changing the PH. For example if m/3 solutions of Na_2HPO_4 and NaH_2PO_4 are mixed in the following amounts PH =

Na_2HPO_4	NaH_2PO_4	PH =
1 cc.	32 cc.	5.11
1	16	5.42
1	1	6.62
2	1	6.92
4	1	7.22
8	1	7.52
16	1	7.82
32	1	8.12

The lungs and the kidneys play an important part in the regulation of the H ion concentration, *e.g.*, CO_2 is excreted by the lungs. It is continuously formed in digestion. Alkaline salts are constantly taken in the foods, especially vegetable foods. NH_3 is formed from the digestion of proteins. Acid salts are formed and these act as diuretics. Hence, under normal conditions formation and excretion take place at such pace that the body holds a reserve or potential alkalinity.

It is thus possible to give an account of the mechanism as it exists or to state reactions as they probably occur. The basic cause, or why, is still beyond the scope of science.

Under some conditions this mechanism fails and acidosis develops. A knowledge of the normal mechanism enables us to modify and treat the acidosis. The importance of this may be realized since it has been shown by Henderson and Palmer that the acid formation in the human organism corresponds to between 600 and 700 cc. n/1 acid solution daily.

ACTUAL AND POTENTIAL ALKALINITY AND BUFFER VALUE

Sodium bicarbonate reacts slightly alkaline to litmus. This alkaline reaction is explained by the fact that in water we have H and OH ions. When $NaHCO_3$ is dissolved in water we also get Na, H, OH and CO_3 ions. Consequently there will be a shifting of the balance. Since the constant of carbonic acid, $\dfrac{\text{H times } CO_3}{H_2CO_3}$ is very small and the constant of $\dfrac{\text{Na times OH}}{NaOH}$ is large, the carbonic acid will be suppressed and the constant of NaOH will tend to be established. This full constant cannot be reached because the $NaHCO_3$ also has a constant $\dfrac{\overset{+}{N}a \times \overset{+}{H} \times \overset{-}{C}O_3}{NaHCO_3} = K$ and in this *case only a certain number of* Na + ions can remain in the ionic state in the presence of $NaHCO_3$. The whole solution, therefore, strikes a balance at a strength which reacts slightly alkaline to litmus. This balance point is known as the *actual* alkalinity of the solution. This is the PH of the solution as represented by the colorimetric or gas chain method.

If we titrate a solution of sodium bicarbonate with an acid, the acid removes the OH ions, but when these are removed,

others are formed from the bicarbonate which will keep forming OH ions in the attempt to form the balance until the whole is neutralized by the acid, in the following way.

$$\frac{NaOH}{Na \text{ times } OH} \quad K.$$
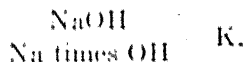
This titratable alkalinity is known as the total or *potential* alkalinity.

POTENTIAL ALKALINITY OF BLOOD

The weak alkaline condition of the blood is guaranteed by a mixture of H_2CO_3, $NaHCO_3$, NaH_2PO_4. These (buffers) are all very weakly dissociating substances and may be considered in the blood in a balanced state.

$$\frac{H_2CO_3}{NaHCO_3} \quad K \text{ and } \frac{Na\, H_2PO_4}{Na_2H\, PO_4} \quad K_2$$

Where K and K_2 are constants, and the sum of these constants in terms of H ions is about PH 7.1 to 7.8

$$\frac{H_2CO_3}{NaHCO_3} \quad K.$$
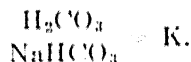
If acid be added to this directly or indirectly, as in cases of acidosis, it liberates H_2CO_3. This will either break into CO_2 and H_2O, and K kept constant; or it will tend to act with Na_2CO_3 if such be present and restore the constant in that way. If enough acid be added or developed, the whole alkali reserve may be exhausted. The phosphates are balanced in the same way. According to Michaelis and Garmendia, the ratio of

$$\frac{Na\, H_2PO_4}{Na_2H\, PO_4} \quad \frac{1}{5.1} \quad \text{Molecules.}$$
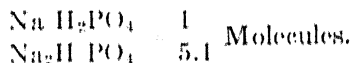
Since the normal blood always contains CO_2, $NaHCO_3$ and $Na_2 HPO_4$ in this balanced state, the H ion concentration at any one time cannot be determined by titration, because as fast as the actual alkalinity is removed, the potential alkalinity is converted into actual. Consequently, the titration alkalinity is the sum of actual and potential.

This difference between the actual and total alkalinity of the blood, is known as the "buffer" value, and $NaHCO_3$ and $Na_2 HPO_4$ are the buffers, $NaHCO_3$ especially. The value of this buffer is illustrated by comparing the effect of acid added to a liter of water, and to a liter of $NaHCO_3$. The reaction of a solu-

tion of pure $NaHCO_3$ is very weakly alkaline.   Water is neutral.
A drop of acid added to a liter of water will definitely acidify it.
When added to a solution of $NaHCO_3$, however, it will not change
the actual alkalinity, and will not exceed the acidity of CO_2 until
all of the $NaHCO_3$ has been decomposed.   The amount of acid
required to do this will depend on the amount of the $NaHCO_3$ in
solution, in other words on the buffer value of the solution.   The
carbonates are the chief biologic buffers, and the constant in
blood plasma of

$$\frac{H_2CO_3}{NaHCO_3} = 1/20.$$

Now PH, or CH as it is sometimes given, is directly proportional
to this ratio.   And any condition in which the ratio of these in
the plasma is greater than $\frac{1}{20}$ may be looked on as an acidosis.

Since CO_2 is the principal reagent used by the organism to
regulate the reaction, it is evident that H ion concentration and
CO_2 concentration run parallel.   Hence knowing the one we can
calculate the other.   Hasselbach (Biochemische Zeitschrift, 1912,
vol. 46, p. 403) thinks that the hydrogen ion concentration is the
real stimulus of the respiration rather than CO_2.   However,
while many accept the view that CO_2 acts because of the hydrogen
ion concentration of its solutions, the question of a specific
action of molecular CO_2 has not been satisfactorily answered.

ACIDOSIS

By acidosis is meant the poisoning of the organism with acids,
due directly to neutralization or depletion of the alkaline reserve
or potential alkalinity.   A better term would be hypoalkalinity.
Acute poisoning by acids due to corrosion or local action of acids
does not come under the term acidosis.   Most cases are due to
faulty metabolism, and in such cases oxybutyric acid, diacetic
acid, lactic acid and acetone are formed and may be found in the
urine.   Acidosis occurs especially in diabetes when as much as
250 grams of acetone bodies may be produced in a day.   The
normal excretion in adults is from 3 to 15 milligrams per day.
Until quite recently (1907) diabetes was the only disease in which
acidosis was known to occur.   We now know that it is present
also in certain nephritic cases, in cholera, in certain intoxications
in children, starvation, phosphorus poisoning, etc.   It often

happens that these acetone bodies are present in the urine when there is no symptoms of acidosis. The presence of acetone bodies in the urine develops after the reserve alkalies or buffers have been somewhat depleted. This form of acidosis is called a ketosis or poisoning by ketone. No special names are given to the other acidoses. This depletion may also be caused by the introduction of weak acids into the body either by mouth or parenterally, and this method of producing the symptoms is largely responsible for the term acidosis.

The symptoms of acidosis are mainly those of asphyxia, labored respiration, air hunger, cyanosis, coma, and convulsions. Death is due to respiratory paralysis. These occur before the blood attains an acid reaction. It requires three hundred times as much acid to render blood acid, as it does to acidify water. This is because of the potential alkalinity or buffer value, due to the proteins, carbonates and phosphates in the blood which neutralize acids. The treatment of acidosis is the administration of sodium carbonate, and even in the last stages this is often effective.

In uremia and diabetes, the acidosis may reach a degree sufficient to produce coma. Fasting, high fat diet, arsenical and phosphorus poisoning, and heavy metals may cause an increase in the H ion content of the blood, but not sufficient to produce coma.

Why depletion of the alkaline reserve should cause death while the blood is still alkaline is like many other whys—hard to answer. We know, however, that certain conditions are necessary for life. These are the presence of certain essential chemical elements and in addition a balance of these elements. Loeb has shown that the ova of fish living in sea water, die in an isotonic solution of sodium chloride sooner than they do in distilled water. In this case the poisonous action of the sodium can be neutralized by traces of calcium. A similar, but perhaps more complex, reaction occurs in the human body when the alkaline reserve is depleted, i.e., after abnormal loss of the Na^+, K^+, Mg^{++}, and other positive ions. When the balance is destroyed other elements like potassium, or hydrogen act more as poisons.

Acidosis is a problem still under investigation and for a clear statement of the problem, the student is referred to the little book by Sellards, Harvard University Press—1917.

THE DETERMINATION OF THE EXISTENCE OF ACIDOSIS

Formerly the presence of acetone bodies in the urine, was the only diagnostic test used. This, however, is a relatively late sign, and in order to be of much value an earlier indication is needed. It was thought, therefore, that in the development of acidosis the blood would become less alkaline, and attempts were made to titrate the blood with a standard acid. But while this method is theoretically sound, it has been found unsatisfactory for several reasons: (1) It is hard to remove the coloring matter of the blood to allow a satisfactory titration; (2) large volumes of blood are required; (3) the proteins of the blood interfere with acid titration; and the "buffers" in normal cases vary to a greater degree than the possible range of a true acidosis. Acidosis is a question of the tissues, hence the blood may not be a true indication of the body state as a whole.

The methods now used to detect acidosis are:

1. Increased tolerance to sodium bicarbonate.

2. Urinary changes:

(a) Increased acidity and acetone bodies. (b) Increase in ammonia. (c) Changes in the fixed bases.

3. Lowered tension of carbon dioxide in the respired air.

4. Lowered carbon dioxide content of blood = lessened amount of carbonate in the blood.

5. Lowered alkalinity of the blood = increased hydrogen ion concentration.

1. **Tolerance to Carbonate.**—The normal individual cannot take more than 5 grams of sodium bicarbonate a day without the urine becoming alkaline. In case of acidosis the sodium bicarbonate is apparently depleted. The tissues absorb and retain as much as 100 grams per day before the urine becomes alkaline. It has been proven in these cases that the retention is not due to defective kidney function.

2. **Urinary Changes.**—(a) Increased acidity and acetone bodies. Acetone bodies indicate mainly disturbance of carbohydrate metabolism and may have no reference to acidosis. Again acidosis may develop in diabetes without the presence of acetone bodies in the urine.

(b) Increase in ammonia. When the fixed bases of the body

are used to neutralize the acids formed in acidosis there is some break-down of protein with the formation of ammonia to aid in the neutralization and to make up the alkaline deficit. It was therefore thought that the free ammonia excretion in the urine would be a measure of the acidosis. But in primary disturbances of protein metabolism the ammonia coefficient may be high, and it may be low in acidosis. This may be because ammonia in some cases is converted into stable salts and in other cases urea may be decomposed yielding ammonia.

(c) Change in the fixed bases of the urine, sodium, calcium, magnesium and potassium are somewhat used to neutralize the acids formed in acidosis. The excretion, of these, therefore, in the urine may be increased. Since, however, it is the depletion of these in the tissues that gives rise to the symptoms of acidosis, their amount in the urine may be lower, at the height of the attack. The determination of these bases, therefore, to be of value must extend over a number of days. Since the determination is tedious and time consuming it is little used.

3. **Lowered Tension of Carbon Dioxide in the Respired Air.** The normal venous blood carbon dioxide exists under a tension of about 6 per cent. (42.6 mms. Hg.) practically 40–50 millimeters. An extreme fall of the carbon dioxide is virtually pathognomic of acidosis. In four cases of uremia Sellards found 10 to 24 mms.

The CO_2 content of the alveolar air is practically the same as that of the venous blood 37.6 mm.: 42.6 mm. Hg. and more closely approaches the content of the arterial blood. For this reason, analysis of the respired air has been used to aid in the diagnosis. The principle is based on the fact that alkaline solutions absorb CO_2 in proportion to the strength of the solution. The reaction does not go on to completion and is reversible.

$$2 \, NaHCO_3 \rightleftarrows Na_2CO_3 + H_2O + CO_2$$
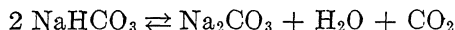
or expressed in another form—

$$\frac{H_2CO_3}{NaHCO_3} = \text{a constant (about 1/20). (Isolated plasma only)}$$

Since $H_2CO_3 \rightarrow H_2O + CO_2$, and the CO_2 readily penetrates the alveolar tissue, a measure of the CO_2 in the alveolar air, is practically a measure of the buffer value of the blood.

4. **Carbon Dioxide Capacity of the Plasma (alkali reserve).** Method of Van Slyke and Cullen—Principle—The plasma from

oxalated blood is shaken in a separatory funnel filled with a CO_2-air mixture approximating the composition of the alveolar air which has a CO_2 tension equivalent to that of arterial blood. In this way the sample of blood plasma combines with as much CO_2 as it is able to hold under normal tension. A measured quantity of this saturated plasma is then acidified within a special pipette, and its CO_2 is liberated by the production of a partial vacuum. The liberated CO_2 is then measured under atmospheric pressure and the volume corresponding to 100 cc. of plasma calculated.

This method is the most useful clinically because of the ease with which it can be carried out and because it directly measures the alkali reserve of the blood under conditions simulating the conditions in the body.

The H ion concentration of the blood varies so little that it is of less value in the diagnosis of acidosis than the measurement of the alkali reserve.[1]

XXXII. PHOSPHORUS

There are two forms of phosphorus, yellow and red or amorphous. The red form is not used in medicine, being inert. The yellow is the medicinal variety and it is in the metallic state. It appears as a translucent, nearly colorless solid, of a waxy lustre, with the consistency of beeswax.

Phosphorus is very slightly soluble in water, and its solubility in alcohol is 1:350; it is easily oxidized and burns when exposed to the air. On this acount, it should be cut and handled under water.

In the body it is rather insoluble, and is active only in the finely divided metallic state. A large mass may pass through the body unchanged, but in the finely-divided state or in solution in oil, it is readily absorbed and highly toxic, 0.05 to 0.1 gram has proved fatal to man.

Phosphorus exists in the blood as such and its actions are due to the element and not to the oxygen or hydrogen compounds. As soon as it is oxidized, it loses its specific action. The chief toxic action is to cause fatty degeneration in various organs. In therapeutic doses, it is used to stimulate bone formation and growth.

This substance resembles arsenic in many of its reactions.

For details, see Hawk's Physiological Chemistry, 6 *Edition*, p. 325.

PH_3, or phosphine, corresponds to AsH_3, or arsine. PH_3 has basic characters like NH_3 and unites with acids to form salts of the general formula PH_4X (phosphonium). These salts are very weak and are decomposed by water into PH_3 and HX. Arsine, AsH_3, and stibine, SbH_3, do not possess this basic property. The H atoms in phosphine can be replaced by alkyl groups to form

$$P\diagup\!\!\diagdown \begin{matrix} H \\ H \\ R \end{matrix} \quad \text{or} \quad R\diagup\!\!\diagdown \begin{matrix} R \\ R \\ H \end{matrix} \quad \text{or} \quad P\diagup\!\!\diagdown \begin{matrix} R \\ R \\ R \end{matrix} \quad \text{or} \quad P\diagup\!\!\diagdown \begin{matrix} R \\ R \\ R \\ OH \end{matrix}$$

| mono alkyl phosphine | dialkyl phosphine | tertiary alkyl phosphine | quaternary phosphoniun base |
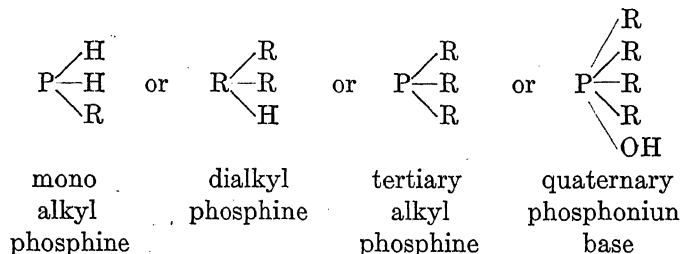
Only the tertiary phosphine and the quaternary phosphonium compounds are formed by the action of alkyl halides RI on PH_3. The mono and di alkyl phosphines are obtained by heating phosphonium iodide, PH_3I, with an alkyl iodide and zinc oxide. These quaternary phosphonium bases, like those of arsenic, antimony, etc., exert a strong curare-like action in animals. They are strongly basic, and when heated, decompose into a hydrocarbon $Cn\ H_2n + 2$ and oxygen compound;

$$(C_2H_5)_4\ P.OH = C_2H_6 + (C_2H_5)_3\ PO$$
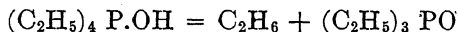
An ammonium base under the same conditions would decompose into an alcohol and trialkyl base:

$$N\diagup\!\!\diagdown \begin{matrix} C_2H_5 \\ C_2H_5 \\ C_2H_5 \\ C_2H_5 \\ OH \end{matrix} \quad = NR_3 + C_2H_5OH$$
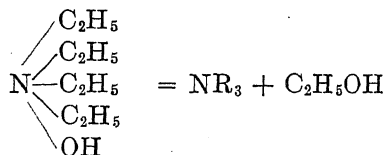
Oxidizing agents oxidize phosphorus to phosphoric acid.

In cases of poisoning with phosphorus, the metal will distil from an acid solution and can be detected by its phosphorescence in a dark room. This phosphorescence is due to the process of oxidation of the metal. Oxidizing agents, like potassium permanganate and hydrogen peroxide in dilute solutions are used as antidotes in phosphorus poisoning.

Ag forms a compound with P, Ag_3P. This test is used in cases of suspected poisoning with P. A piece of filter paper moistened with $AgNO_3$, suspended over a solution containing P turns black if phosphorus is present, due to the formation of silver phosphide Ag_3P. Other substances like H_2S in the solution will also cause a blackening of the $AgNO_3$ paper, and the test for P is valuable only in proving its absence. Copper also forms compounds with P. The formula of the copper phosphide is not definite, probably Cu_3P or Cu_2P_6. In cases of acute poisoning with phosphorus, the administration of dilute copper sulphate 0.5 gram in 100 cc. may be of value in preventing the absorption of P. which is still in the gastro-intestinal tract. In addition, the copper solution will also act as an emetic.

The name phosphine may lead to confusion at times, for an acridine dye, Philadelphia Yellow, is also known by the same name. Acridine, $C_{13}H_9N$, is prepared from ortho-amino-diphenyl-methane;

$$C_6H_4\begin{matrix} CH_2.C_6H_5 \\ \\ NH_2 \end{matrix} \quad = C_6H_4\begin{matrix} N \\ | \\ CH \end{matrix}C_6H_4$$

<div align="center">o. amino diphenyl   acridine
methane</div>
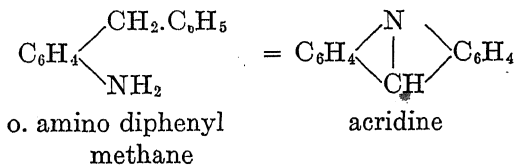
Phosphine, or Philadelphia Yellow, is a beautiful yellow dye which forms red colored salts, and is a mixture of the hydrochlorides of asymetrical diamido-m-tolyl acridine. It is obtained as a by product in the manufacture of rosaniline. Its formula is;

$NH_2.C_6H_4$ ———— N ————

NH_2

Phosphine
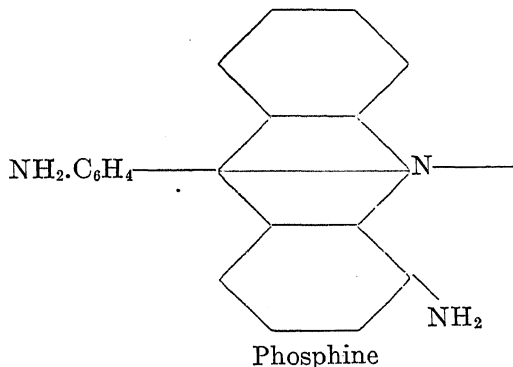
It is a protoplasm poison, especially for protozoa, but has been used without success in malaria.

The Fate of Phosphorus in the Body

The fate in the body is obscure. It is highly probable that it is oxidized to some extent in the body. It is hard to tell this from direct chemical examination because the phosphates vary normally, more than a toxic dose of phosphorus could change the phosphate content of the urine. Some may be excreted by the lungs; but the statement that the breath may become phosphorescent is not given much weight: Unknown organic combinations of phosphorus have been found in the urine.

ARSENIC COMPOUNDS

Metallic arsenic is non-toxic, while its compounds are all toxic. White arsenic, As_2O_3, which is an anhydride of arsenious acid, $As_2O_3 + 3H_2O = 2H_3AsO_3$, is the most important compound. Arsenious acid, however, cannot be isolated since on evaporation of its solution arsenic trioxide is again obtained. This is also known as white arsenic. A 1 per cent. solution of this in 2 per cent. potassium bicarbonate solution is known as Fowler's solution, and is a favorite preparation in medicine. AsI_3, arsenious iodide, is also used in medicine in the form of liquor arseni et hydrargyri iodidi. This is a 1 per cent. solution each of AsI_3 and red mercuric iodide HgI_2 in water. Sodium arsenate, $Na_2H.AsO_4.7H_2O$ is used to some extent.

Atoxyl, sodium arsinalate, or sodium p amino-phenyl arsenate is a compound formed when anilin and arsenic acid are heated together

$$C_6H_5NH_2 + As(OH)_3 = C_6H_5NH_2 - O - As{\overset{\displaystyle OH}{\underset{\displaystyle OH}{=}}}O$$

p. amino-phenyl arsenate

$$NH_2C_6H_4 - As{\overset{\displaystyle OH}{\underset{\displaystyle OH}{=}}}O \ = \ + H_2O$$
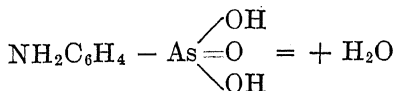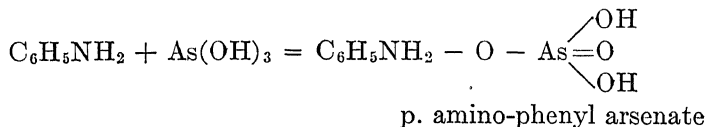
p. amino-phenyl arsenic acid.

The sodium salt of this is atoxyl. The Na replaces an hydroxyl H.

Acetyl atoxyl $CH_3.CO.NH.C_6H_4. - As \underset{\diagdown OH}{\overset{\diagup OH}{=}} O$ is also employed.

Arsacetin is the sodium salt of this, or

$$CH_3CO.NH.C_6H_4 - As \underset{\diagdown ONa}{\overset{\diagup OH}{=}} O$$
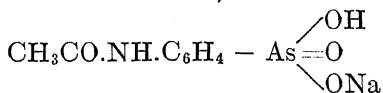
Arsenic acid has the formula H_3AsO_4 or $As \overset{\diagup OH}{\underset{\diagdown O}{\equiv}} \begin{matrix} OH \\ OH \end{matrix}$

When two of the OH. groups are replaced by methyl groups, we have cacodylic acid:—

$$As \begin{matrix} \diagup CH_3 \\ - CH_3 \\ \diagdown OH \\ \ \ O \end{matrix}$$
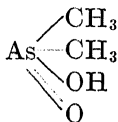
Cacodylic acid is formed when potassium acetate is distilled with arsenious acid:—

$$As_2O_3 + 4CH_3COOK \rightarrow (CH_3)_2 = As - O - As = (CH_3)_2$$
$$+ 2K_2CO_3 + 2CO_2$$
$$\text{cacodyl oxide}$$
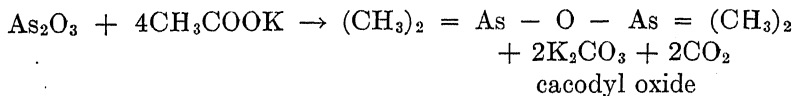
Cacodylicoxide when treated with HCl yields cacodyl chloride:

$$(CH_3)_2 = As - O - As = (CH_3)_2 + HCl = 2(CH_3)_2 As - Cl.$$
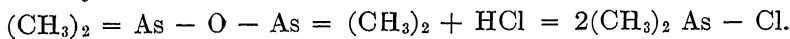
On oxidation this yields cacodylic acid:

$$As \begin{matrix} \diagup CH_3 \\ - CH_3 \\ \diagdown Cl \end{matrix} + 2H_2O + 2O \rightarrow 2 \ As \begin{matrix} \diagup CH_3 \\ - CH_3 \\ \| \diagdown OH \\ O \end{matrix}$$

$$As \begin{matrix} \diagup Cl \\ - CH_3 \\ \diagdown CH_3 \end{matrix}$$
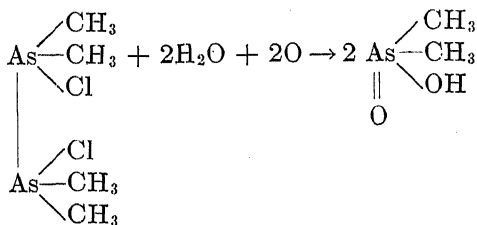
Sodium cacodylate is the most important salt of cacodylic acid.

$$O = As \begin{matrix} \diagup CH_3 \\ - CH_3 \\ \diagdown ONa \end{matrix}$$
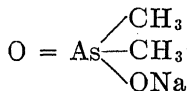
If the three hydroxyl hydrogens of arsenic acid are replaced by Na, sodium arsenate is the product. This, acted upon by methyl iodide in alkaline solution, yields sodium methyl arsenate or arrenhal.

$$O = As \begin{array}{l} \diagup ONa \\ -ONa \\ \diagdown ONa \end{array} + CH_3I \quad = \quad O = As \begin{array}{l} \diagup CH_3 \\ -ONa \\ \diagdown ONa \end{array}$$

<center>Sodium arsenate   arrenhal</center>
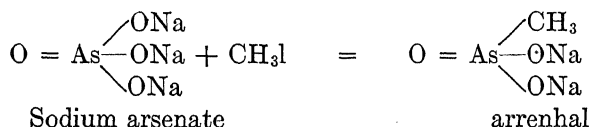
Arsphenamine or salvarsan "606" dioxy diamino arseno benzol The number "606" refers to the laboratory research number. This substance is a derivative of arseno benzene,

$$C_6H_5 - As = As - C_6H_5,$$

which is analogous to azo benzene,

$$C_6H_5 - N = N - C_6H_5.$$
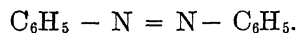
The following reactions illustrate its preparation:

(I) When phenol and arsenic acid are heated together a conden-sation takes place in the para position:

<center>p. phenol arsenic acid</center>
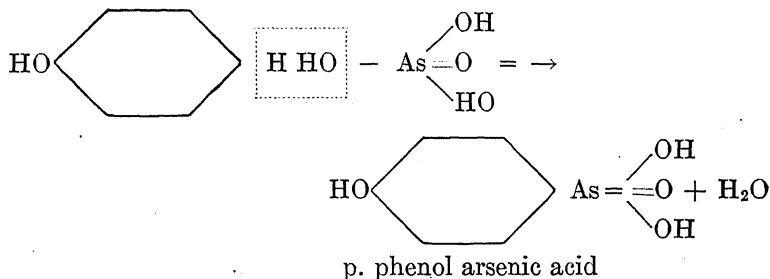
When this is treated with nitric acid, a nitro derivative is formed:
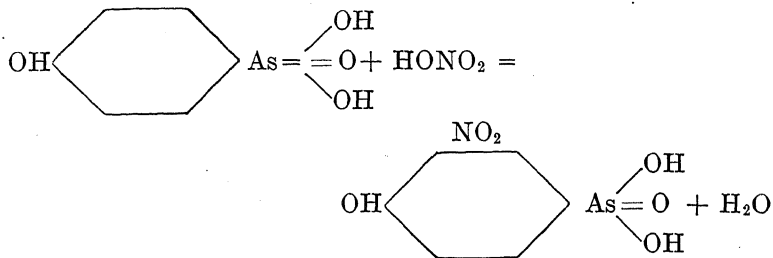
On complete reduction, this yields a condensation product:

(2) OH — [benzene ring with NO2] — As $= O + 2$ OH $\rightarrow$ with OH, OH branches

As — As [two benzene rings joined, with NH2, OH, salvarsan, NH2, OH]
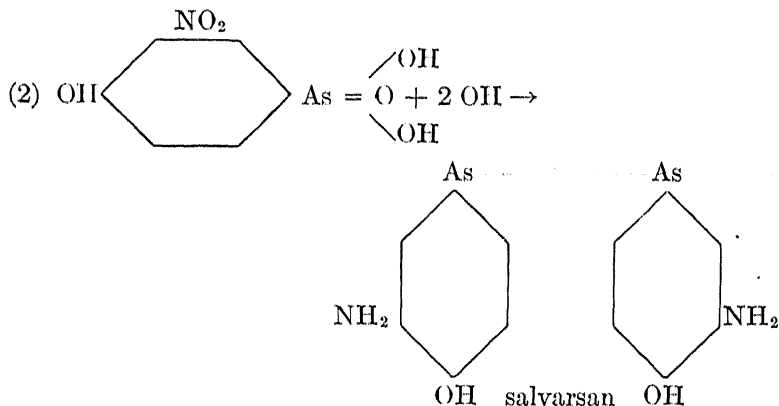
OH salvarsan OH

Arsphenamine or salvarsan is a light yellow crystalline powder and yields a solution in water with an acid reaction. When given intravenously, the solution should be well diluted and slightly alkaline.

Neo-arsphenamine or neo-salvarsan, (914) is a soluble preparation of salvarsan. It is sodium di-amino dihydroxy arsenobenzene methanal sulphoxylate;

As — As [two benzene rings, with NH2, OH, OH, NH(CH2O)OSNa]

NH2 ... OH OH NH(CH$_2$O) OSNa
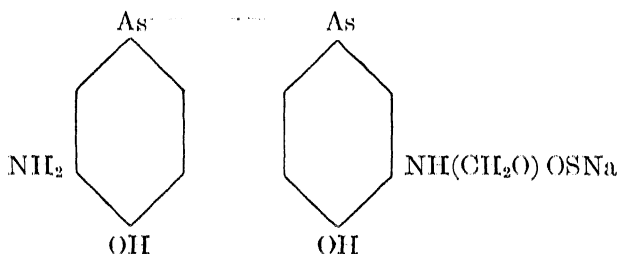
It is prepared by precipitating a salt of arsphenamine with sodium methanal sulphoxylate and dissolving the precipitate in alkalies. It is an orange yellow powder of peculiar odor and is unstable in the air.

Fate of Arsenic in the Body

Arsenic is absorbed rapidly and excretion by the urine begins in about seven hours and lasts several days, though it may con-

tinue for three months.   It is excreted mainly through the kidneys.   Since it irritates the kidneys the amount of urine in toxic cases is greatly diminished.

Regarding the retention of arsenic by the various organs, the liver retains the most, but the kidneys, spleen and muscles all may contain arsenic.   Only traces are found in the brain.   It has been detected in the cancellous bones of the skull and vertebræ after it has disappeared from all the other organs.   The poison is probably combined in the organs as arseno-nucleins.   Since the nucleins are the most active seats of life it probably kills by an action here.

Binz and Schultz thought that the action of arsenic was due to an alternate reduction and oxidation of it in the tissues. Arsenious acid being oxidized to arsenic acid and the reverse reaction occurring also.   In this way oxygen is alternately withdrawn from and supplied to the protoplasm.   If such a process takes place it must be very gradual otherwise we cannot explain why arsenious acid is so much more powerful than arsenic acid.

Gautier thought arsenic to be a normal constituent of the thyroid gland, but there seems to be no basis for this, and what Gautier found must have been taken as medicine or otherwise.

For a complete report on the Chemistry of the Organic Compounds of Arsenic and Antimony—see Organic Compounds of Arsenic and Antimony by Gilbert T. Morgan, Longmans Green and Co. 1918.

XXXIII. HEAVY METALS

We include under the term heavy metals, antimony, mercury, iron, lead, copper, zinc, silver, bismuth, aluminum, gold, platinum, manganese, cadmium, nickel, cobalt, tin, thallium, vanadium, tungsten, uranium, etc.   Of these, only the first twelve are of importance in medicine, the others being of toxicologic interest only.   Phosphorus and arsenic are important, but they are not usually classified with heavy metals.

The metals themselves are inactive, and it is only in the form of soluble salts that they exert any action.   It must be remembered, however, that the solubility in albumen may be different from that in water, although usually only those salts that are soluble in water are active.

Heavy metals have two actions: (1) local, and (2) general, or the action after absorption.

The salts of the heavy metals form combinations with proteins, and local action is due to this combination. According to the reactivity, strength, and extent of the combination, the salts of the heavy metals may be astringent, irritant, styptic, caustic or corrosive. Since the same salt in different concentrations may exhibit all these actions, it is impossible to classify metals under these heads. From a practical standpoint, however, they may be classified as follows:

1. Styptics—ferric chloride, dried alum.

2. Astringents—alum, lead acetate, basic lead acetate, zinc oxide, bismuth subnitrate, ammoniated mercury.

3. Astringent and corrosive—iron salts, zinc sulphate, zinc acetate, copper acetate, silver nitrate, lead nitrate, lead iodide.

4. Corrosive—mercury salts, zinc chloride, tin chloride, antimony chloride, copper sulphate.

As a rule, the greater the ionization, the greater the action.

The salt formed by the union of a metal with protein is a proteinate, *e.g.*, argenti proteinas or protargol. It is not of constant composition, but varies with the kind of protein and the amounts of the protein and metal used. Thus the salts are not true chemical compounds. The precipitate when formed may redissolve, or go again into solution if too much of the reagent or of the protein solution is added. This is especially true in the case of lead salts, and is readily understood in the light of the phenomenon of precipitation.

Explanation of Precipitation

Proteins are emulsoid colloids. Colloids remain in solution, because they are electrically charged, either negatively or positively. Proteins belong to the class of colloids, which are usually negative, and remain in solution as long as they retain this charge. Because the charge is the same throughout, and as like charges repel each other, the protein remains in solution but when the charge is neutralized, precipitation occurs. According to the cause, precipitation may be due to:

1. Spontaneous precipitation.

2. Gelatinization.

3. Coagulation by enzymes and heat.

4. The addition of electrolytes.

5. Other colloids of opposite sign.

Examples of these changes in drug chemistry are:

1. The spontaneous decomposition of a solution of silicic acid or water glass.

2. The precipitation of gelatin or agar due to loss of water by evaporation. Their solution may be considered as hydrophylic compounds. Evaporation necessitates an internal rearrangement and a loss or neutralization of the charge. These charges are reversible, an addition of water again causing the formation of a colloidal solution.

3. Heat coagulation, and the changes caused by enzymes are well known in the coagulation of white of egg, and the souring of milk. These coagulations are irreversible.

4. The precipitates formed by electrolytes are divided into two groups (reversible and irreversible), depending on the nature of the precipitate or coagulate.

Salts of Ba.Sr. and the heavy metals form precipitates which are irreversible.

The difference between reversible and irreversible precipitates is due to a fundamental change and molecular rearrangement in the case of the irreversible; while in the reversible there is merely a neutralization of the electrical charge. Accordingly, proteins may be precipitated in three forms:

1. Unaltered, *i.e.*, by salting out or neutralization of the charge—reversible.

2. As albuminates, by coagulation ⎫
3. Insoluble salts of metals   ⎬ irreversible.
                                      ⎭

Both ions of a salt are important in precipitation. Which of the two is more important depends on the nature of the colloid to be precipitated. For example: colloidal iron is a positive colloid, and is much used to remove proteins from the blood. The positive charge on the iron salt is neutralized by the negative charge on the protein and both are precipitated. Colloidal iron is also precipitated by a solution of $MgSO_4$, or Na_2SO_4 or almost any salt. In this case it is the negative ion or anion which acts to neutralize the positive charge of the iron.

In the precipitation of proteins, however, the same explanation

holds; but since the proteins are negatively charged it is the positively charged ion or cathion that is more important as a protein precipitant. Since the precipitation is due to a neutralization, it follows that if the colloid is negative the precipitating *ion* is always the cathion, if positive, the anion.

Bivalent ions are more active in causing precipitation than monovalent, and polyvalent more powerful than bivalent. . The valence of the ion of the same sign as the colloid has no influence on the action.

Aside from the neutralization, there are, of course, especially with the heavy metals, proteinates formed that can not be explained on this simple basis. These salts, while not so definite as the heavy metal combinations with sulphates, carbonates, etc. are of the same nature.

The action of heavy metals when taken internally is due to the chemical local action of the metal on the stomach and intestine. The nature of the acid in the salt is of importance, as is also the nature of the precipitate, slimy or granular.

Nitrates are more irritant than acetates because the nitric acid liberated in the reaction is a more powerful irritant than acetic acid.

When the precipitate is granular, the acid liberated penetrates to the tissue below more readily than when the precipitate is slimy in nature. Corrosive sublimate, for these reasons, penetrates deeper and is more corrosive than lead acetate.

Local reactions of the heavy metals when taken internally are; loss of appetite, pain and discomfort, nausea, vomiting, purging, congestion, hemorrhages. These are all the result of the irritant and corrosive action of the metal. Ulcers may result after a time due to bacterial action on the dead tissue.

The action after absorption is also the result of a combination of the metal with the protein.

There is little difference in the action of the metals after absorption. Iron is just as toxic as arsenic when it is introduced into the blood, but it is not absorbed rapidly from the stomach; consequently it is not ordinarily toxic.

The toxic action of the heavy metals on the central nervous system is manifested by delirium, hallucinations, mania, stupor, and coma. Convulsions indicate that the motor areas, basal

ganglia and spinal cord are affected. Peripheral neuritis occurs especially with lead and antimony, not differing from the neuritis caused by alcohol, arsenic or toxins.

The astringent action of the heavy metals is due to several factors:

1. The metal and protein unite to form an albuminate, and the resultant liberated acid has an astringent effect.

2. The metal may be absorbed locally and exert a constricting action on the local vessels.

3. Insoluble salts like cerium and bismuth cover and protect the surface mechanically.

Absorption of heavy metals is slow, with the exception of salts of mercury. Mercury is the only volatile metal and volatility aids absorption. Whether the volatile character of the free metal conveys any properties on the ion in the salt is not known.

The matter of excretion of heavy metals may be described as follows; the body stores up the metals in the liver, spleen and other organs, slowly eliminating it from them. This is done by the kidneys and intestine, thus showing the reason that nephritis is a prominent symptom. Heavy metals are also excreted into the gut, and have a specific action on the gastro-intestinal tract. This effect is more marked with arsenic, phosphorus and antimony than with the heavy metals. By whatever course they enter the body, there is always an inflammation of the gastro-intestinal tract throughout its extent, as much of the metal leaves the body by this route.

COLLOIDAL METALS

The colloidal metals especially used in medicine are gold, copper, platinum and silver. These are simply finely divided metals having an electrical charge, which is positive. They are suspensoid colloids.

The methods for preparing colloidal metals are:

1. The disintegration of heavy metals by means of an electric current strong enough to cause sparks under water. The metal is used as electrodes.

2. Reduction of dilute solutions of the salts of the metals by various reducing agents. They are prepared in water free from electrolytes as they can not be kept for any time in the presence of salts.

The method of preparation by an electric current, and the effect of electrolytes in causing precipitation, together sustain the opinion that colloids bear electric charges. This properly differentiates true suspensions from suspensoid colloids. True suspensions will settle out on standing at rest, while suspensoid colloids are little influenced by gravity and remain suspended.

The basis for the use of colloidal metals in medicine is that traces of copper and other heavy metals in water in a vessel of one of these metals, contain none of the metal detectable by chemical means, yet they prevent the growth of, and sometimes kill, unicellular organisms. When the metallic surface is increased as in the colloidal solutions, a greater chance is given for this action, and the colloidal solutions can be injected into tumors or applied to mucous surfaces. The value of colloidal metal solutions is still problematical, for while solutions such as argenti proteinas unquestionably is efficient in some infections of the eye, it is probably less efficient than a 1 per cent. solution of silver nitrate.

XXXIV. INORGANIC ACIDS

The inorganic acids of importance in pharmacology are boric, hydrochloric, sulphuric, nitric and phosphoric. Chromic and hydroflouric acid are of small importance.

The acids when used as such owe their action to the hydrogen ion, and are protoplasm poisons. Protoplasm, which is essentially alkaline in reaction, cannot contain life if this alkalinity is neutralized by acids. If strong acids come in contact with protoplasm, they may disintegrate it, hence they are corrosive poisons. For this reason, strong acids, when applied to the skin, destroy the epidermis. Acids, because of this corrosive action, are sometimes used to destroy warts. The corrosive action is more marked when the acids are applied to mucous membranes; even a small quantity of a strong acid in the eye may destroy the sight. The mucus membrane of the mouth, esophagus and stomach may be destroyed if such acids are swallowed. In dilute solutions, they are absorbed rapidly, and are neutralized, and exist in the blood in the form of salts.

The process of neutralization differs in different animals. Herbivora, because of their food, have a greater reserve of fixed

alkalies, mainly sodium and potassium, which are first used to neutralize any acid that may be taken. When these alkalies are used below a certain level, proteins are broken down and ammonia is formed to neutralize the acids. Carnivorous animals, on the other hand, are accustomed to the development of acids from their protein food, and as their food contains a limited quantity of fixed alkali, the normal process of neutralization is the formation of ammonia. Hence carnivorous animals, because they can more readily form ammonia are in a better position to protect themselves from the neutralizing influence of acids. Herbivorous animals consume large quantities of organic salts of the alkalies in their food, and have a greater immediate reserve of these salts than carnivorous animals, but the mechanism to form ammonia quickly is lacking, which is always at work in the carnivora, and, in case of poisoning, requires only a little speeding up. Herbivora, then, are more easily poisoned with acids than carnivora. The absorption of dilute acids in dogs does not materially change the available alkali of the blood, while in rabbits, the same amount of dilute acid causes a reduction of from twenty five volumes to two volumes per cent. in the carbonic acid in the blood. When this occurs, respiration becomes deep, labored and rapid, afterwards, weak and shallow, and finally ceases. The heart continues to beat after respiration has ceased.

The acids are excreted by the kidney in the form of salts. If any considerable quantity has been taken, the body conserves its alkali reserve and the salts are excreted as acid salts.

To counteract the effect of acids, alkalies are used: Since most alkalies themselves are corrosive, one must exercise care in their use. The most available is sodium bicarbonate or baking soda. This may be used without much danger. Lime water can also be used, but its neutralizing power is little since calcium oxide is soluble only in about 800 parts of water. If sodium carbonate, or sodium hydroxide be used, very dilute solutions can be used without injury, but if stronger solutions are used they exert a caustic action perhaps more harmful than the acids.

XXXV. SALT ACTION

By salt action in pharmacology, we understand those actions which are not specific but which may be elicited by any salt,

and are due fundamentally to processes of osmosis, diffusion, and dialysis. The effects of sodium chloride on red blood corpuscles are an example of salt action. If the salt is iso-tonic, no action takes place, while if it is hyper tonic, crenation occurs. If the salt is hypotonic, the cell will absorb water and a swelling or edematous condition results. If the salt is applied to the nerve in hypertonic solutions, it will cause a twitching of the muscle through its action on withdrawing water from the nerve.

Ion action differs from salt action in that the action is specific. Thus, $\overline{KCN}$ is a pronounced poison because it ionizes into $\overset{+}{K}$ and $\overline{CN}$. The $\overline{CN}$ is a violent poison. The same amount of CN in potassium ferro cyanide which does not ionize but remains as a salt is without action.

Diffusion.—When two or more gases are brought together with no physical barrier to separate them, they soon form a homogeneeous mixture; e.g., when gas is liberated in a room, it soon spreads throughout the whole space and mixes uniformly with the oxygen and nitrogen of the air. This process of mixing is called diffusion.

Osmosis.—If two miscible liquids are placed in the same vessel, in a short time they will diffuse or mix uniformly just as gases. This process is due to the movement of the molecules and is slower in liquids than in gases. If the liquids are separated by a membrane and the diffusion occurs through the membrane, the process is known as osmosis. Not only water but salts and crystalloids generally will pass through the membrane. Colloids diffuse through a membrane very slowly.

If the process of osmosis is used to separate one substance from another, as in the separation of crystalline substances from colloids, the process is known as dialysis.

GAS PRESSURE IN RELATION TO OSMOTIC PRESSURE

It has been proved that the osmotic pressure, or osmotic suction, of a crystalloid is the same as would be exerted by the same number of particles of a gas if it were confined in the same space. To illustrate; if a gram molecular weight of any gas oxygen $H_2 = 2$ grams $O_2 = 32$ grams $N_2 = 28$ grams is confined in a liter volume at 0° (zero) centigrade, it will exert a pressure of 22.32 atmospheres, or the converse of this a gram molecular

weight of any gas at ordinary pressures occupies a volume of 22.32 litres. This is in accordance with the gas law; Pressure times volume = pressure times Volume, or $Pv = pV$.

Crystalline substances do not pass into the gaseous state without decomposition, but when in solution they exert the same pressure as they would if they were in a gaseous state in the same volume. For instance, the gram molecular weight of cane sugar, $C_{12}H_{22}O_{11}$, is 342 grams. If this amount of cane sugar is dissolved in water and made up to 1 litre, it will exert a pressure of 22.32 atmospheres. An ion exerts the same influence as a molecule, consequently, if a substance which contains two ions in the molecule is completely ionized, the pressure will be doubled, as in a very dilute solution of sodium chloride. In the case of sodium sulfate, which ionizes into $\overset{+}{Na} - \overset{+}{Na} - \overset{-}{SO_4}$, complete ionization would make the pressure three times the molecular pressure. In sodium phosphate, $Na_2H\,PO_4$, in complete ionization $\overset{+}{Na} - \overset{+}{Na} - \overset{+}{H} - PO_4$ the complete pressure would be four times the molecular. Calculation of osmotic pressure of solutions that do not ionize is an easy task. All that is necessary is to know the molecular weight of the substance and the concentration. For example:

1. To calculate the osmotic pressure of 5 per cent. cane sugar solution. 342 grams in 1 liter or 34.2 per cent. = 22.32 atmospheres. 5 per cent. = $\dfrac{5}{34.2}$ times 22.32 atmospheres.

II. 5 per cent. solution of NaCl—assuming no ionization— 58.5 grams in 1 liter or 5.85 per cent. = 22.32 atmospheres

$$5 \text{ per cent.} = \dfrac{5}{5.85} \text{ times } 22.32 \text{ atmospheres.}$$

If there is a certain percentage of ionization however the osmotic pressure will be increased accordingly.

DIFFICULTIES IN DETERMINING OSMOTIC PRESSURE

The pressure exerted by a molecular solution is so enormous that it is hard to get a semi-permeable membrane that will stand the strain. Before the theoretic level is reached, most membranes rupture. The nearest approach to a semi-permeable

·ane that would stand the strain was devised by Pfeffer.
:d a porous clay cell and filled it with a solution of copper
and set it in a solution of potassium ferro cyanide. As
ɔ solutions permeated the porous clay they met and formed
:pitate of copper ferro cyanide, which functions as a semi-
ɪble membrane. Most animal membranes and collodion
are only partially semi-permeable. Salts will pass in both
ons and while they answer for the ordinary purposes of
s they cannot be used to determine or measure the extent of
ic pressure. In biological work the osmotic pressure is
:termined directly, but indirectly, from the freezing point.

:ION OF OSMOTIC PRESSURE TO THE BOILING POINT AND FREEZING POINT OF SOLUTIONS

rise in the boiling point of a water solution of a substance,
led the substance does not change on heating, bears a
relation to the number of molecules or ions in the solution.
n exerts the same influence as a molecule. Since most
ical fluids contain proteins, and change in physical proper-
ɪ heating, the boiling point method cannot be used.

ezing Point Method.—This method is available in biological
It is simple and convenient. Each mol-ion added to a
ɪf water depresses the freezing point 1.85°C. This depres-
f the freezing point is designated by Δ. Solutions with the
freezing point have the same osmotic pressure. To calculate
eezing point of a pure substance in water, we must know its
ɪla and the per cent. of the solution. For example; to calcu-
he freezing point of 1 per cent. NaCl. A molecular solution
lium chloride is 58.5 grams to the liter, or 5.85 per cent.
depresses the freezing point 1.85°C. 1 per cent. solution
sses it $\frac{1}{58.5}$ of 1.85° C. or. 316°C. This assumes no ioniza-

In actual work it is found that $\Delta = 0.589$ which shows a
per cent. of ionization. The freezing point of a 1 per cent.
ɪon of cane sugar, since a molecular solution of sugar—342
s in the liter or 34.2 per cent. is $\frac{1}{34.2}$ of 1.86°C. or -0.054°C.

Calculate the Osmotic Pressure from the Freezing Point.
ɔsmotic pressure of a molecular solution is 22.32 atmospheres
5,986 millimeters of mercury. This height of mercury is

equivalent to a temperature reduction of 1.86°C. The osmotic pressure of 1 per cent. cane sugar is therefore 16,986 : 1.86 : .054 : X. or $\frac{0.054}{1.86}$ times 16,986 = 493 millimetres of mercury.

SALTS IN THE BODY

Certain salts are necessary for life, but the amount of these is small (see p. 2). They exist in the body mainly as ions. The freezing point of mammalian blood is .526; (varies from .480 to .605); hence the osmotic pressure is $\frac{.60}{1.85}$ times 22.3 atmosphere or about 7.25 atmospheres. This is due almost entirely to salts, sugar and urea. The proteins contribute but a small part to the total osmotic pressure.

The average freezing point of serum is 0.6°C. 0.95 per cent. NaCl has this same freezing point and is, therefore, iso-osmotic or isotonic. The osmotic pressure calculated from this is $\frac{.6}{1.85} \times$ 22.32 = 7.24 atmospheres.

Calculated on the percentage basis and assuming no ionization, a molecular solution of NaCl = 58.5 grams in a litre or 5.85 per cent. = 22.32 atmospheres. .95 per cent. NaCl should equal $\frac{95}{585}$ of 22.32 atmospheres = 3.62 atmospheres. Assuming no ionization, the osmotic pressure here is just one half of that found by direct determination, hence normal saline must be completely ionized.

The action of sodium chloride when injected into the circulation is not noticeable on the blood pressure or circulation. A solution of KCl of the same osmotic pressure causes a pronounced depression of the heart. Since Cl, as judged from the action of NaCl, has no action, the action obtained from KCl must be due to the K ion. This illustrates the difference between salt action and ion action. Isotonic saline solutions can exert no salt action, and if an action results, it must be an ion action. Both ions usually have some action, but in most salts one of the ions is much more powerful pharmacologically than the other. K in the KCl is the important ion, but in the case of KCN the CN ion is so much more toxic than the K that the action of KCN is

attributed almost entirely to the CN ion. Some drugs are not at all dissociated in the body and therefore the only action they exert is the molecular or salt action. Ether, sugar and alcohol are not ionized. They exert only a salt action. Some of these, however, may be broken down in the body and their cleavage products may form ionizable compounds. Alcohol and sugar yield CO_2. This may react with the fixed bases of the body to form carbonates, Na_2CO_3, etc. The carbonates may be hydrolyzed to form NaOH which ionizes into $Na + OH$. While alcohol contains the group OH, it does not ionize and it exerts only a molecular action unless broken down.

SALT ACTION IN PHARMACOLOGY

Salts have the same importance in pharmacology as in physiology, but in addition, many salts used as drugs owe most of their action to osmosis, dialysis, and diffusion. This is especially true of the cathartic salts. Because these are not absorbed from the gut, the physical properties above enumerated suffice to explain their action. In most cases when salt is administered some is absorbed, and may either be excreted into the gut again or by the kidneys. When excreted by the kidneys, salts exert osmotic effects on the convoluted tubules. Some are reabsorbed from the tubules, others such as sodium sulphate, are but little reabsorbed and hence act as better diuretics than the chloride. The diuretic action of these salts can be seen best when they are injected into the circulation. Other instances of the osmotic effects of salt might be cited, but none more impressive.

XXXVI. TOXICOLOGY

THE ISOLATION OF POISONS

For analytical purposes, poisons may be divided into groups as follows:

Group I.—Volatile poisons which distil with steam from acid solution without decomposition, and can be detected in the distillate. They are arranged in the order of their boiling point—which is about the order in which they would appear in the distillate:

Yellow phosphorus		Chloral hydrate	97°
		Iodoform m.p.	119°
Hydrocyanic acid	26°	Benzaldehyde	179°
Carbon disulphide	46°	Phenol	180°
Acetone	57°	Aniline	183°
Chloroform	61°	Creosote	200° ǂ
Methyl alcohol	67.4°	Nitrobenzene	208°
Ethyl alcohol	78°		

Group II. Non-volatile organic substances which can be extracted from extraneous matter with hot alcohol, after acidification with tartaric acid. The principal members of this group are:

The alkaloids, neutral principles, some glucosides and bitters, synthetic organic drugs such as the sulphone hypnotics, the antipyretics, phenacetine, acetanilide, antipyrine, pyramidone, etc. After separating protein, fats, gums, resins, etc. that may be mixed with these drugs in cases of poisoning, non-volatile poisons may be subdivided into groups based on analytical methods. One of the methods is the Stas-Otto process which consists in extracting the liquid in a separatory funnel with immiscible solvents. Those extracted with ether when the solution is acid are:

A. Acetanilide   Colchicine   Picrotoxin
     Antipyrine   Picric acid   Salicylic acid
     Caffeine   Phenacetin   Veronal

B. Those extracted with ether when the solution is made alkaline with sodium hydroxide:

Aniline   Codeine   Pilocarpine
Antipyrine   Coniine   Pyramidone
Atropine   Hydrastine   Quinine
Brucine   Narcotine   Scopolamine
Caffeine   Nicotine   Strychnine
Cocaine   Physostigmine   Veratrine

C. Those extracted with ether, in a solution made alkaline with ammonia. The solution from the sodium hydroxide extract, is first made slightly acid, and then alkaline with ammonia. Ether will extract from this alkaline solution apomorphine and traces of morphine.

D. Those extracted by chloroform. After the ether extract from the ammoniacal solution has been removed, chloroform will extract the following, if present:

Antipyrine
Caffeine
Morphine
Narceine

Group III. Metallic Poisons.—These may be found in the residue after the extraction of the organic poisons, or an original portion may be used to test for them. Before testing for these, all organic matter must be destroyed. The most important metallic poisons are:

Antimony	Cadmium
Arsenic	Chromium
Barium	Lead
Bismuth	Mercury
Tin	

Group IV.—Poisons not in groups and for which special direct tests must be made—the most important are:

(a) The mineral acids—HNO_3, HCl, H_2SO_4.
(b) Oxalic acid.
(c) Alkalies—NH_4OH, $NaOH$, KOH.
(d) Chlorates.
(e) Miscellaneous organic:

Cantharidin	Opium
Cytisine	Santonin
Digitalis—glucosides	Saponins
	Solanin
Ergot principles	Sulphonal
Pilocarpine	Trional
Ptomaines	Toxalbumins—
	Abrin
	Crotin
	Curcin
	Ricin

CHEMICAL PHARMACOLOGY

METHODS OF ISOLATING POISONS

The tests made with pure substances, give one but little conception of toxicology. The isolation of poisons, from stomach contents or from the liver, and the preparation of these for testing is more important than the tests, and much more difficult.

THE ISOLATION OF VOLATILE POISONS

The volatile poisons include those that are volatile in steam in acid solution. The acid used must be non-volatile, especially suitable is tartaric, but dilute sulphuric or phosphoric may be used. Note that this group does not contain the volatile alkaloids—nicotine, coniine, sparteine. Because the solution is acid, salts of the alkaloids are formed, and these are not volatile. Before distilling, certain preliminary tests are made. These may shorten or obviate the necessity of much work.

Preliminary Test for Phosphorus

Scherer's test.

This is founded on the fact that phosphorus in a solution of silver nitrate, acidified with nitric acid, forms silver phosphide (Ag_3P).

The vapor of phosphorus will give this test with filter paper moistened with the silver nitrate solution. Hydrogen sulphide will also darken silver nitrate so a control test must be made along with the preliminary test, as follows: (See Fig. 3.)

Place some of the solution to be tested in a distillation flask, with a cork stopper. Moisten a strip of filter paper about 6–10 cm. along, and 1 cm. in width, with the silver nitrate solution, and insert this in a V-shaped slit in one side of the cork, moisten another, similar piece of paper, with lead acetate, and place this in a slit in the other side of the cork. Be sure that the papers do not touch each other. Place the cork in the flask, and set the flask on a water bath at about 50°C.

It is advisable to protect the papers from light, since light colors the silver to some degree.

Discussion of Results

(a) If the silver paper only is darkened phosphorus may be present.

(*b*) If both papers are darkened H₂S is also present, and in either case the test for phosphorus should be made. Any volatile organic reducing substance such as formaldehyde or formic acid may also darken the papers.

(*c*) If neither paper is darkened, phosphorus is absent and further tests for phosphorus need not be made. The preliminary test is more important therefore in establishing the absence of P. than its presence.
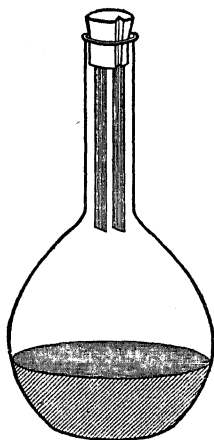
FIG. 3.—(After Autenrieth-Warren.)   FIG. 4.
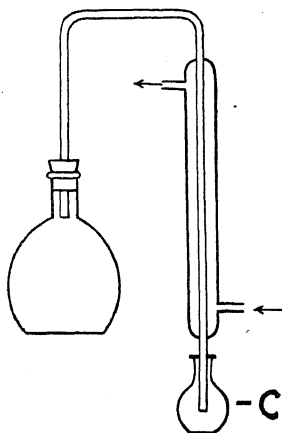
Principal Test for Phosphorus

I. Mitscherlich's Test.—In examining animal material such as stomach and contents, liver, spleen, kidney, etc. It is ground to a fine pulp in a mortar, a little clean sand may be used, and placed in a flask of suitable size, sufficient water is added to give it a mash like consistence. The flesh present may be cut with scissors to about the size of peas, before grinding. If the preliminary test does not rule out P. set up a distillation apparatus as in Fig. 4.

The glass tube in this case should be about 130 cm. long, 45 high and about 8 mm. internal diameter. The lower end of the tube from the condenser should dip one or two centimeters under water in the flask *C* to collect any gases like HCN that may come over in the distillate. If yellow phosphorus is present a character-

istic phosphorescence appears in the tube—and may be seen best in a dark room or when the distilling apparatus is covered with a black cloth.   The phosphorescence is due to oxidation of the phosphorus.   It may be prevented or masked by alcohol, ether, formaldehyde, formic acid, chloroform, chloral hydrate, benzin, petroleum, turpentine, ethereal oils, hydrogen peroxid, mercuric chlorid, phenol, creosote, hydrogen sulphide, and putrefactive products.   When the presence of P. is established by the
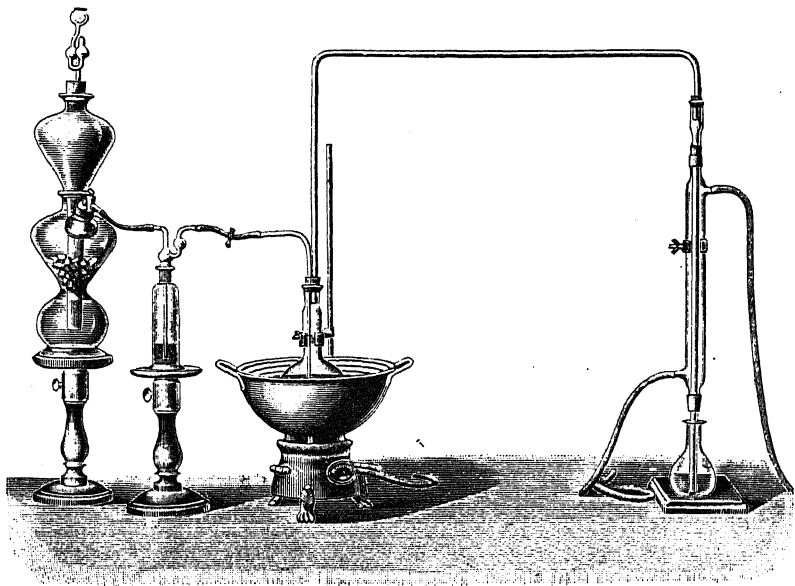
FIG. 5.—(After Kippenberger.)

phosphorescence, it is advisable to let the apparatus cool, and change the distillation to the regular Liebig condenser, see Fig. 6.

In heating organic matter in a flask over a free flame, there is danger of breaking the flask, consequently some advise the heating on a water bath or on an oil bath.   Again in heating the flask in presence of oxygen some of the phosphorus may be oxidized to P_2O_5 which is not volatile, and to prevent this some advise distillation from an atmosphere of CO_2, see Fig. 5.

To test for phosphorus in the distillate, add an excess of chlorine water, or fuming nitric acid and evaporate to dryness

ter bath. This oxidizes the phosphorus to H_3PO_4.
'ith a few drops of HNO_3 and dissolve in 10 cc. water.
for each of the following tests.
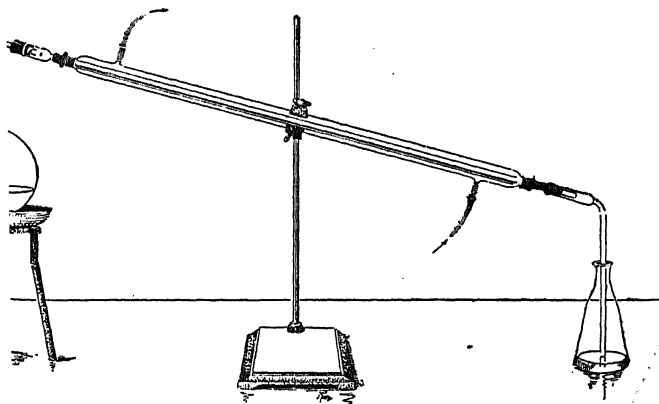
FIG. 6.—(After Autenreith-Warren.)   ience

ionium **Molybdate Test.**—Add 5 cc. of the solutio'
5 cc. ammonium molybdate solution and war'
a at 40°C. A yellow precipitate of ammonium phospho-
s is formed.
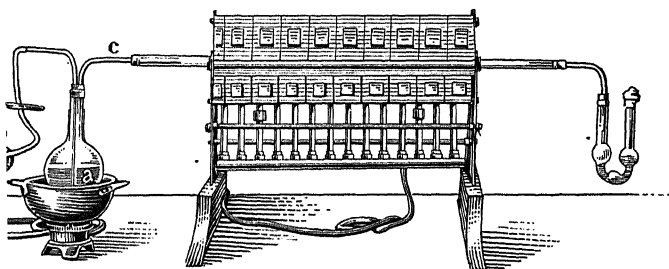
FIG. 7.—(After Kippenberger.)

ionium **Magnesium Phosphate Test.**—Add an equal
magnesia mixture to 5 cc. phosphate solution. Be sure
in is slightly alkaline. Ammonium magnesium phos-
cipitated $(NH_4) Mg.PO_4.6H_2O$.
cipitate is formed slowly and is facilitated by shaking.
over night if necessary.

In an elementary course in toxicology where the object is training in principles only, quantitative work is unnecessary, yet in many cases quantitative work is of more value as an aid to correlation and assimilation, than qualitative work.

The Mitscherlich-Scherer Method for the Qualitative and Quantitative Estimation of Phosphorus.—A weighed portion of the substance to be analyzed, is placed in flask and acidified with H_2SO_4, and a little ferrous sulphate added. This last is added to
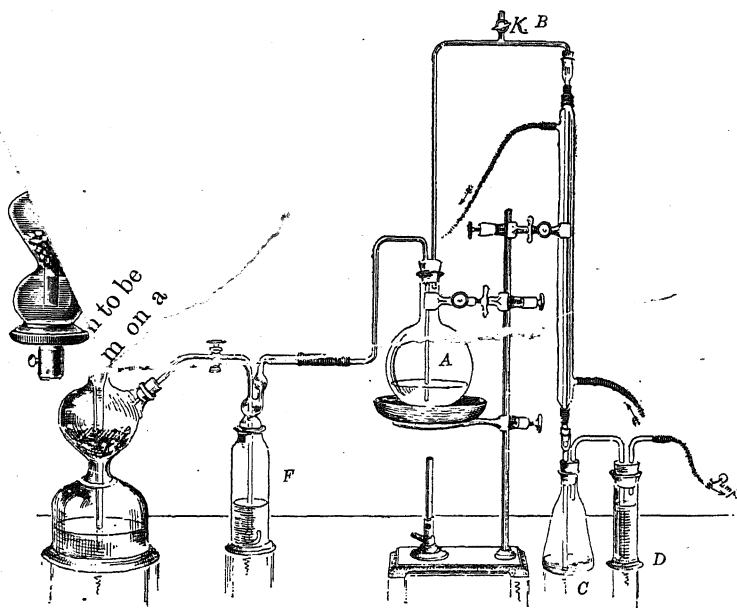
Fig. 8.—(After Autenreith-Warren.)

prevent oxidation of the P. Before heating the air is expelled from A, by CO_2, from the Kipp generator E. The CO_2 is washed with water in F. C contains water, and D contains a silver nitrate solution. The stop-cock B permits the entrance of air, if desired to increase the phosphorescence. When this has been seen no more air is admitted. The P collected in C is oxidized with bromine water or HNO_3, on a water bath and evaporated to dryness. The P. is oxidized to phosphoric acid. This is precipitated with magnesium mixture, filtered, dried, ignited and weighed as magnesium pyrophosphate, $Mg_2P_2O_7$.

The P. in the silver nitrate in D as Ag_3P is heated with nitric acid which oxidizes the P. The silver nitrate is precipitated and removed as $AgCl$ by the addition of $NaCl$. This is filtered off, and the filtrate treated as the contents of C and added to C.

This method will detect .00006 gram of yellow phosphorus.

Detection of Phosphorus in Oils

Straub's Test. Copper sulphate in contact with phosphorus, forms copper phosphide $Cu_3P_2(?)$ and at the same time tends to oxidize the phosphorus. Because of this copper sulphate is used in the treatment of phosphorus poisoning.

Test. In a test tube shake equal volumes of oil containing phosphorus and 1 per cent. copper sulphate. A black emulsion is formed, or a black ring at the junction of the liquids when the emulsion settles.

ACETONE

Acetone is not an important poison. To test for its presence in the distillate use tests, page 63.

ANILINE

For tests see page 113.

OIL OF BITTER ALMONDS OR BENZALDEHYDE

See pages 76 and 104. Pure benzaldehyde is not poisonous, but it occurs in oil of bitter almonds in the form of the cyanhydrin of benzaldehyde

$$C_6H_5 - C \diagup \overset{H}{\underset{CN}{OH}}$$
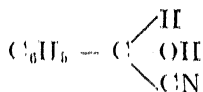
This is readily hydrolyzed by KOH into $\rightarrow KCN + H_2O + C_6H_5CHO$. (Benzaldehyde.)

Test for KCN. To 2 cc. oil of bitter almonds or the same volume of the distillate add 10 cc. KOH 5 per cent., heat gently, add a few drops of freshly prepared ferrous sulphate containing a drop or two of ferric chloride. Prussian blue is formed. See test for nitrogen, page 8. To test for benzaldehyde: add KOH to the original solution. Extract with ether in a separatory funnel, remove and evaporate the ether on a water bath at 40°C.

If benzaldehyde is present it is deposited as globules. Heat these globules with 10 cc. 5 per cent. potassium dichromate and dilute sulphuric acid under a reflux condenser. The benzaldehyde is converted into benzoic acid. Cool the liquid and again extract with ether. Evaporate the ether. Benzoic acid remains, its melting point is 120°–121°C. When dissolved in dilute NaOH, ferric chloride produces a flesh colored precipitate.

CARBON BISULPHIDE

Carbon bisulphide distils slowly with steam and is found but little in the first third of the distillate.

I. **Lead Acetate Test.**—CS_2 is not precipitated by lead until after decomposition. Add an equal volume of lead acetate to CS_2 shake—no reaction. Now add an excess of KOH and boil. A black precipitate of Pb.S will appear (*cf.* H_2S).

II. When an aqueous solution of carbon bisulphide is heated with an alcoholic solution of NH_4OH—ammonium sulphocyanate is formed together with ammonium sulphide. Evaporate nearly to dryness on water bath to expel $(NH_4)_2S$. Dissolve in dilute HCl. When ferric chloride is added to this a deep red color due to iron sulphocyanide appears. .05 gram of CS_2 will give this test.

The reaction is:

$$1 \quad 4NH_3 + CS_2 - (NH_4)\,CNS + (NH_4)_2S$$
$$2. \quad FeCl_3 + 3\,(NH_4)\,CNS = Fe\,(CNS)_3 + 3NH_4Cl$$
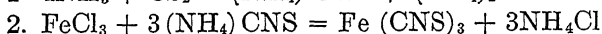
III. **Xanthogenate Test.**—When CS_2 is shaken with 3–4 times its volume of saturated alcoholic KOH it gives potassium xanthogenate as follows:

$$CS_2 + C_2H_5OK \quad = \quad \underset{\displaystyle OC_2H_5}{\overset{\displaystyle SK}{C = S}}$$
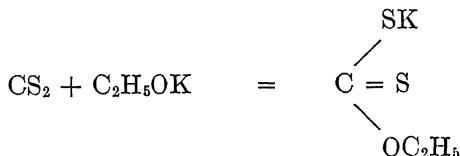
This is a yellow compound, when this is acidified with acetic acid and copper sulphate added, a black precipitate of cupric xanthogenate is formed.

$$2\,C \!\!\begin{array}{c} \nearrow SK \\ = S \\ \searrow O\,C_2H_5 \end{array} + CuSO_4 = \left(S = C \!\!\begin{array}{c} S\!\!-\!\!\!\!\!\! \diagup \\ \nearrow \\ \searrow O\,C_2H_5 \end{array}\right)_2 Cu + K_2SO_4$$
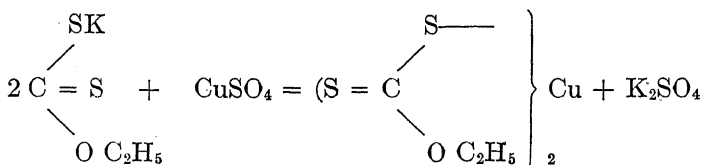
The cupric xanthogenate then decomposes into cuprous xanthogenate and ethyl xanthogen disulphide, as follows:

$$2\left\{\begin{array}{c} OC_2H_5 \\ \diagup \\ S = C \\ \searrow \\ S \\ \searrow \\ Cu = \\ \diagup \\ S \\ \diagup \\ S = C \\ \searrow \\ OC_2H_5 \end{array}\right. = \begin{array}{c} OC_2H_5 \\ \diagup \\ S = C \\ \searrow \\ S \\ | \\ S \\ \diagup \\ S = C \\ \searrow \\ OC_2H_5 \end{array} + \begin{array}{c} OC_2H_5 \\ \diagup \\ S = C \\ \searrow \\ S\!\!-\!\!Cu \\ | \\ S\!\!-\!\!Cu \\ \diagup \\ S = C \\ \searrow \\ OC_2H_5 \end{array}$$

Cupric xanthogenate $\longrightarrow$ Ethyl xanthogen disulphide + Cuprous xanthogenate
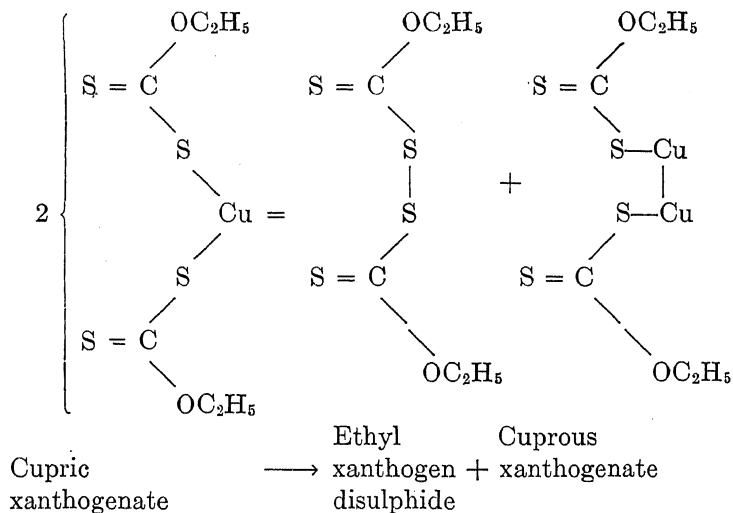
Chloroform: Tests see p. 42.

Introduce 5 cc. chloroform into flask a (Fig. 7); heat on a water bath and blow current of air through the flask and through the heated tube c. This decomposes the chloroform vapor with formation of HCl, which can be demonstrated by collecting it in the U tube d. which contains a one per cent. solution of $AgNO_3$.

CHLORAL HYDRATE

Chloral hydrate distils very slowly with steam. The solution should be distilled for a long time and quite completely in order to get most of it over. It is decomposed by distillation. For tests, see page 60.

ETHYL ALCOHOL

This would be present in the same distillate as methyl alcohol. It is quite impossible to separate them but tests for each may be made. For tests see page 23.

METHYL ALCOHOL

This would be all distilled over when one third of the original volume is distilled. For tests see page 18.

IODOFORM

Iodoform distils readily with steam giving a milky distillate which may be recognized by its odor. For tests and reactions see page 80.

NITROBENZENE

$C_6H_5NO_2$. The boiling point of this oily liquid is 208°C. which is higher than that of phenol (183°C.) consequently most of it will appear in the last part of the distillate: It is nearly insoluble in water but very soluble in ether and if only traces are present, the distillate should be shaken with ether, the ether evaporated at about 40°C. and tests made on the residue. For tests see page 110. Convert it into aniline, by reduction with hydrogen and then make the aniline tests, page 112.

PHENOL

Phenol boils at about 180° and distils readily with steam. The distillate may be cloudy and is recognizable by its odor, though this may be masked by putrefactive odors. Traces of phenols are formed in all putrefactions. For tests see page 99.

Quantitative Estimation of Phenol

An excess of saturated bromine water precipitates phenol in aqueous solution as tribromophenyl hypobromite—$C_6H_2Br_3OBr$.

Method.—Place an aliquot part of the liquid under examination in a stoppered flask. Add bromine water from time to time and shake until the supernatant liquid has a red brown color and bromine vapor is visible above the liquid. Let stand 2–4 hours and filter through a weighed Gooch crucible. Dry in a desiccator over H_2SO_4 to constant weight. The weight of the dried precipitate multiplied by 0.2295 gives the amount of phenol, since

$$\frac{C_6H_2Br_4O}{409.86} : \frac{C_6H_5OH}{94.05} = \frac{94.05}{409.86} \doteq .2295$$

CREOSOTE (Creosols)

See page 96. Creosotes are methyl phenols and distil over similar to carbolic acid. Some commercial creosotes contain

phenol. The tests are in many cases similar to phenol and hard to distinguish from it.

1. With pure creosote iron chloride gives a green color, while" with phenol it gives a blue-purple color.

2. HNO_3 when added to creosote gives picric acid, HNO_3^- does not form picric acid directly with phenol.

3. When equal volumes of colloidon and creosote are shaken together there is no visible change while with phenol, a gelatinous coagulum is formed.

NON-VOLATILE ORGANIC POISONS

Before non-volatile organic poisons can be extracted from stomach contents, organs, etc. the proteins, fats, carbohydrates and resinous material must be removed. As an aid to their removal and to lessen the likelihood of removing poisons with these materials, the organs are cut, or ground so that no piece is larger than a pea. The finely chopped material is then placed in a flask of suitable size and three times the volume of absolute alcohol which has been redistilled from tartaric acid is added. The alcohol has been redistilled to remove basic material which often is present in commercial alcohol. Just enough tartaric acid is added to acidify the mixture. The whole is extracted on a water bath for 30 minutes using a reflux condenser. Cool the flask and contents, in order to help solidify fats present, and filter through cheese cloth if much solid material is present. Wash with absolute alcohol, and filter through paper to remove fat and solid matter. Wash again with alcohol. Evaporate the filtrate in a glass or porcelain dish on a water bath to a syrupy consistency, and thoroughly mix with about 100 cc. water. This precipitates resins. Filter, wash with water and again evaporate to a syrup. Mix thoroughly with 150 cc. absolute alcohol. This precipitates proteins, albumoses, peptones, dextrin-like bodies, some inorganic salts—while the tartrate salts of the poisons are dissolved. Filter and wash with alcohol. Again evaporate off the alcohol and dissolve the residue in about 50 cc. of water. This should be relatively clear and free from proteins, fats, carbohydrates and resins, but if not the above processes should be repeated until a clear solution is obtained. This is the most important part of the analysis, as upon the removal

of all foreign matter depends the success of the tests which follow. At all stages the solution should be acid—but a large excess of acid should be avoided as its presence interferes with the tests. When the solution is so prepared it is ready for the Stas-Otto method of extraction. This method consists in extraction of the poisons with immiscible solvents first with acid alcohol, then changing the solvent to water solution; and then successive extractions of the prepared liquid with ether and chloroform in acid and alkaline reactions as given below.

Acid Extraction—Stas-Otto Method.—Place a portion, or all, of the prepared acid extract in a separatory funnel. Add an equal volume of ether, shake well, allow to settle and remove the ether into an evaporating dish. Repeat the extraction 3 or 4 times. Unite all extracts and allow to stand for 30 minutes. If water separates out, it may be removed by filtering through a dry filter. A dry filter will absorb and retain considerable water. Evaporate the ether at a temperature of 40°C. Since only a small residue may be expected after evaporation, it is best not to have this spread over a large surface. To avoid this let the ether extract drop from a separatory funnel into a small evaporating dish at a rate about equal to the evaporation. In this way whatever residue remains is on a small surface and more easily examined. The completion of the evaporation may be carried out on a water bath at a higher temperature if the residue remains too moist for examination.

Even when none of the first group of poisons is present, some little residue may remain which consists of tartaric acid, lactic acid, resins, etc. which are not completely removed in the process.

The residue may contain any of the following poisons.

Acetanilide	Caffeine
Antipyrine	Picrotoxin
Phenacetine	Picric acid
Salicylic acid	Veronal
Colchicine	

Also traces of mercuric cyanide:

Cantharidin
Digitalin
Veratrine

and Atropine may occur in this extraction. An examination of the general appearance, taste, odor, color, etc. of the residue should be made. Then a microscopic examination for crystals should be made. Since usually only one of the poisons of the group is expected, tests for the most likely should be made first.

II. After the acid solution has been extracted with ether, it is made alkaline with sodium hydroxide. The alkali liberates most alkaloids from this salts, and these are then readily extracted with ether. Morphine, apomorphine, and narceine are more soluble in the water alkaline solution than in ether, consequently are not extracted, with ether. Note this exception to the general alkaloidal solubilities. The water solution should be saved for further investigation. The ether extract from alkaline sodium hydroxide should be examined for:

The figures refer to pages in the text where the tests are given.

III. The alkaline sodium hydroxide solution, after extraction with ether, is slightly but distinctly acidified with tartaric or sulphuric acid. Then made alkaline with ammonia, and extracted in a separatory funnel with ether, and afterwards with chloroform.

A. The ether extract may contain, apomorphine and traces of morphine.

B. The chloroform extract may contain morphine, narceine and antipyrine and caffeine that was not previously removed.

METALLIC POISONS

To detect poisonous metals, in animal or vegetable matter, it is first necessary to destroy· or remove the organic material after which the tests are made in the same way as in inorganic chemistry. In toxicological analysis therefore a most important part of the process is the removal of the organic material.

Method

Various methods may be used, the principle in all is essentially the same. The Fresinius v. Babo method is taken as the type. Since all the organic poisons are also destroyed when the organic matter is being destroyed, one may work either with an original portion of the material or with the residue that remains after the organic poisons have been removed. A portion of the material is mixed to a fluid mass and placed in a large flask Fig. 9.

About 30 cc. concentrated HCl is added per 100 cc. material, and 1–2 grams of $KClO_3$ added. The flask is heated on a boiling water bath in a hood. Nascent chlorine is evolved which destroys the organic matter. When the flask is hot, it is frequently shaken and a trace of $KClO_3$ added from time to time until the solution is a pale yellow color and longer heating produces no further change.   Fat is very resistant to oxidation in this way, yet is easily oxidized in the body.

When oxidation is complete dilute with hot water and add a little sulphuric acid to precipitate possible barium, filter and evaporate in a porcelain dish on a water bath nearly to dryness to remove excess of acid. The decomposition of some $KClO_3$ may give a brown color at this point. If necessary filter, wash with water and evaporate again almost to dryness. Dissolve in water, and filter. There will be some insoluble white residue wholly unaffected by the action of chlorine (see test for Ba).

Examination of Filtrate

This should have only a faint yellow color, and be slightly acid. Place in a flask and heat on a water bath. While heating saturate the solution with H_2S from a Kipp generator. The gas should be run for 30 minutes in the hot solution, and again for 30 minutes after the flask has cooled, then the flask is tightly stoppered

and allowed to stand for several hours—preferably over night—and filtered. The filtrate may contain chromium or Zn. The precipitate may contain As, Sb, Sn, Cu, Hg, Pb, Bi, Cu, Cd.
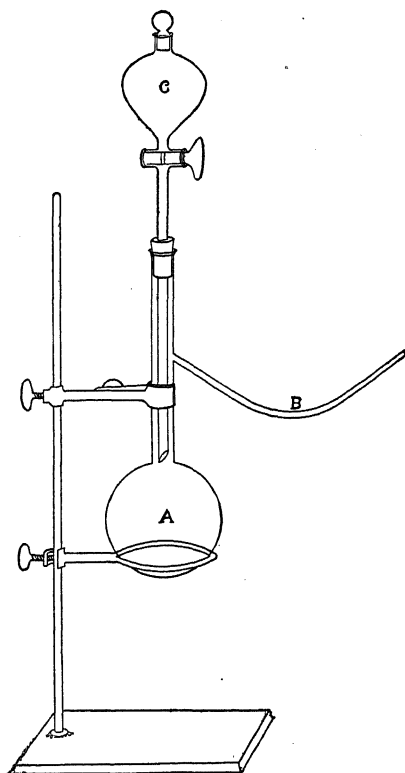
FIG. 9.—(After Autenreith.)

Examination of the Precipitate

The precipitate is thoroughly washed with hydrogen sulphide water, then the moist precipitate is dissolved in about 25 cc. of a mixture of equal parts of ammonium hydroxid and yellow ammonium sulphide and heated to boiling—filter and wash several times with some of the hot ammonium—sulphide mixture: The filtrate may contain As, Sb, Sn, or Cu. The precipitate Hg, Pt, Bi, Cu or Cd.

Examination of the Filtrate

Evaporate the solution to dryness on a water bath—cool, moisten with HNO_3 and again evaporate to dryness. Then mix the residue with 3 times its volume of a mixture containing 2 parts sodium nitrate and 1 part sodium carbonate. Evaporate this mixture to dryness and add it little by little to a crucible containing a little sodium nitrate heated to redness. The heating is continued until the whole is fused. If copper is present the melt is gray or black. Sodium arsenate, sodium pyroantimonate and sodium stannate may also be present. When the crucible is cold, add a little hot water and wash into a flask. If sodium stannate is present a little sodium bicarbonate is added to precipitate the tin as stannic oxide. Filter. The filtrate may contain As as sodium arsenate and the residue will contain sodium pyroantimoniate $(Na_2H_2Sb_2O_7)$, stannic and copper oxides.

Arsenic Test

Acidify the filtrate with arsenic free sulphuric acid. Evaporate over a free flame, and add sufficient sulphuric acid to expel nitric acid. Heat until copious white fumes of sulphuric acid appear. Arsenic if present is in the form of arsenic acid and is tested in the Marsh Apparatus, see Fig. 10 (Autenrieth, Warren).

Place 30 grams of arsenic free zinc in flask A. Pour 15 per cent. arsenic free sulphuric acid on the metal. The flask should be kept cool during the analysis by keeping it surrounded with cool water and by generating hydrogen slowly. If the temperature gets too high SO_2 is formed and this in presence of hydrogen is reduced to H_2S, which interferes with the test. All joints of the apparatus should be tight to avoid escape of AsH_3 and also to prevent explosions. Air should be completely expelled before igniting also to prevent explosion, to determine whether the air is expelled catch some of the escaping hydrogen in a test tube and test from time to time until it ignites without detonation. It may require 10 minutes to expel the air. When lighted and before adding the solutions to be tested, one should test to see that no arsenic is present in the chemicals. If the hydrogen is arsenic free, the solution to be tested is gradually introduced into the sulphuric acid—zinc flask, A, through the funnel—at the

same time the tube *C*. is heated to redness just back of the constriction *D*. If the solution contains As, a shining metallic arsenic mirror is deposited, just beyond the point of ignition.

2. If the flame is removed from *C*. and a cold porcelain dish pressed down on the arsine-hydrogen flame a brownish black spot is formed upon the dish. This spot dissolves readily in sodium hypochlorite solution. Antimony spots will not dissolve.

3. If the hydrogen flame is extinguished, and the end of the tube dipped into a dilute silver nitrate solution, arsine produces a black precipitate of metallic silver.
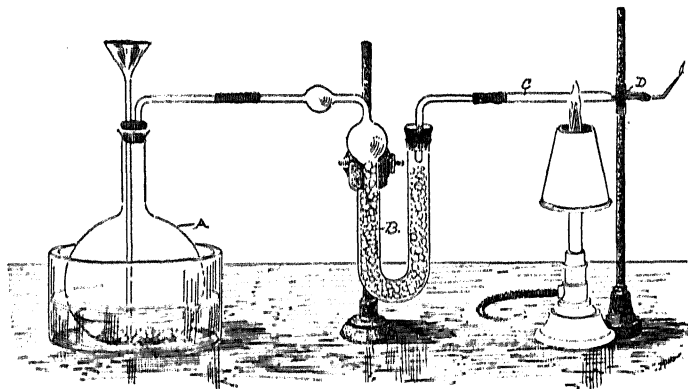
FIG. 10.

4. Arsine produces a yellow stain on a piece of filter paper moistened with conc. silver nitrate solution. A drop of water added to this changes the yellow spot to black. This is Gutzeit's test.

Detection of Antimony

The insoluble residue after fusion may contain Cu, Sb, or Sn.

1. **Test for Cu.**—Dissolve in dilute HCl. The solution may be colored light blue, excess of NH_4OH produces a deep blue color. Potassium ferrocyanide gives a deep red precipitate.

Test for Tin.—The insoluble residue is dissolved in HCl as in testing for copper. The tests for tin depends on the fact that tin chloride is a reducing agent.

1. Add a few drops of mercuric chloride. If tin is present it

reduces this to calomel which precipitates. When heated this precipitate is changed to metallic mercury.

Test for Antimony

Dissolve in dilute hydrochloric acid by aid of heat. Introduce into Marsh gas apparatus and test in the same way as for arsenic.

1. **Differences between Arsenic and Antimony.**—The antimony mirror in the Marsh gas apparatus is deposited on both sides of the flame. The metal in contact with the heated flame fuses to the glass and is silver white. It sublimes with difficulty. Arsenic volatilizes readily.

2. Nitric acid dissolves both antimony and arsenic mirrors. When neutralized with ammonium hydroxid, silver nitrate precipitates silver arsenate Ag_3AsO_4 which is reddish, with antimony there is no reddish precipitate.

3. The spot produced on a cold porcelain surface when held to the Marsh gas flame by arsenic is not heavy, is brown and lustrous, and dissolves readily in sodium hypochlorite.

The antimony spot is heavy velvet like, not lustrous and is insoluble in hypochlorite.

Detection of Metals Whose Sulphides are Insoluble in Ammonium Sulphide

This group includes:

Bismuth	Copper
Cadmium	Lead

Mercury

1. Treat these sulphides on the filter with dilute nitric acid. All dissolve except mercury—save the filtrate for further work.

Test for Mercury.—Dissolve the sulphide with hot dilute HCl containing a crystal of potassium chlorate. Filter, evaporate to dryness on a water bath, and dissolve in 5 cc. 5 per cent. HCl, filter and test filtrate for mercury, as follows:

1. To a portion add a few drops of stannous chloride. The mercuric chloride is reduced to calomel which is precipitated. Excess of stannous chloride especially if heated reduces the calomel to metallic mercury.

2. Place a few drops of the solution to be tested on a piece of clean copper. A gray spot with silver luster is deposited if

mercury is present.   Wash with water, alcohol, and ether, dry
and place the copper in a small test tube.   Heat over free flame.
Mercury sublimes and collects in metallic globules on the cool
sides of the tube.   A crystal of iodine placed in the warm tube
vaporizes and scarlet mercuric iodide is formed.

3. Dilute potassium iodide added to a solution of $HgCl_2$ pre-
cipitates the red iodide HgI_2.

Examination of the Nitric Acid Solution

This may contain Pb, Cu, Bi and Cd nitrates.

Evaporate to dryness and dissolve in a little hot water, add
dilute sulphuric acid.   Lead precipitates—filter.   The sulphates
of Cu, Bi and Cd are soluble.   Test the filtrate for these.

Copper and Bismuth Tests.—Add excess of ammonium hy
drate, if Cu is present it produces a blue color.   If Bi is present,
it is precipitated as $Bi(OH)_3$.   Filter dissolve ppt. in dilute HCl.
Pour into 50 cc. water.   A white precipitate of BiOCl proves the
presence of bismuth.   If cadmium be present, it will give a
yellow precipitate with hydrogen sulphide.   If present with
copper, add solid KCN to the blue color, until the color dis-
appears.

Then pass hydrogen sulphide.   The copper remains in solu-
tion.   As $K_4Cu_2(CN)_6$ while yellow CdS is precipitated.

CHROMIUM AND ZINC

If present these are found in the H_2S filtrate.

Detection of Zn

Make one half of the filtrate alkaline with ammonium hydrate
and add ammonium sulphide.   This will precipitate Zn, but
there may be a precipitate even if no Zn is present, because
solutions from animal matter contain traces of iron, alkaline
earths, phosphates, etc.   Add acetic until faint acid reaction;
this dissolves phosphates except ferric phosphate.   Filter, wash
with water, dry and ignite in porcelain crucible.   A drop of
ammonium nitrate aids oxidation—cool.   Add dilute sulphuric
acid, boil and filter.   This converts Zn into $ZnSO_4$—divide the
filtrate into two equal parts.

(a) Add dilute NaOH to precipitate iron which may be present

as ferric phosphate. Filter, add a few drops of ammonium sulphide. This precipitates ZnS as a white flocculent precipitate.

(b) Add ammonium hydroxide and filter to remove ferric phosphate. Acidify filtrate with acetic acid. Zn if present can be precipitated with hydrogen sulphide as a white precipitate.

Detection of Chromium

Evaporate a portion of the hydrogen sulphide filtrate almost to dryness, add about 1 gram each of sodium carbonate and potassium nitrate—dry and add a little at a time to a hot crucible containing fused potassium nitrate. Heat until fusion is complete. This oxidizes chromium to chromates. Cool and dissolve in water, and filter. The filtrate is yellow if chromium is present, acidify with acetic acid and add a little lead acetate; yellow lead chromate is precipitated.

Detection of Lead, Silver and Barium

The residue from the fusion with potassium chlorate may contain lead, silver or barium. The residue is dried in an air oven, and ground in a mortar. Then 3 times the amount of a mixture of potassium nitrate and sodium carbonate is added and the mixture fused in a crucible adding a little potassium nitrate to complete the fusion. This destroys fats and other organic matter. Cool and dissolve in water. Transfer to a flask and pass CO_2 through the flask. The precipitates lead as the carbonate. Filter, the precipitate may contain lead and barium carbonate and metallic silver and silver oxide. This silver gives the precipitate a gray color. Wash with water and dissolve in dilute nitric acid. Evaporate to dryness and dissolve in hot water. Add HCl and heat, this precipitates silver, filter and add H_2S to precipitate lead. Filter and heat to expel the excess of H_2S. Add dilute H_2SO_4 to precipitate barium. The confirmatory tests need not be given.

SYNOPSIS OF METALLIC POISONS

The material is boiled with dilute hydrochloric acid (about 12 per cent.) and potassium chlorate added until a pale yellow solution results. This destroys organic matter and dissolves the heavy metals. A little sulphuric acid is added and the solution filtered.

Filtrate may contain—As, Sb, Sn, Cu, Hg, Pb, Bi, Cu, Cd, Cr, Zn. Add H_2S	Precipitate may—contain—Pb, Ag, Ba.
Precipitate—Dissolve precipitate with yellow ammonium sulphide and ammonium. Filter.	Filtrate contains—Cr and Zn.

Filtrate contains— As, Sb, Sn, Cu.	Residue—Hg, Pb, Bi, Cu and Cd.

SULPHURIC ACID

Sulphates are present in small amounts in all vegetables and animal matter. The appearance of the tongue and stomach as well as the amount after sulphuric acid poisoning should settle any case of doubt. The tongue may be dark or boiled looking due to the formation of methemoglobin, hematin, etc.

I. The finally divided stomach and tissues reacts strongly acid. When extracted with water and filtered, the filtrate is acid.

II. The barium chloride gives a precipitate which is insoluble in HCl. The amount of H_2SO_4 may be determined by igniting the precipitate, and weighing in a weighed crucible or by titration of the water extract as under HCl.

III. When the water extract is evaporated on a water bath and then over a free flame white fumes of SO_2 are evolved. A particle of sugar, or any organic matter added to this heated solution will be carbonized.

Nitric Acid.—Nitrates occur only in traces in foods and organic matter. In a case of poisoning with nitric acid, the parts of the body touched by it are yellow—xantho-protein test. If taken in dilute form nitric acid is excreted in the urine as nitrates.

Tests

I. The water in extracts gives the tests for mineral acids.

II. It distils after it reaches a certain concentration. The

protein material in the distillation flask is yellow—xantho-pr
tein. If distillation is carried far enough, the brown vapors
nitrogen peroxid appear.

III. Brucine test: Mix part of the distillate with an equ
volume of a solution prepared by mixing 1 gram brucine in 5 c
dilute sulphuric acid and 95 cc. water. Pour this mixture ca r
fully on concentrated sulphuric acid in a test tube. If nit ı
acid is present, a black ring is formed between the solutio r

IV. Saturate the liquid to be tested with ferrous sulphate. Po
this upon concentrated H_2SO_4. A black zone appears betwe
the liquids.

V. Nitric acid evolves red brown vapors of NO_2 when cle
metallic copper is added.

OXALATES AND OXALIC ACID

Extract the finely divided material with 3–4 volumes of l
absolute alcohol acidified with HCl. Cool to about 10°C. a
filter through dry paper. Fats and proteins are removed. A
20 cc. water to prevent the formation of ethyl oxalate and eva
rate the alcohol. The residue may again be extracted w
alcohol and evaporated. Make alkaline with ammonia, fi l
if there is a precipitate and to the clear filtrate add calci
chloride solution. A precipitate of octahedron crystals or
velope shaped crystals of calcium oxalate results. These sho
be examined under the microscope. If it is desired to determ
the amount of oxalic present, this may be done by igniting
precipitate in a weighed crucible as CaO.
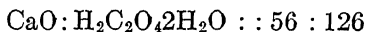
$$CaO : H_2C_2O_42H_2O \; : : 56 : 126$$
$$56 : 126 = 0.444$$

Consequently the weight of the precipitate multiplied by 0.44 ·
gives the amount of oxalic acid.

To get purer crystals of calcium oxalate, for identificatio r
is sometimes advised to extract the water solution from
alcohol filtrate with ether, and use the residue after evapora
for the test. This gets rid of some interfering bodies which ı
be present in the alcohol extract.

ALKALIES

The tissues after alkali intoxication react blue to litmus and are soft and greasy, if poisoning has occurred from ammonia it may be recognizable by its odor. To detect ammonia, or to estimate the amount, it will be sufficient to extract with water, filter—add 20 cc. strong NaOH and distil. The distillate reacts alkaline and the amount may be titrated with N/1 NaOH, using cochineal as the indicator.

FIXED ALKALIES

Extract with water, filter. The filtrate reacts alkaline, the fingers moistened with it feel slimy. The amount may be titrated with N/1 acid using phenolphthalein as the indicator and alcoholic extract of the tissues shaken with freshly precipitated washed mercurous chloride gives a black compound, which is soluble in nitric acid.

POTASSIUM CHLORATE

I. Extract the tissues with water and filter, add excess of silver nitrate and filter if there is a precipitate; add a little sulphurous acid and heat. If chlorate is present this decomposes it with the formation of a chloride, which gives a precipitate with the excess of $AgNO_3$ in the solution:

$$AgClO_3 + 3H_2SO_3 = AgCl + 3H_2SO_4$$
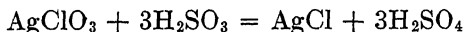
Add dilute HNO_3—silver sulphite dissolves, if present, silver chloride is insoluble.

II. Chlorates liberate chlorine from hydrochloric acid and the gas will liberate iodine from potassium iodide.

(a) Heat a solution containing a chlorate with concentrated HCl—free chlorine is given off. Pass the gas into a solution of potassium iodide; free iodine is liberated and can be separated by dissolving in chloroform.

Chromic acid and bichromates also liberate chlorine from hydrochloric acid.

ACTIVE SUBSTANCES WHICH MAY CAUSE POISONING, BUT WHICH ARE HARD TO DETECT, AND WHICH FIND NO PLACE IN THE STAS-OTTO METHOD

Cantharidin is the vesicating principle of Spanish fly. Chemically it is the anhydride of cantharidic acid.

$$
\begin{array}{c}
\text{H} \\
\text{C} \quad\quad \text{CH}_2 - \text{COOH} \\
\text{H}_2\text{C} \quad | \quad \text{C}-\text{O}\underline{\text{H}} = \\
| \quad \text{CH}_2 \,| \\
\text{H}_2\text{C} \quad \diagdown \text{C}-\text{CO} \,\underline{\text{OH}} \\
\text{C} \\
\text{H}_2
\end{array}
\qquad
\begin{array}{c}
\text{H} \\
\text{C} \quad\quad \text{CH}_2-\text{COOH} \\
\text{H}_2\text{C} \quad | \quad \text{C}-\text{O} \quad\quad + \text{H}_2\text{O} \\
| \quad \text{CH}_2\,| \quad | \\
\text{H}_2\text{C} \quad \diagdown \text{C}-\text{CO} \\
\text{C} \\
\text{H}_2
\end{array}
$$

Cantharidic acid   Cantharidin
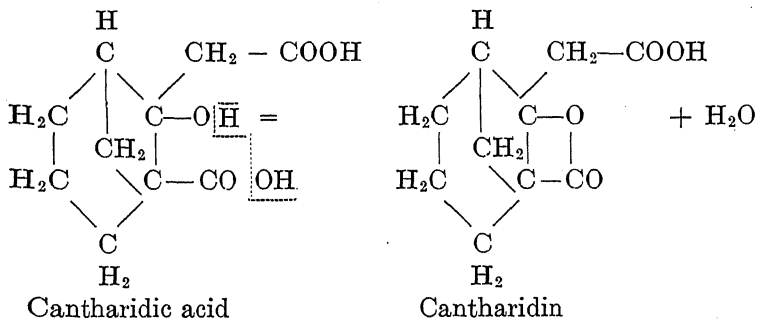
It occurs as small, colorless glistening crystals which melt at 214°–218°C. and sublimes at higher temperatures in white needles. The pharmacopeia gives a method for the extraction of the active substance from Spanish fly. There is no chemical test for it. The physiological test consists in dissolving a little of the substance in a fatty oil and rubbing it on a spot on the arm or chest. A blister will be formed in a short time if cantharidin be present.

SANTONIN, SULPHONAL, TRIONAL

These substances are not extracted under the conditions of the Stas-Otto process. They are not soluble in acid ether solution. Extract the tartaric acid solution of the organs with hot alcohol, filter. If a colored solution results add a little animal charcoal and heat again. Filter while hot, cool and extract the acid solution several times with chloroform. Evaporate the chloroform which may contain sulphonal, trional, santonin.

1. Santonin, see page 220.
2. Sulphonal, see also page 46.
3. Trional, see page 46.

Cytisine is an alkaloid of unknown structure, $C_{11}H_{14}ON_2$, found to the extent of 1.5 per cent. in the ripe seeds of Golden Chain—Cytisus Laburnum. Cytisine forms large colorless rhombic crystals which melt at 153°. It causes convulsions similar to strychnine, but it is also irritating to the gastro-intestinal tract, and for this reason may cause vomiting, and it also stimulates the vomiting center directly. Cytisine also resembles nicotine in action. In the tartaric extract in the Stas-Otto

method, it can be extracted with chloroform in alkaline solution of NaOH.

Test I. Ferric chlorid colors cytisine and salts blood red. The color is discharged by hydrogen peroxid which changes to blue when heated on water bath.

Test II. Nitrobenzene containing dinitro-thiophene produces a reddish violet coloration.

Digitalis. Nothing is known regarding the fate of digitalis in the body, consequently extracts of the tissues cannot be tested chemically for it. It has been claimed that more of it accumulates in the heart than in other tissues. This has been shown by physiological tests; no test for the drug as a whole is at hand.

Digitonin when dissolved in sulphuric acid, gives a red color with bromine water.

Digitoxin. I. This dissolves in concentrated HCl, with a brownish green coloration, which is unchanged by the addition of bromine.

II. Kiliani's test. Digitoxin dissolved in a little glacial acetic acid containing a trace of ferric sulphate. When superimposed on strong sulphuric acid containing a trace of ferric sulphate gives a dark ring. On standing the acetic acid layer becomes a deep indigo blue.

Digitalin. This dissolves in concentrated sulphuric acid with an orange yellow color, which changes to red on addition of bromine water, or ferric chloride, or after an hour with the addition of these oxidizing agents.

ERGOT

Ergot contains a red pigment—sclererythrin—which is characteristic of ergot. This cannot be found in tissues poisoned with ergot, but the material containing ergot, like flour, bread, etc. will give the following test.

Test I. If flour containing ergot be treated with a very dilute solution of anilin violet, the stain is absorbed by the damaged particles of the grain, while the normal particles are not stained.

Test II. Extract the flour with 10 to 15 times its volume of 40 per cent. alcohol heated to 40°. Filter and add basic lead acetate to the filtrate. Filter. Press the precipitate between

filter papers warm and add a few drops of saturated borax solution. If ergot be present a red violet color appears.

REAGENTS AND SOLUTIONS

Ammonium Molybdate Solution for Phosphates.—Dissolve 50 gm. of molybdic acid in 72 cc. conc. ammonia and 136 water; slowly and with constant stirring pour the solution into 245 cc. of nitric acid, conc., and 574 cc. of water. Keep this mixture in a warm place for several days. Decant and preserve in glass stoppered bottles.

Barfoed's Reagent is prepared by dissolving 45 grams of neutral cupric acetate crystals in 900 cc. of water and filtering. Add 6 cc. of 10 per cent. acetic acid to the filtrate and dilute to a liter. A portion of the reagent when heated on the water bath should show no reduction.

Benedict's Qualitative Reagent for Glucose.

Copper sulphate	17.3 gm.
Sodium citrate	173.0 gm.
Sodium carbonate, anhydrous	1000.0 gm.

Dissolve the copper sulphate separately in about 150 cc. of water and add slowly to the filtered solution of the other two in about 800 cc., and make up to 1000 cc.

Esbach's Reagent.—Dissolve 10 grams of picric acid and 20 grams of citric acid in 1 liter of water.

Fehling's Solution

A.	Copper sulphate	69.28 gms.
	Water	1000.00 cc.
B.	Potassium and sodium tartrate	346.0 gms.
	Potassium hydroxide	100.00 gms.
	Water to	1000.00 cc.

Mix equal volumes of A and B, and then add four volumes water just before using. This mixed solution does not keep well.

Froehde's Reagent is a solution of molybdic acid in sulphuric acid prepared by dissolving 0.5 gram of molybdic acid in 100 cc. of hot, pure concentrated sulphuric acid. The solution should be colorless and it does not keep long.

Gold chloride is used in a 3 per cent. aqueous solution.

Iodine Solution, aqueous (Lugol's).—Dissolve five grams of iodine and ten grams of potassium iodide in about 20 cc. of water. When completely dissolved add a sufficient quantity of distilled to make the product weight 100 grams.

Iodine solution; alcoholic, about 1 gram of iodine in 100 cc. of alcohol (95 per cent.).

Mayer's Reagent (mercuric potassium iodide solution) is prepared by dissolving 1.36 grams of corrosive mercuric chloride in 60 cc. of distilled water, and 5 grams of potassium iodide in 10 cc. of water. Mix the two solutions and then add sufficient water to measure 100 cc.

Millon's Reagent.—Dissolve 100 grams of mercury in 200 grams of strong nitric acid, by the aid of heat finally, and after cooling dilute the solution with twice its volume of water.

Nessler's Reagent.—Place 35 grams of potassium iodide and 50 grams of mercuric iodide, both finely powdered, in a 500 cc. volumetric flask and add about 200 cc. of water: Now add to this mixture in the flask; with constant shaking, 250 cc. of a cooled 20 per cent. solution of sodium hydroxide. Then make up to 500 cc. Set aside in a warm place for several days and decant the clear liquid for use.

Phospho-tungstic acid solution is prepared by adding a little 20 per cent. phosphoric acid to an aqueous solution of sodium tungstate.

Platinum chloride is used in a 5 per cent. solution.

Sodium Hypochlorite Solution.—Prepare a solution of calcium hypochlorite from bleaching lime and then precipitate the calcium by adding an excess of sodium carbonate—allow to settle and use the clear supernatant liquid.

Magnesia Mixture.—Dissolve 52.5 grams of crystallized magnesium sulphate and 105 grams of ammonium chloride in about 300 cc. of water and add 180 cc. of concentrated ammonium hydroxide. Dilute to 600 cc. Filter off turbidity which may develop on standing.

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