Fundamentals of Organic Chemistry

THE MACMILLAN COMPANY
NEW YORK • BOSTON • CHICAGO
DALLAS • ATLANTA • SAN FRANCISCO

MACMILLAN AND CO., LIMITED
LONDON • BOMBAY • CALCUTTA
MADRAS • MELBOURNE

THE MACMILLAN COMPANY
OF CANADA, LIMITED
TORONTO

FUNDAMENTALS OF

Organic Chemistry

A Brief Course for Students Concerned with
Biology, Medicine, Agriculture, and Industry

JAMES BRYANT CONANT
President of Harvard University
Formerly Sheldon Emery Professor
of Organic Chemistry

ALBERT HAROLD BLATT
Professor of Chemistry, Queens College

NEW YORK : The Macmillan Company : 1950

Printed in the United States of America

Preface

The present volume was first planned as a simplified and abbreviated version of the third edition of our *Chemistry of Organic Compounds*. We soon found, however, that something more than an abridgment was required for the type of student we had in mind. There are many young men and women in college today who desire to have some knowledge of organic chemistry but who do not plan to become professional chemists. For them, many of the special methods and factual details are not essential; for example, the determination of the position of the substituents in the benzene ring and the consideration of factors affecting equilibria and rates may well be omitted. On the other hand, a considerable number are planning to enter a vocation connected in one way or another with applied biology; therefore a rather full treatment of subjects connected with biochemistry is of great importance.

All students are future citizens and as such must be concerned with the economic life of the nation. In an industrial society such as ours the organic chemical industry is of unusual importance for it provides such essential products as synthetic rubbers, liquid fuels, and synthetic fibers and plastics. Further, this industry is unique in that it is not confined to a single raw material for the manufacture of a given product. Starting with agricultural crops, or coal, or petroleum, or natural gas, it is possible to produce any of the products mentioned above — thus giving flexibility to the economy. We have sought, therefore, to make the central theme of the book twofold, — a consideration of the organic chemistry of living things and the utilization for practical ends of the products of life processes. In so doing one can connect the transformations of the materials manufactured by plants in the geologic past (coal and oil) with the agricultural output of today. Comparisons can be made between several different sources of the accumulated stores of the sun's energy both from the point of view of fuel and the availability for the synthesis of complex materials.

In rewriting completely many sections of the book we have aimed at simplification. For example, the treatment of the heterocyclic compounds makes no pretense of following the orthodox methods of classification. Only those substances are considered which are of importance to biologists, medical men, and industrialists. A guide to the complexities of the formulae is offered in terms of the relation of some of the substances to the recurring urea pattern. Such pedagogic devices we believe better suited to this type of book than a more systematic treatment of such complex subjects as heterocyclic rings.

The conventions for the nomenclature and stereochemical representation of carbohydrates and related compounds definitively adopted by the American Chemical Society in March 1949 have been made the basis for the perspective drawings of the lactic acids, the chlorohydroxysuccinic acids, and the tartaric acids in Chapter 12. These perspective drawings and their planar projections are in the correct configurational relation to D(+)- and L(−)-glyceraldehyde, but we do not discuss configurational relationships in this chapter. D(+)-glyceraldehyde as the basis for configuration is mentioned on page 202 of Chapter 13 so that instructors who wish to consider configurational relationships can do so.

Every effort has been made to bring up-to-date our discussion of topics of current interest both in the industrial field and in the area of biochemistry. This has not been easy, as changes have been rapid in these postwar years. Exciting events have taken place, particularly in the fields connected with medicine. New developments and new discoveries will undoubtedly be made in the years immediately ahead. It is our hope, however, that within the areas covered by this book the fundamentals as they appear to us in late 1949 will provide an adequate foundation on which the student may subsequently expand his knowledge.

James B. Conant
A. H. Blatt

Cambridge, Massachusetts
Flushing, New York
December 1, 1949

Table of Contents

Introduction

We shall be concerned in this book with the chemistry of the carbon compounds, particularly with those substances intimately associated with the life processes in plants and animals. A variety of complex materials are manufactured in green plants with the aid of radiant energy from the sun. The oxidation of those materials in the plant or after assimilation in an animal yields the energy essential for the life processes. The source of the carbon atoms is the carbon dioxide of the atmosphere, and the ultimate product of the oxidation is the same oxide of carbon. Therefore we speak of the carbon cycle in nature. A somewhat similar cycle involves the use of ammonia or inorganic nitrates from the soil which supply the nitrogen atoms for some of the plant substances; the final decomposition of these substances returns the nitrogen largely as ammonium salts. In any study of elementary chemistry the significance of the carbon and nitrogen cycles is emphasized. The student will therefore recall the facts just stated and will also remember that coal and petroleum were formed in the geologic past from plants. These sources of carbon and carbon compounds likewise represent carbon dioxide which has been transformed by the sun's energy into either essentially elementary carbon (coal) or complex hydrogen and carbon compounds (petroleum).

The ultimate source of carbon and carbon compounds for industrial use is either plant materials produced currently or deposits of coal or petroleum. The formulas of the many, many separate compounds formed in plants or present in coal and petroleum are far from simple. In a book of this size only a beginning can be made in the study of the complexities of nature. Nevertheless one can sum up all the processes which go on in the green plant by speaking of **photosynthesis.** This is the series of reactions by which the radiant energy of the sun absorbed by the green coloring material of the plant brings about a *reduction* of carbon dioxide. That is, all the products of photosynthesis contain less oxygen per atom of carbon than the oxide from which they were formed. The overall reaction may be regarded as the transfer of the hydrogen atoms of water to the carbon dioxide molecule; the oxygen is evolved as oxygen gas. Clearly the burning of carbon compounds is exactly the reverse of this process.

Photosynthesis:

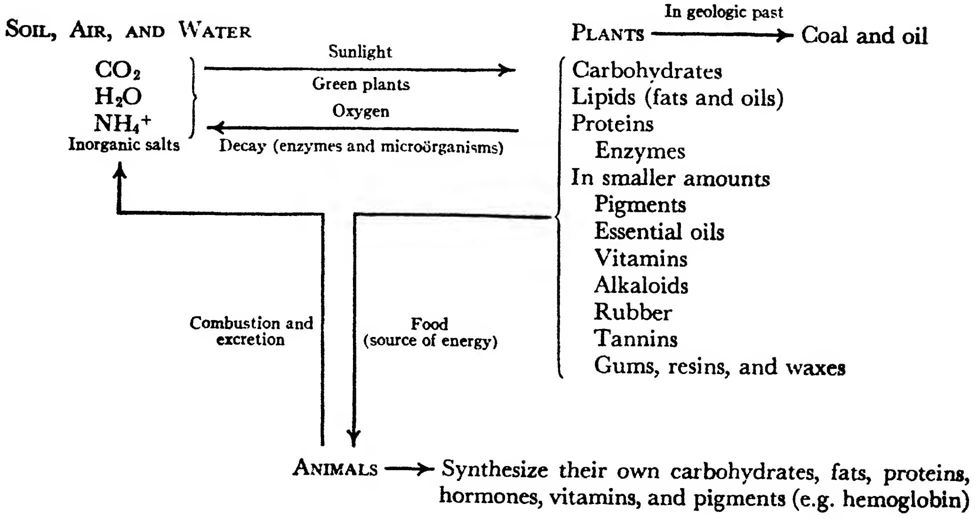
$$CO_2 + H_2O + \underset{\text{(sunlight)}}{\text{Energy}} \longrightarrow \underset{\text{containing hydrogen}}{\text{Complex carbon compounds}} + O_2\ \text{(gas)}$$

Combustion:

$$\underset{\text{containing hydrogen}}{\text{Complex carbon compounds}} + O_2 \longrightarrow CO_2 + H_2O + \underset{\text{(as heat)}}{\text{Energy}}$$

The diagram on p. 3 may well serve as an introduction to the study of organic chemistry by those who are particularly interested in the biological or industrial applications of the subject. There are so many different substances produced in even the simplest green plant that no one has any idea of their number. It is possible to recognize certain classes of compounds, and over the course of a hundred years we have learned a great deal about the structures of those types of compounds which are present in the largest amounts. We are even beginning to know something about the transformations which some of these substances undergo in the oxidation processes which are the basis of the life of plant and animal cells.

The important classes of compounds found in plants are (1) carbohydrates, (2) lipids (largely fats and oils), and (3) proteins. The first is represented by such common materials as sugar, starch, and cellulose (cotton fiber), all of which have the


SOIL, AIR, AND WATER
CO_2
H_2O
NH_4^+
Inorganic salts
Sunlight
Green plants
Oxygen
Decay (enzymes and microörganisms)
PLANTS
In geologic past
Coal and oil
Carbohydrates
Lipids (fats and oils)
Proteins
Enzymes
In smaller amounts
Pigments
Essential oils
Vitamins
Alkaloids
Rubber
Tannins
Gums, resins, and waxes
Combustion and excretion
Food (source of energy)
ANIMALS
Synthesize their own carbohydrates, fats, proteins, hormones, vitamins, and pigments (e.g. hemoglobin)

composition $C_x(H_2O)_y$. The second is represented by such vegetable oils as soybean oil or olive oil, or by animal fats like lard; these materials contain more hydrogen than the carbohydrates and can be regarded as resulting from a more nearly complete reduction of carbon dioxide. The third class is represented by such diverse materials as skin, silk, wool, white of egg, and the nitrogenous materials present in seeds; all proteins contain nitrogen and usually sulfur and phosphorus as well. Without proteins life would appear to be impossible, for the special catalysts which bring about the chemical changes in plants and animals are proteins; they are known as *enzymes*. As we shall see throughout this book, transformations of carbon compounds rarely take place at a useful rate at ordinary temperatures without a catalyst.

Many of the most important plant and animal products are made up of very large molecules. These substances of high molecular weight include all the proteins and the so-called reserve carbohydrates, of which starch, cellulose, and glycogen (present in animals) are the most common The sugars and the fats and oils are substances of low molecular weight and relatively simple structure. So too are many volatile compounds which give to various plants characteristic odors and flavors; these are known as the *volatile* or *essential oils*. So too are certain nitrogenous materials valuable in medicine because of their action as drugs; these are the *alkaloids*. The coloring materials (pigments) found in plants are for the most part of low molecular weight (below 1000) but of complex structure; one in particular, *chlorophyll*, the green coloring material in plants, deserves special mention because it is necessary for photosynthesis.

The chemical changes involved in the growth and multiplication of plant and animal cells are all catalyzed by specific enzymes; the changes are so numerous and so complex that we cannot yet say what substances are most important. Traces of some substances (*vitamins*) we know are essential for the normal functioning of many plants and animals, while traces of other substances (*antibiotics*, *growth inhibitors*) can kill certain types of cells or halt their growth. Reference to some aspects of physiology and chemotherapy which deal with these phenomena will be made in later chapters.

Finally we may mention the fact that certain plant products represent specialized activities of nature. For example, rubber is a material found in only a relatively few species. It is a compound of high molecular weight composed of carbon and hydrogen. The gums and resins used in industry also represent complex materials produced by certain types of plants. Modern chemistry has shown how to start with such cheap materials as coal, or petroleum, or starchy plants and produce by a series of industrial operations synthetic materials which rival the plant products and which for certain uses are superior to them. Thus we have today synthetic rubbers, synthetic resins (plastics), and even synthetic fibers. Most of the processes involved are relatively simple and they will be considered at the appropriate places in this book.

We cannot begin to understand the nature and behavior of the various types of substances which have been mentioned in this introduction until we have mastered the basic principles of the chemistry of the carbon compounds. We start our study, therefore, with some simple compounds which contain only a few atoms in the molecule. After we have learned how the structural formulas of these compounds are determined and how the compounds can be transformed into other materials, we shall proceed to a consideration of the more complex substances that are of special interest to the users of this text.

CHAPTER 1

The Alcohols

Ethyl alcohol is a substance of outstanding practical importance both because of its own extensive and varied uses and because, being available from agricultural sources, from petroleum, and from coal, it is the link between these three primary competing sources of raw material. In addition a study of ethyl alcohol leads at once to the problems of isomerism and structure which are fundamental to an understanding of organic chemistry. Consequently we choose ethyl alcohol as the starting point in our study.

Pure ethyl alcohol is a liquid boiling at 78°; a quantitative analysis shows that it contains carbon, hydrogen, and oxygen in such amounts as correspond to the presence of two carbon atoms, six hydrogen atoms, and one oxygen atom. The **empirical formula** is therefore C_2H_6O. Such a formula tells us only the relative number of atoms in the molecule. To establish the **molecular formula** of a compound we must determine its molecular weight. This is readily done by finding the density of the vapor or by noting the depression of the freezing point (or elevation of the boiling point) of a suitable solvent in which a weighed amount of the substance has been dissolved. The results of many such experiments have shown that the molecular weight of ethyl alcohol is 46. The molecular formula of ethyl alcohol is therefore C_2H_6O $(2 \times 12 + 6 + 16 = 46)$.

Isomerism. In an elementary study of inorganic chemistry we should hail this result with satisfaction, since the determination of the kind and number of atoms in the molecule is usually sufficient to establish an adequate formula; for example NH_3, HCl, H_2O_2. These are called *molecular formulas.* Quite the reverse is true in organic chemistry: such formulas are inadequate in dealing with the compounds of carbon. This may be illustrated by a simple example. **Dimethyl ether,** a gas related to the ether used in anesthesia, has exactly the same percentage composition and the same molecular weight as ethyl alcohol. Therefore it must be also represented by the formula C_2H_6O. There can be no doubt about the difference between these compounds, since one is a liquid boiling at 78° and is miscible with water, while the other is a gas at room temperature and is almost insoluble in water. Their chemical reactions are also entirely different. *Two compounds which have the same molecular formula are said to be* **isomers;** the phenomenon is known as *isomerism.*

The Necessity for Structural Formulas. Isomerism was encountered early in the development of organic chemistry and it was soon realized that the explanation of isomerism was to be found in the way in which the atoms are linked together in the compounds. As long ago as 1827 the great Swedish chemist Berzelius wrote with reference to the first example of isomerism: "It would seem as if the simple atoms of which substances are composed may be united with each other in different ways." There was, however, at that time no way to write formulas which represented the differences between isomers. As the number of isomers known increased rapidly, the chemistry of the carbon compounds became hopelessly confused, and it was not until about the middle of the nineteenth century that Kekulé, sometimes called the father of organic chemistry, developed a satisfactory method of formulating organic compounds. With the introduction of structural formulas by Kekulé organic chemistry developed by leaps and bounds.

The Theory of Linkages. The theory which was advanced to explain the differences between the various isomers may be called the *theory of atomic linkages.* This assumes that isomerism is due to the different ways in which the same atoms are joined together in the molecule. The organic chemist, thus, seeks to express in his structural formulas not only the number and kinds of atoms in the molecule but *the way in which they are linked together*. In other words his formulation must represent the structure of the compound. Let us see how this may be done for ethyl alcohol.

Hydroxyl Group in Alcohols. Ethyl alcohol is very similar to water in many of its chemical properties, as is illustrated by their reactions with metallic sodium and phosphorus trichloride.

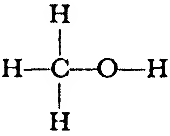
$$\begin{array}{lll}
1.\ (a) & 2H_2O + 2Na & \longrightarrow 2HONa + H_2 \\
\ (b) & 2C_2H_6O + 2Na & \longrightarrow 2C_2H_5ONa + H_2 \\
2.\ (a) & 3H_2O + PCl_3 & \longrightarrow 3HCl + P(OH)_3 \\
\ (b) & 3C_2H_6O + PCl_3 & \longrightarrow 3C_2H_5Cl + P(OH)_3
\end{array}$$

It will be noticed that in the first two reactions, sodium hydroxide and a compound, C_2H_5ONa (sodium ethoxide), are formed by the replacement of one hydrogen atom of the molecule. In the second set of reactions, the phosphorus atom becomes attached to a hydroxyl group which in one case has been removed from water and in the other must come from the alcohol. The facts of inorganic chemistry show that the atoms in the water molecule must be arranged H—O—H; the existence of the hydroxyl group (OH) is evident. Since the phosphorous acid is formed from alcohol as well as from water (equations 2*a*, 2*b*), we may conclude with considerable assurance that *ethyl alcohol has a hydroxyl group*.

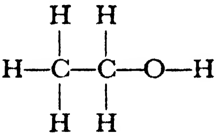
These two reactions are also characteristic of another well-known substance, **methyl alcohol.** This compound (commonly called *wood alcohol*) has the molecular formula CH_4O. Since it reacts with sodium evolving hydrogen, and with phosphorus trichloride forming phosphorous acid, $P(OH)_3$, we conclude that it also contains a hydroxyl group. We may, therefore, write the formulas CH_3OH for methyl alcohol and C_2H_5OH for ethyl alcohol. These formulas, however, are still not perfectly clear. How are the carbon and hydrogen atoms arranged in the groups CH_3 and C_2H_5?

Structure of Methyl and Ethyl Alcohols. The founders of the structural theory assumed that in organic compounds carbon always has a valence of four, oxygen of two, and hydrogen of one. With this as a basis the question just raised concerning the structure of methyl alcohol is easily answered. *There is only one possible arrangement of the atoms in* CH_3OH, and that is, the three hydrogen atoms must be attached to the lone carbon and this, in turn, must be bound to the hydroxyl group. Thus we have a complete **structural or graphical formula.**

The dash (—), whether vertical or horizontal, stands for a valence bond, a link, which joins the atoms together. There are four bonds from the carbon atom, two from the oxygen atom, and only one from each hydrogen atom. Applying the same principles we arrive at the complete structural formula of ethyl alcohol.



$$\begin{array}{ccccccc} & & \mathrm{H} & & & & \\ & & | & & & & \\ \mathrm{H} & - & \mathrm{C} & - & \mathrm{O} & - & \mathrm{H} \\ & & | & & & & \\ & & \mathrm{H} & & & & \end{array}$$

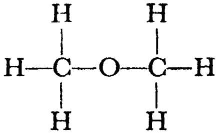


$$\begin{array}{ccccccccc} & & \mathrm{H} & & \mathrm{H} & & & & \\ & & | & & | & & & & \\ \mathrm{H} & - & \mathrm{C} & - & \mathrm{C} & - & \mathrm{O} & - & \mathrm{H} \\ & & | & & | & & & & \\ & & \mathrm{H} & & \mathrm{H} & & & & \end{array}$$

By attempting to write a variety of other structures for ethyl alcohol it is easy to convince oneself that there is only one way of writing C_2H_5OH, *provided* that the valence of hydrogen is one, oxygen two, and carbon four. It is, of course, immaterial whether the formula be written from right to left or left to right or at what angle the various atoms are connected. The structural formula simply says that the two carbon atoms in ethyl alcohol are joined to each other, and that one is attached to three hydrogen atoms, the other to two hydrogen atoms and the hydroxyl group.

Writing Structural Formulas. A study of a great variety of organic compounds has made certain the original assumption in regard to the valence of carbon, oxygen, and hydrogen. Carbon has a valence of four, except in a few very unusual substances. Therefore, in writing structural formulas we must arrange the atoms in such a way that each carbon atom always is connected with four linkages, oxygen with two, and hydrogen with one. *Every formula should be tested by noting the valence of each atom.*

Structure of Dimethyl Ether. Dimethyl ether, spoken of above as the isomer of ethyl alcohol, reacts neither with phosphorus trichloride nor with sodium; therefore, it has *no* hydroxyl group. It has the following formula, which, it is easy to see, represents a molecule of an entirely different nature from that of ethyl alcohol. This case of isomerism is thus explained satisfactorily by the structural theory.



$$\begin{array}{ccccccccc} & & H & & & & H & & \\ & & | & & & & | & & \\ H & — & C & — & O & — & C & — & H \\ & & | & & & & | & & \\ & & H & & & & H & & \end{array}$$

Dimethyl ether

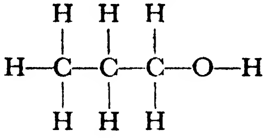
The Alcohols as a Class of Compounds. Besides the well-known methyl and ethyl alcohols, there are a great many other substances which are called *alcohols* by the organic chemist. They all show the reactions which we have learned are characteristic of a hydroxyl group, and their structural formulas, therefore, must show the linkage —O—H. They form a graded series with an increasing number of carbon atoms. Such a series of compounds is called a *homologous series* and is illustrated on the following page.

We may define a homologous series as a series of compounds of similar structure in which *each member differs from the one below it and the one above it by CH_2.* It will be noted that all the compounds of this series correspond to a **general formula** $C_nH_{2n+1}OH$. That is, the number of hydrogen atoms (not including that of the OH group) is one more than twice the carbon atoms.

Isomeric Propyl and Butyl Alcohols. When we come to the substance C_3H_7OH in the homologous series of alcohols, we find

Name	*General Formula*	*Difference*	*Number of Isomers*
Methyl alcohol	CH_3OH		One substance
		$\rangle CH_2$	
Ethyl alcohol	C_2H_5OH		One substance
		$\rangle CH_2$	
Propyl alcohols	C_3H_7OH		Two substances
		$\rangle CH_2$	
Butyl alcohols	C_4H_9OH		Four substances
		$\rangle CH_2$	
Amyl alcohols	$C_5H_{11}OH$		Eight substances

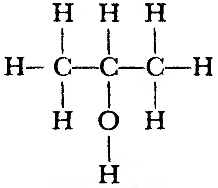
that *more than one substance is represented by the formula.* In other words, a more subtle type of isomerism than that shown by ethyl alcohol and dimethyl ether is now at hand. The reason for this is evident from a consideration of the complete structural formulas of such substances. Bearing in mind the rules in regard to the valence of the different atoms and the fact that all the substances contain one hydroxyl group, we find that there are two and *only two* ways of arranging the atoms in C_3H_7OH.



$$\begin{array}{ccccccccccc} & & H & & H & & H & & & & \\ & & | & & | & & | & & & & \\ H & - & C & - & C & - & C & - & O & - & H \\ & & | & & | & & | & & & & \\ & & H & & H & & H & & & & \end{array}$$

Normal propyl alcohol

and



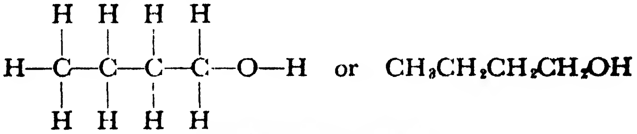
$$\begin{array}{ccccccccc} & & H & & H & & H & & \\ & & | & & | & & | & & \\ H & - & C & - & C & - & C & - & H \\ & & | & & | & & | & & \\ & & H & & O & & H & & \\ & & & & | & & & & \\ & & & & H & & & & \end{array}$$

Isopropyl alcohol

These formulas are usually written as $CH_3CH_2CH_2OH$ and $CH_3CHOHCH_3$. There are actually two and *only* two substances C_3H_7OH; one is normal propyl alcohol boiling at 98°, the other is isopropyl alcohol which boils at 82°.

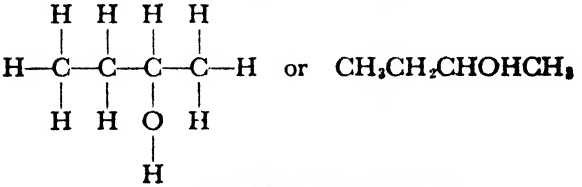
At first sight it might appear that there were many different ways of arranging the atoms in the molecule C_3H_7OH, all of which conformed to the rules of valence. That this is not so will be most quickly and convincingly demonstrated by actual trial with a pencil and paper. It will be remembered that the linkage of two carbon atoms through oxygen is excluded from the possibilities by the fact that the compound has a hydroxyl group; it is an alcohol. Hydrogen has only one valence bond and therefore cannot serve to join two other atoms together. Therefore the three carbon atoms must be joined in a chain. The position of the hydroxyl group is the only variable left. This group may be placed at the right end, in the center, or at the left end. The seven hydrogen atoms of C_3H_7OH now will be found sufficient to occupy the seven remaining bonds of the three carbon atoms. A moment's consideration will convince one that there is no difference between the two ends of this symmetrical chain of carbon atoms. Whether the hydroxyl group is written at the left end or the right end is without significance. Both arrangements represent the same linkage; they could be cut out and superimposed on each other by merely turning through 180°. The arrangement with the hydroxyl group in the center is different. This cannot be superimposed on the other formula because the hydroxyl group is attached to a carbon atom in the middle of the chain. Thus, in one formula we have the group $>CHOH$, in the other $-CH_2OH$.

The **isomerism of the butyl alcohols,** C_4H_9OH, is represented by the following structural formulas.



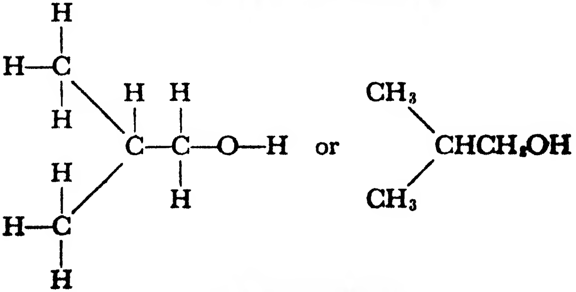
$$\begin{array}{ccccccccccc} & & H & & H & & H & & H & & \\ & & | & & | & & | & & | & & \\ H & - & C & - & C & - & C & - & C & - & O-H \\ & & | & & | & & | & & | & & \\ & & H & & H & & H & & H & & \end{array} \quad \text{or} \quad CH_3CH_2CH_2CH_2OH$$

Normal primary butyl alcohol

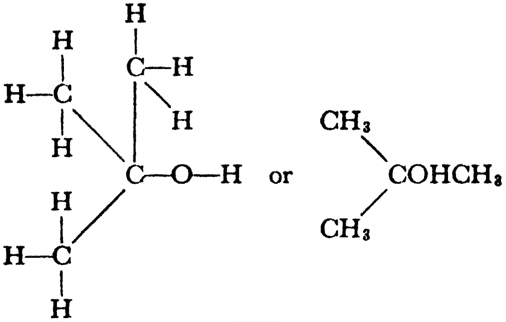


$$\begin{array}{ccccccccccc} & & H & & H & & H & & H & & \\ & & | & & | & & | & & | & & \\ H & - & C & - & C & - & C & - & C & - & H \\ & & | & & | & & | & & | & & \\ & & H & & H & & O & & H & & \\ & & & & & & | & & & & \\ & & & & & & H & & & & \end{array} \quad \text{or} \quad CH_3CH_2CHOHCH_3$$

Normal secondary butyl alcohol



Primary isobutyl alcohol



Tertiary butyl alcohol

Thus, with the aid of the structural theory, we can predict the number of isomeric propyl alcohols and butyl alcohols and test the prediction by experiment. Repeated trials in many laboratories have shown that such predictions of the structural theory are always verified. By working long enough and hard enough, it is usually possible to make the number of isomers required by the theory, but more than this number have never been found. Since the number of isomers increases very rapidly as one goes up a homologous series, many isomers of the higher members have not yet been prepared. However, since our experimental facts and the predictions of the structural theory coincide so precisely in the lower members of this and other series, we feel perfectly confident that in time exactly the number of isomers demanded by the theory could be prepared in each case.

Conventions Used in Writing Formulas. Organic chemists write structural formulas in a condensed form, and the student would do well to master the conventions employed. The extended formulas of the butyl alcohols (sometimes called *spider-web formulas*) which are printed on the left on pp. 12 and 13 are helpful at first in understanding the theory of linkages, but the student should use them as little as possible. The conventions used will be apparent from these examples; the usual formula is printed on the right. It should be noted that we write the group of carbon and hydrogen atoms after each other in straight-chain compounds and show their connection by bonds in branched-chain compounds; other groups or atoms follow the hydrogen.

Three-Dimensional Models. The theory of linkages was developed to explain the isomerism of organic compounds. The structures of many substances were deduced from their reactions and transformations very much as we have done for ethyl alcohol and dimethyl ether. In the last twenty years evidence as to the correctness of these conclusions has accumulated as a result of the work of physicists and physical chemists. Their work has put structural theory on a quantitative basis by determining the distances between the centers of the atoms in various compounds and by determining the angles between the valence bonds. As a result we can construct three-dimensional models of simple organic molecules with considerable assurance. It is important for the student to get used to thinking of formulas in three-dimensional terms as quickly as possible. This can best be done by handling models built to scale.

The information about atomic distances in organic compounds has come from measurements of the diffraction of x rays by crystals and the diffraction of an electron beam by gases. The interatomic distances which are of most interest to us are:

Interatomic Distance		*Sum of Radii of Atoms*
C—C	1.54 Å[*]	0.77 + 0.77 Å
C—H	1.07 Å	0.77 + 0.30 Å
C—O	1.43 Å	0.77 + 0.66 Å
O—H	0.96 Å	0.66 + 0.30 Å

Such distances would result if the atomic radii were essentially the same in all related compounds and were as follows: carbon 0.77, oxygen 0.66, hydrogen 0.30. These radii are modified in certain types of compounds.

Examination of three-dimensional models will show that in all but the simplest compounds there are many ways in which the atoms in a chain may be placed with regard to each other. In the solid state there is one stable relation which is believed to correspond in most compounds to a zigzag chain. In the liquid form, in solution, or in gases, however, the molecules through thermal agitation take various shapes though certain configurations may be more favored than others. But the different shapes into which the same model can

[*] The Ångstrom unit, Å, is one one hundred millionth (10^{-8}) of a centimeter.

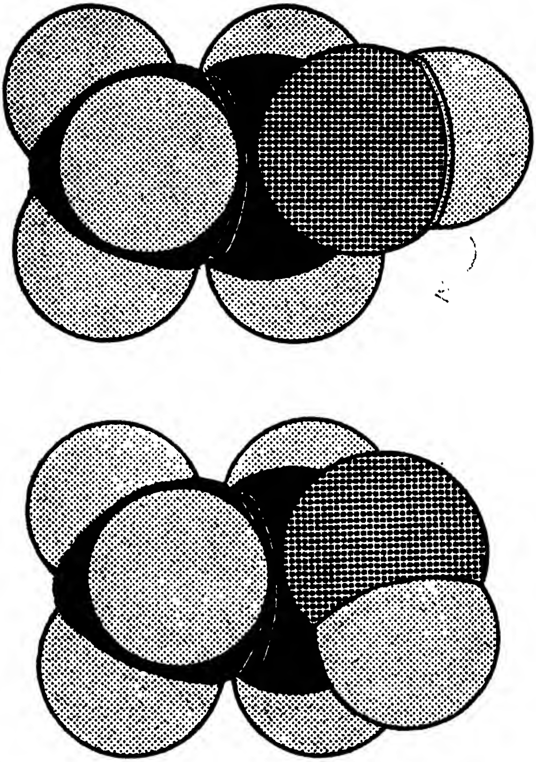


Fig. 1. These scale drawings show two of the shapes which can be assumed by the ethyl alcohol molecule, CH_3CH_2OH. In the drawings the carbon atoms are black, the hydrogen atoms are lightly dotted, and the oxygen atom is heavily dotted. The arrangement in the lower drawing is obtained from that in the upper drawing by a clockwise rotation of some 90° of the hydroxyl group along the bond between the oxygen atom and the carbon atom of the CH_2 group. Larger or smaller rotations around the same bond and around the bond between the two carbon atoms can give rise to many other arrangements of this simple molecule. The two arrangements shown above were selected because they can be illustrated clearly.

be twisted *do not correspond to different isomers.* This is an important point for the student to understand at the outset in considering the spatial arrangements of the atoms in a molecule.

The energy required to change any one arrangement into another (a change which involves no breaking of bonds, only rotation about bonds) is so slight that all the molecules in a gas or a liquid or solution would never be lined up in this one way; rather they would be distributed at random among the many different spatial relations which would result by twisting the atoms with reference to each other.

Because a model may be twisted into so many shapes, it is difficult to depict it on paper without implying that one relationship is more important than another. Therefore, we shall use pictures of three-dimensional models only occasionally and continue to use the two-dimensional formulas to represent the structures of almost all the organic compounds considered in this book. It is essential, however, for the student to construct three-dimensional models for himself and to learn to visualize organic structures in three dimensions.

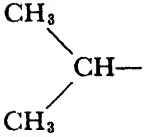
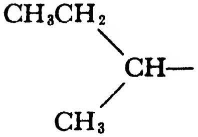
Classification of Alcohols. Since there are only two isomeric propyl alcohols, it is possible to refer to them by using the terms *normal* and *iso.* By using the word *normal* to indicate a straight chain (abbreviated by *n*-, thus *n*-propyl alcohol) and the prefix *iso-* to denote a forked chain, a fairly satisfactory method of naming the butyl alcohols can also be developed. Furthermore, an examination of the various butyl alcohols will show that they can be arranged into the three following groups: (1) those having the grouping $—CH_2OH$ which are called *primary* alcohols; (2) those having the grouping $\rangle CHOH$ which are called *secondary;* (3) those with the grouping $-\!\!\rangle COH$ which are designated as *tertiary* alcohols.

Naming Primary Alcohols. The first five normal straight-chain alcohols are named in the table below. The alcohols with six or more carbon atoms are usually named with a Greek prefix indicating the number of carbon atoms. For example, the normal alcohol $C_{10}H_{21}OH$ is *n*-decyl alcohol. The general formula for each group of alcohols is easily written by recalling that a general formula for the series is $C_nH_{2n+1}OH$.

Naming Secondary and Tertiary Alcohols. Where there are only a few isomers, it is possible to find simple names for the different isomeric alcohols as is done with the butyl alcohols given in the table on p. 19. There is only one secondary and only one tertiary butyl alcohol. But higher in the series we get into difficulty. There are three secondary alcohols isomeric with *n*-amyl alcohol, $C_5H_{11}OH$. How are they to be named?

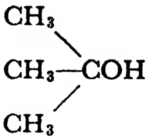
A convenient method of naming alcohols is to regard them as though they were built up by taking methyl alcohol, CH_3OH, and replacing one or more of the hydrogens of the CH_3 by groups of carbon and hydrogen atoms called *alkyl groups*. These groups in turn are named from the alcohol to which they are related. Thus the CH_3 group of methyl alcohol is known as the *methyl group*, the CH_3CH_2 or C_2H_5 of ethyl alohol is known as the *ethyl group*, and so on.

The following are the common alkyl groups.

CH_3—	**Methyl group**
CH_3CH_2— or C_2H_5—	**Ethyl group**
$CH_3CH_2CH_2$—	**Normal propyl group**
	**Isopropyl group**
	**sec-Butyl group**

When we consider complex alcohols as derivatives of methyl alcohol, CH_3OH, this latter substance is called *carbinol*. We then name the alkyl groups which are attached to the carbon atom which holds the OH group. Such alkyl groups are *substituents* since they may be regarded as having been substituted in place of hydrogen atoms of the parent substance, CH_3OH or carbinol.

Trimethylcarbinol is:

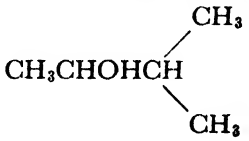


This is also written as $(CH_3)_3COH$.

The three isomeric secondary amyl alcohols are:

Methylpropylcarbinol, $CH_3CHOHCH_2CH_2CH_3$

Methylisopropylcarbinol,



which is also written $CH_3CHOHCH(CH_3)_2$; and

Diethylcarbinol, $CH_3CH_2CHOHCH_2CH_3$

Physical Properties of Alcohols. If we compare the boiling points of the normal primary alcohols in the homologous series $C_nH_{2n+1}OH$, we find a gradual and regular increase in the boiling point as the molecular weight increases. Beginning with the second member of the series the boiling point increases by about 20° with each added CH_2 group.

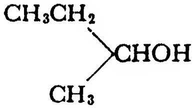
PHYSICAL PROPERTIES OF NORMAL PRIMARY ALCOHOLS

Name	*Formula*	*Boiling Point*	*Density at 25°*	*Solubility Grams per 100 grams of Water at 20°*
Methyl alcohol	CH_3OH	65°	0.792	∞
Ethyl alcohol	CH_3CH_2OH	78°	0.785	
Propyl alcohol	$CH_3CH_2CH_2OH$	98°	0.799	
Butyl alcohol	$CH_3CH_2CH_2CH_2OH$	118°	0.805	8.3
Amyl alcohol	$CH_3C_2CH_2CH_2CH_2CH_2OH$	138°	0.816	2.6
Hexyl alcohol	$CH_3CH_2CH_2CH_2CH_2CH_2OH$	156°	0.820	Less than 1

The higher members of the series are solids at room temperature. Thus *n*-decyl alcohol, $C_{10}H_{21}OH$, melts at 7°. The normal primary alcohol with the formula $C_{32}H_{65}OH$ melts at 89°.

The isomeric alcohols differ in boiling point as illustrated by the table just below. In general, for a group of isomeric alcohols, branching the carbon chain lowers the boiling point but increases the solubility in water.

PHYSICAL PROPERTIES OF THE ISOMERIC BUTYL ALCOHOLS

Name	*Formula*	*Boiling Point*	*Density at 25°*	*Solubility Grams per 100 Grams of Water at 20°*
n-Butyl alcohol (butanol)	$CH_3CH_2CH_2CH_2OH$	118°	0.805	8.3
Isobutyl alcohol	$(CH_3)_2CHCH_2OH$	108°	0.804 (at 16°)	23
Secondary butyl alcohol	 $\begin{matrix} CH_3CH_2 \\ \\ CH_3 \end{matrix}\!\!>\!CHOH$	100°	0.807	13
Tertiary butyl alcohol	$(CH_3)_3COH$	83°	0.780	Completely miscible

Industrial Alcohol. Industrial ethyl alcohol is prepared in America from petroleum by a process to be described later (p. 78) and by the fermentation of the residues from the purification of cane sugar, which are known as *molasses*. These are fermented with yeast until a 6 to 10 per cent solution of alcohol is obtained which is then fractionally distilled yielding 95 per cent alcohol. Industrial alcohol can be made from potatoes, grain, or other starchy substances by first allowing malt to change the starch into sugar and then fermenting and distilling. The transformations involved in these processes are brought about by enzymes present in the malt and in the living yeast cell; they will be considered in detail in Chap. 15.

Methyl alcohol was formerly prepared by the destructive distillation of wood and hence was called *wood alcohol*. It is now made industrially by the combination of hydrogen and carbon monoxide, a reaction which will be discussed in detail in Chap. 9.

Uses of Methyl and Ethyl Alcohol. At present, methyl and ethyl alcohols are used as starting materials for the manufacture of many other organic substances, since they are relatively cheap. They are also used widely as solvents, because they dissolve a great variety of substances which do not dissolve in water. The paint and varnish industry, for example, uses large quantities of both alcohols. The perfume, flavoring, and pharmaceutical industries use ethyl alcohol for preparing solutions of perfumes, flavors, and drugs. Extract of vanilla is an ethyl alcoholic solution of the flavoring constituent of the vanilla bean. Tincture of iodine is an ethyl alcoholic solution of iodine. Indeed, the words *extract* and *tincture*, when thus used, almost invariably denote ethyl alcoholic solutions. Because of its poisonous effect on the human system, methyl alcohol cannot be used for such purposes. Methyl and ethyl alcohols are widely used in antifreeze mixtures for automobiles.

Ethyl alcohol is subject to a very heavy tax in all countries, and its sale is strictly regulated in the United States. If it is made unsuitable for drinking by the addition of methyl alcohol or other substances, it can be sold tax-free in most countries, including the United States. Such alcohol is said to be *denatured*. Methyl alcohol is the principal substance used for denaturing ethyl alcohol. In addition, certain amounts of evil-smelling substances are often included in order to afford a warning that the liquid is poisonous. The use of specially denatured alcohol with only slightly poisonous ingredients is allowed under government supervision in the manufacture of pharmaceutical preparations and in certain other industries. *Solid alcohol* is denatured alcohol containing a small amount of soap or nitrocellulose which causes the formation of a jelly.

Absolute Alcohol. Specially purified methyl and ethyl alcohols, free from water and other impurities, are known as *absolute methyl alcohol* and *absolute ethyl alcohol*. By careful distillation with a fractionating column, methyl alcohol can be obtained practically free from water. The last 5 per cent of water cannot be removed from ethyl alcohol in this way. It can be removed by boiling the 95 per cent alcohol with calcium oxide. The calcium oxide combines with the water, forming calcium hydroxide, and the alcohol is left unchanged and can be finally distilled. This is the method commonly employed in the laboratory. Industrially, absolute ethyl alcohol is prepared by taking advantage of the fact that a mixture of benzene (C_6H_6), water, and ethyl alcohol in the proportions 74.1 per cent benzene, 7.4 per cent water, 18.4 per cent alcohol distils at a lower temperature than any one of the three pure substances. Benzene is added to the 95 per cent alcohol, and the mixture carefully distilled; the first fraction (bp 65°) consists of the azeotropic mixture of benzene, water, and alcohol just mentioned. After all the water has thus been removed, the boiling point rises to about 68°, and the distillate is a mixture of alcohol and benzene; finally absolute alcohol distils at 78.3° and is collected. Absolute alcohol slowly absorbs water from the air, and must be kept carefully sealed in order to remain free from water.

Industrial Uses of Higher Alcohols. A number of the higher alcohols are produced industrially; they are used as solvents either directly or in the form of their esters (compounds which are readily formed from the alcohols as will be described in Chap. 7). They are also used as the starting point in the manufacture of a number of other organic compounds of industrial importance. The most important higher alcohol from the industrial standpoint is ***n*-butyl alcohol (butanol),** $CH_3CH_2CH_2CH_2OH$, prepared from cornstarch. **Normal propyl alcohol,** $CH_3CH_2CH_2OH$, two secondary alcohols, **isopropyl alcohol,** $CH_3CHOHCH_3$, and **secondary butyl alcohol,** $CH_3CHOHCH_2CH_3$, and a tertiary alcohol, **tertiary butyl alcohol,** $(CH_3)_3COH$, as well as a number of the isomeric amyl alcohols, $C_5H_{11}OH$, are manufactured from petroleum and natural gas (Chap. 5).

Some normal alcohols of longer straight chains are now of industrial importance. Among these are lauryl alcohol, $C_{12}H_{25}OH$, cetyl alcohol, $C_{16}H_{33}OH$, and stearyl alcohol, $C_{18}H_{37}OH$. These alcohols are used as emulsifying agents, as bases for pharmaceutical preparations, and in making detergents (p. 133). They are manufactured by methods to be described later.

Chemical Properties of the Alcohols. The characteristic grouping of the alcohols is the hydroxyl group. We have already seen that this group in ethyl alcohol can react in two different ways (equations 1*b* and 2*b*, p. 8). The hydrogen atom attached to oxygen may be replaced, as in the formation of **sodium ethoxide** (C_2H_5ONa), by the action of metallic sodium. This is a general reaction of alcohols; metallic potassium reacts in the same manner as sodium, and aluminum and magnesium react similarly in the presence of a very small amount of mercury. The resulting compounds, which are obtained as colorless crystalline solids by boiling off the excess alcohol, are known as *alkoxides*. The student will readily recognize that in this reaction the alcohols resemble the inorganic acids by having a hydrogen replaceable by metals. However, the common metals such as zinc and iron, which will react with acids, are without effect on alcohols; furthermore, alcohols in water solution are not neutralized by bases; instead the compound C_2H_5ONa is completely hydrolyzed by water, forming alcohol and sodium hydroxide.

$$C_2H_5ONa + H_2O \longrightarrow C_2H_5OH + NaOH$$

For these reasons we do not usually regard alcohols as acids.

The alkoxides form an important and useful group of derivatives of the alcohols. They are the organic equivalents of the strong inorganic bases, sodium or potassium hydroxide, and they can be used as such in organic solvents. Besides this general use, the student will encounter special uses from time to time (see p. 89). Sodium methoxide and several of the aluminum alkoxides are now available commercially.

The interaction of phosphorus trichloride and ethyl alcohol illustrates a second type of reaction in which the whole *hydroxyl group* is replaced. We shall consider in the next chapter a number of reactions of the alcohols which lead to the production of many interesting and important substances. All these reactions fall into one of two classes; either the hydrogen atom of the hydroxyl group is involved or the entire hydroxyl group is replaced by another atom or group. These replacement reactions are characteristic of all the compounds $C_nH_{2n+1}OH$ irrespective of whether they are primary, secondary, or tertiary alcohols.

The lower members of the alcohol series resemble water, as might be expected from the presence of a hydroxyl group. With the increase of the number of carbon atoms in the molecule, the influence of the hydroxyl group becomes less pronounced and the similarity to water becomes less evident. This is clearly seen in the progressive decrease in the solubility in water of the alcohols above propyl. Another illustration of the same principle is seen in the fact that methyl and ethyl alcohol combine with a number of inorganic salts such as calcium chloride forming crystalline compounds containing *alcohol of crystallization;* for example, $CaCl_2 \cdot 4C_2H_5OH$; $MgCl_2 \cdot 6CH_3OH$. The analogy between alcohol of crystallization and water of crystallization is evident. The higher alcohols do not combine with inorganic salts in this manner.

QUESTIONS AND PROBLEMS

1. Write balanced equations for the reaction between phosphorus trichloride and each of the following alcohols: isopropyl alcohol, methylpropylcarbinol, and isobutyl alcohol.

2. Write structural formulas for all the amyl alcohols.

3. What is absolute alcohol, and how is it prepared?

4. Define and illustrate the following terms: *structural formula*, *empirical formula*, and *molecular formula*.

5. How are the alkoxides prepared, and what are their uses?

6. Do the following pairs of formulas represent the same or different substances?

(*a*) $CH_3CH_2CH_2CHOHCH_3$ and $CH_3CH_2CHOHCH_2CH_3$

(*b*) $CH_3CH_2CH_2CH_2CH_2OH$ and $HOCH_2CH_2CH_2CH_2CH_3$

Name each of the substances.

7. Define and illustrate the terms *isomerism* and *homologous series.*

8. Write balanced equations for the reactions between: (*a*) magnesium and methyl alcohol, (*b*) potassium and *tert*-butyl alcohol, (*c*) aluminum and ethyl alcohol.

9. Classify the following alcohols according to whether they are primary, secondary, or tertiary: $(CH_3)_3CCH_2CH_2CH_2CH_2OH$, $CH_3CH_2CHOHCH_3$, $(CH_3)_3COH$, $(CH_3)_2CHCH_2OH$.

10. Arrange the following primary alcohols in the order of (*a*) decreasing solubility in water, (*b*) increasing boiling point: CH_3CH_2OH, $CH_3CH_2CH_2CH_2CH_2CH_2OH$, $CH_3CH_2CH_2CH_2OH$.

CHAPTER 2

Alkyl Halides and Ethers

In this chapter we shall continue our study of the alcohols by examining in more detail some of their general reactions and the substances which can be prepared from them by these reactions. We have already seen that a substance C_2H_5Cl is formed by the interaction of phosphorus trichloride and ethyl alcohol. It is a representative of one of the most important classes of organic compounds, the *alkyl halides.* Since they are readily prepared from the alcohols and in turn can be transformed into many compounds, we shall find that the alkyl halides are of great value to the chemist.

ALKYL HALIDES

The alkyl halides are compounds in which the hydroxyl group of an alcohol has been replaced by a halogen atom. For example, **methyl chloride,** CH_3Cl, may be prepared from methyl alcohol, CH_3OH, or **ethyl chloride,** C_2H_5Cl, from ethyl alcohol, C_2H_5OH. If we let **R** represent any alkyl group, **ROH** is an alcohol and **RCl** an alkyl chloride.

Preparation of Alkyl Halides. Alkyl chlorides, bromides, and iodides are readily prepared by either of two methods. These may be illustrated by the equations for preparing ethyl iodide.

1. $C_2H_5OH + HI \xrightarrow{\text{Distil}} C_2H_5I + H_2O$
2. $3C_2H_5OH + P + 3I \longrightarrow 3C_2H_5I + P(OH)_3$

Both methods can be used with any simple alcohol. The second is commonly employed for preparing iodides; the iodine and phosphorus first react, forming phosphorus triiodide, this then reacts with the alcohol. Similarly, if one uses phosphorus tribromide or phosphorus trichloride instead of a mixture of phosphorus and iodine, the corresponding bromide and chloride can be prepared. Indeed, this is the reaction we first used to prove that ethyl alcohol contained a hydroxyl group.

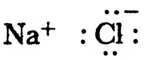
Physical Properties. The properties of certain of the alkyl halides are tabulated below. It is convenient to remember that the simplest chloride which is a liquid at room temperature is the propyl compound, the simplest bromide the ethyl compound, and that methyl iodide is the only methyl halide which is not a gas under ordinary conditions. The general effect on the boiling point of increasing the molecular weight is well illustrated by the alkyl halides. The alkyl halides are all practically insoluble in water, and the bromides and iodides have a density greater than one.

REPRESENTATIVE ALKYL HALIDES

Name	*Formula*	*Boiling Point*	*Density at 20°*
	Chlorides		
Methyl chloride	CH_3Cl	−24°	0.991 (at −24°)
Ethyl chloride	CH_3CH_2Cl	+12°	0.910
n-Propyl chloride	$CH_3CH_2CH_2Cl$	47°	0.890
Isopropyl chloride	$CH_3CHClCH_3$	37°	0.860
	Bromides		
Methyl bromide	CH_3Br	+5°	1.732 (at 0°)
Ethyl bromide	CH_3CH_2Br	38°	1.430
n-Propyl bromide	$CH_3CH_2CH_2Br$	71°	1.353
Isopropyl bromide	$CH_3CHBrCH_3$	60°	1.310
	Iodides		
Methyl iodide	CH_3I	+43°	2.279
Ethyl iodide	CH_3CH_2I	72°	1.933
n-Propyl iodide	$CH_3CH_2CH_2I$	102°	1.747
Isopropyl iodide	CH_3CHICH_3	90°	1.703

Ionic and Covalent Bonds. A comparison of the alkyl halides with the halides of the alkali metals will bring out a distinction that is essential to an understanding of organic chemistry. The student will certainly have encountered earlier in his study of chemistry the distinction between a **covalent linkage** or bond and an **electrovalent linkage** or bond: in a covalence two electrons are shared between two atoms; in an electrovalence one electron is transferred from one atom to another and electrostatic charges on the atoms result. In the alkyl halides we have covalences; in the alkali halides, electrovalences.

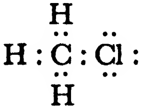
Ionic Bond



$\mathrm{Na^+}\ \ :\!\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{Cl}}}\!:^-$

Complete transfer of one electron. Ions independent and move freely in the molten salt or in solutions; held in rigid crystal lattice in the solid. Sodium and chlorine in the molecules of the gas (above *ca.* 1500°) held together by electrostatic force.

Covalent Bond



$\mathrm{H}:\underset{\mathrm{H}}{\underset{\cdot\cdot}{\overset{\mathrm{H}}{\overset{\cdot\cdot}{\mathrm{C}}}}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{Cl}}}:$

Two electrons shared between carbon and chlorine, as between carbon and hydrogen. Four covalent bonds; no ions.

These two different types of linkages are reflected in the different properties and behavior of the compounds in which they occur. In their physical properties we have the following contrasts.

Alkyl Halides, e.g., CH_3Cl	Alkali Halides, e.g., NaCl
Low-boiling liquids; boiling points increase regularly with increasing molecular weight.	High-melting solids; vaporized only at extremely high temperatures.
Nonconductors of electricity.	Conduct electricity with electrolytic decomposition in the molten state or in solution.
Soluble in non-ionic solvents. Insoluble in water.	Soluble in water. Insoluble in non-ionic solvents.

In their reactions we have the equally striking contrast that the ionic compounds in solution react practically instantaneously and show the reactions characteristic of the ions involved; while the non-ionic compounds require appreciable time for reaction, and each compound differs slightly in its behavior from the others.

Most molecules are neither so completely ionic nor non-ionic as the examples just cited. And some molecules are so nicely balanced that their character depends upon the environment. Most organic compounds, however, are essentially non-ionic, with the result that low melting and boiling points, solubility in organic solvents, and appreciable reaction times are the rule in organic chemistry. The exceptions to the rule will be noted as they are encountered.

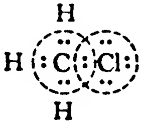
Electronic Theory of Valence. The difference in physical properties and chemical behavior of the alkyl halides and the halides of the alkali metals is explained very satisfactorily by the electronic theory of valence. This theory, which has been developed in the last thirty-five years, now stands on as firm ground as did the atomic theory seventy-five years ago. The student would do well to review the elements of this theory which are given in modern elementary books on inorganic chemistry. Here we may summarize for convenience that portion of the theory which is of particular significance to the study of organic chemistry.

Each atom is composed of a dense nucleus and a surrounding group of electrons which it is convenient to think of as arranged in shells. In the electrically neutral atom the positive charge on the nucleus is numerically equal to the total number of surrounding electrons. Only the electrons in the outermost shell of the common elements are concerned in chemical reactions. Therefore it is not the total number of electrons around an atom that is worth remembering, but the normal number in the outer shell. For the elements commonly met with in organic chemistry, the numbers are as follows.

Hydrogen	*Carbon*	*Nitrogen*	*Oxygen*	*Sulfur*	*The Halogens*
H	C	N	O	S	X
1	4	5	6	6	7

(The halogens, Cl, Br, I, are here represented by the symbol X, a convention often used in organic chemistry. Fluorine is not included in this summary formulation, for, as we shall see, the alkali fluorides are rather unlike the chlorides, bromides, and iodides.)

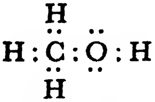
When an ionic or electrovalent bond is established there is a complete transfer of an electron from one atom to another as in sodium chloride. The reason why such a transfer takes place seems to be closely connected with the great stability of a grouping of eight electrons (an octet) in the outer shell of the many nonmetallic elements. This same arrangement of electrons can also be achieved, however, by the sharing of electrons, as in the covalent bond of two electrons. Thus in methyl chloride the carbon and chlorine atoms can both be considered to have complete octets if we count in both octets the two electrons shared by carbon and chlorine, and if we count the hydrogen-carbon bond electrons also as part of the carbon octet. In the following diagram each octet is circumscribed by a dotted line; it will be seen that the octets interpenetrate.



$$\begin{array}{ccccccc} & & \mathrm{H} & & & & \\ \mathrm{H} & : & \underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{C}}} & : & \underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{Cl}}} & : & \\ & & \mathrm{H} & & & & \end{array}$$

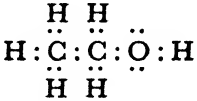
The electrons of a covalent bond need not be shared equally by the two atoms involved. In methyl chloride the electrons of the carbon-chlorine bond are held more firmly by chlorine than carbon. This results in a *polar molecule* in which one part is electrically charged with respect to another part but which is electrically neutral as a whole. The gradations between completely ionic and completely non-ionic molecules referred to above correspond to the *degree of polarity* of individual bonds.

Electronic Formulas of Alcohols. We are now in a position to write electronic formulas also for the compounds discussed in Chap. 1, the alcohols.



$$\begin{array}{ccccccc} & & \mathrm{H} & & & & \\ \mathrm{H} & : & \underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{C}}} & : & \underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{O}}} & : & \mathrm{H}\\ & & \mathrm{H} & & & & \end{array}$$

Methyl alcohol



$$\begin{array}{ccccccccc} & & \mathrm{H} & & \mathrm{H} & & & & \\ \mathrm{H} & : & \underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{C}}} & : & \underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{C}}} & : & \underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{O}}} & : & \mathrm{H}\\ & & \mathrm{H} & & \mathrm{H} & & & & \end{array}$$

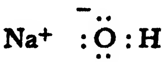
Ethyl alcohol

$$\mathrm{H} : \underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{O}}} : \mathrm{H}$$

Water

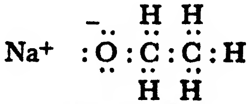
The electronic formula for water is given for comparison.

The linkages in these three compounds are all covalences. However, by the replacement of the hydroxyl hydrogen atom by a metal such as sodium (p. 8) a substance is formed which has one ionic bond. Thus with water we have sodium hydroxide; with ethyl alcohol, sodium ethoxide.



$$\mathrm{Na^+} \quad \overset{-}{:\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{O}}}} : \mathrm{H}$$

Sodium hydroxide



$$\begin{array}{cccccccc} & & & \mathrm{H} & & \mathrm{H} & & \\ \mathrm{Na^+} & \overset{-}{:\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{O}}}} & : & \underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{C}}} & : & \underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{C}}} & : & \mathrm{H}\\ & & & \mathrm{H} & & \mathrm{H} & & \end{array}$$

Sodium ethoxide

In each compound we have a positive sodium ion and a negative ion in which the oxygen atom has a negative charge, namely the hydroxyl ion and the ethoxide ion.

The reason for the negative charge on oxygen is evident if we remember that the neutral oxygen atom has only six electrons in the outer shell. If we count the electrons in the above formulas we see that one electron in the oxygen octet has been obtained by transfer. Or, to put it another way, the oxygen has seven electrons, one more than its normal quota, and carries a negative charge.

Reactions of Alkyl Halides. The alkyl chlorides, bromides, and iodides enter into a number of characteristic reactions which are of great importance in organic chemistry. The halogen atom in an organic molecule usually represents a point of attack and can often be replaced by another atom or group. Several illustrations of this type of *metathetical reaction* are given below.

$$CH_3\boxed{I + Na}CN \longrightarrow CH_3CN + NaI$$

$$CH_3\boxed{I + Na}OCH_3 \longrightarrow CH_3OCH_3 + NaI$$

$$CH_3\boxed{I + Ag}OH \longrightarrow CH_3OH + AgI$$

$$R\boxed{X + Ag}OH \longrightarrow ROH + AgX$$

In all such metathetical reactions the iodides react most rapidly, the chlorides least rapidly, the bromides occupying an intermediate position.

Another metathetical reaction of alkyl halides is the replacement of one halogen atom by another. This is carried out by heating an alkyl halide with an inorganic halide in an anhydrous solvent (anhydrous acetone and lithium or potassium halides are often employed).

$$C_2H_5Br + KI \longrightarrow C_2H_5I + KBr$$

Variations in Rates of Reaction. Reactions involving covalent bonds are obviously very different from the ionic reactions with which the student is familiar from his study of the behavior of simple inorganic salts in aqueous solution. Almost all the transformations of organic chemistry involve the breaking and making of covalent bonds: as examples, the four metathetical reactions of the alkyl halides just given may be mentioned. Such reactions, unlike ionic reactions, take an appreciable time for completion. The speed or rate of the reactions usually varies enormously with changes in the experimental conditions. The factors affecting the rate of reaction of a given substance are in general: (1) concentration of the reacting substance (in the gas phase, pressure), (2) temperature, (3) solvent, (4) catalysts. To attempt to give the exact or quantitative relation between the rates of each type of reaction and these variables is beyond the province of this book. In a general or qualitative sense, the following rules are valid: the rates of most organic reactions are increased by increasing the concentration of both reactants, by increasing the temperature, and by the presence of small amounts of materials known as *catalysts*.

If one of the reactants is an ionic substance (as in the metathetical reactions given on p. 29), its solubility in the non-ionic organic compound is very low. Therefore a solvent which will dissolve both reactants is employed. This increases the concentration of the ionic substance very greatly. Ethyl alcohol is frequently employed for this purpose as most non-ionic substances of low molecular weight are very soluble in it, and even ionic substances are slightly soluble. It is thus common practice to use ethyl alcohol in the reaction between sodium cyanide and an alkyl halide. Where no solvent can be found, as in the reaction involving silver hydroxide, the solid is used in as fine a state of subdivision as can be achieved. The size of the particles and the way the material is prepared have profound effects on the rate.

Obviously one wants a reaction to proceed as rapidly as possible in the laboratory or in industry (provided it does not go with explosive speed!), therefore it is usual to operate at a temperature at which the reaction is nearly complete in a few hours. **In general, raising the temperature 10° doubles the rate of an organic reaction.** In the laboratory the boiling point of the reactants or the solvent conveniently determines the temperature when a return or reflux condenser is employed. If one of the reactants is a gas or a very volatile liquid, however, for example, ethyl chloride, temperatures above room temperature can be obtained only under pressure. In such cases the reaction mixture is placed in a tightly closed metal cylinder known as an *autoclave* (Fig. 13, p. 286). These autoclaves are of many sizes for use in the laboratory or in industry. They are built to stand high pressures and are often equipped for heating electrically or by steam under pressure.

As a reaction proceeds toward completion the rate diminishes because the concentrations of the reactants fall off as they are used up. If one substance is much more valuable than another, it is common practice to use a large excess (two- or threefold, perhaps) of the cheaper reactant; under these conditions only the concentration of the other reactant diminishes toward the end and the speed does not fall off so rapidly. As the student soon learns from his experience in the laboratory, very few reactions in organic chemistry ever are quantitative; that is, go to 100 per cent completion. Not only would it take a very long time to use up the last fraction of a per cent of initial material, but also side reactions leading to other products almost always occur. Indeed, it is to avoid these competing side reactions and thus obtain the maximum yield of the desired product, that the chemist in the laboratory seeks to find the most advantageous combination of temperature, solvent, concentration of reactants, and catalysts. Herein lies the art of organic chemistry as a laboratory science.

Effect of Structure on Reaction Rates. As already stated, in the metathetical reactions of the alkyl halides the iodides react more rapidly than the bromides, which in turn react more rapidly than the chlorides. The methyl halides react somewhat more rapidly than the derivatives of the higher normal alcohols, but the differences are not great. On the other hand the rates of reaction of the halides derived from secondary and tertiary alcohols are often markedly different from those of the primary compounds. For example, in the interaction with an alkali metal iodide (e.g., sodium iodide) tertiary butyl chloride requires about fifty times longer than does normal butyl chloride for the reaction to reach a given point; in general the secondary halides lie in between such extremes.

Reaction between Alcohols and Halogen Acids. While the rates of the metathetical reactions of the halides of isomeric alcohols are in the order primary > secondary > tertiary, the speed of formation of the halides from the alcohol and an acid is just the opposite. Tertiary butyl alcohol, for example, when mixed with concentrated hydrochloric acid at room temperature forms tertiary butyl chloride in a few minutes. Normal butyl alcohol in the same reaction, however, reacts so slowly that zinc chloride must be used as a catalyst to give an appreciable yield in a practical period of time. It should be pointed out in this connection that, with those alcohols which are slightly soluble in water, aqueous acids cannot be used. Instead the alcohol is saturated with dry hydrogen halide gas. The speed of the reaction under these conditions is in the following decreasing order: $HI > HBr > HCl$.

Significance of Conditions. When we write the equation for a reaction in organic chemistry we should note the special conditions over the arrow. If no special conditions are noted we mean that the reaction takes place at a convenient rate in a common solvent at temperatures between about 20 and 100°. Always bearing in mind that variations in rates of reactions are the rule, we shall not emphasize variations in rates or special conditions of solvent, temperature, or catalysts in this book unless the variations are so great as to make the reaction in question a special one. We shall have many occasions, however, to direct the reader's attention to such special conditions.

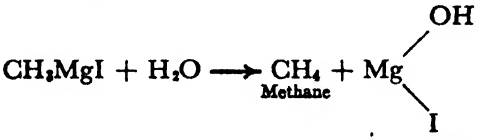
It has become accepted usage to say that a reaction "does not go" at a certain temperature, but "takes place" at another, and higher, temperature. Such phrases often lead to confusion. Unless otherwise specified we mean by statements of this sort that below a certain temperature range the reaction in question goes so slowly as to be immeasurable, while above this temperature range it proceeds at a convenient rate. The critical temperature is often recorded as though it were as definite as a boiling point, but in fact it represents always a narrow critical range rather than a point.

The Grignard Reagent. A special reaction of the alkyl halides is of so much importance in the synthesis of organic compounds as to deserve individual attention. This reaction was discovered by the French chemist Victor Grignard. In recognition of the discovery he was awarded one-half the Nobel Prize for the year 1912. The equations are:

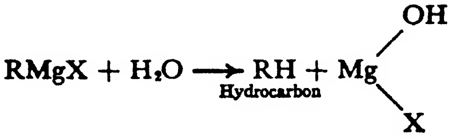
$$\mathrm{CH_3I} + \mathrm{Mg} \xrightarrow[\text{ether}]{\text{Dry}} \underset{\substack{\text{Methylmagnesium}\\ \text{iodide}}}{\mathrm{CH_3MgI}}$$

$$\mathrm{RX} + \mathrm{Mg} \xrightarrow[\text{ether}]{\text{Dry}} \mathrm{RMgX}$$

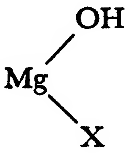
Compounds of the type RMgX are called *Grignard reagents;* they are prepared and used in ether solution. They react with water violently at room temperature; this reaction enables us to prepare a type of substance known as a *hydrocarbon* which we are going to discuss in detail in the next chapter. The reaction between a Grignard reagent and water may be illustrated using methylmagnesium iodide.



$$\mathrm{CH_3MgI} + \mathrm{H_2O} \longrightarrow \underset{\text{Methane}}{\mathrm{CH_4}} + \mathrm{Mg}\begin{array}{l} \diagup \mathrm{OH} \\ \diagdown \mathrm{I} \end{array}$$



$$\mathrm{RMgX} + \mathrm{H_2O} \longrightarrow \underset{\text{Hydrocarbon}}{\mathrm{RH}} + \mathrm{Mg}\begin{array}{l} \diagup \mathrm{OH} \\ \diagdown \mathrm{X} \end{array}$$



(For convenience we write $\mathrm{Mg}\begin{array}{l} \diagup \mathrm{OH} \\ \diagdown \mathrm{X} \end{array}$ to represent a mixture of $\mathrm{Mg(OH)_2}$ and $\mathrm{MgX_2}$.)

Other reactions of the Grignard reagent will be discussed as they are encountered in later chapters.

Alkyl Fluorides. Just as the element fluorine differs considerably from the other members of the halogen family, so the alkyl fluorides have but little in common with the alkyl chlorides, bromides, and iodides. They are usually prepared by a special reaction—the interaction of an inorganic fluoride and an alkyl halide—though they may be formed by heating an alcohol with hydrofluoric acid. The lower alkyl fluorides are gases; propyl fluoride boils at −2°, *n*-amyl fluoride at 63°. Unlike the chlorides, bromides, and iodides the halogen atom in the fluorides is very unreactive. Methyl fluoride reacts but very slowly with even strong sodium hydroxide or sodium ethoxide.

ETHERS

Another important class of substances which are prepared directly from the alcohols are the ethers. The nature of these compounds will be best understood by studying the commonest representative, diethyl ether, usually called simply *ether*. It has been an important substance for nearly a hundred years; without this anesthetic modern surgery might never have developed.

Ethyl ether is a colorless liquid which boils at 35° and has a rather pleasant odor. It is highly inflammable, and, on standing, it slowly absorbs oxygen from the air to form dangerously explosive peroxides of unknown structure. In addition to its uses as an anesthetic, it is a valuable solvent. Unlike alcohol, it is nearly insoluble in water and is therefore a favorite solvent for extracting substances from water solution.

Ether is readily prepared from ethyl alcohol by heating this substance with sulfuric acid. The following reactions take place.

$$C_2H_5OH + H_2SO_4 \longrightarrow \underset{\text{Ethylsulfuric acid}}{C_2H_5OSO_3H} + H_2O$$

$$C_2H_5OSO_3H + C_2H_5OH \xrightarrow{130^\circ\text{–}140^\circ} CH_3CH_2OCH_2CH_3 + H_2SO_4$$

The preparation of ether from alcohol by this method is one of the oldest known organic reactions and is still the commercial process although much ethyl ether is obtained as a byproduct in the manufacture of ethyl alcohol from petroleum. Ether was manufactured in this way long before the nature of the reaction had been discovered. The alcohol is allowed to flow into a mixture of alcohol and sulfuric acid heated to 130° to 140°; ether and some alcohol and water distil and are condensed. The equations written above show that there are really two steps in the process: in the first, ethylsulfuric acid is formed by interaction of ethyl alcohol and sulfuric acid; in the second, this substance reacts with more alcohol forming ether and regenerating sulfuric acid. The regenerated acid then reacts with more alcohol forming ethylsulfuric acid (first reaction). At first sight it would appear that a given amount of sulfuric acid could thus convert an unlimited amount of alcohol into ether. Actually this is not so in the laboratory because, as the sulfuric acid becomes more dilute, water and alcohol distil with the ether and the process becomes too inefficient.

The temperature of the reaction mixture must be controlled rather carefully. At temperatures below 130°, the second reaction is so slow that unchanged alcohol will distil; at high temperatures (150° to 200°), ethylsulfuric acid decomposes (p. 51). This is an excellent illustration of the principle mentioned earlier, namely, that the *conditions are of supreme importance in determining the course of an organic reaction.* In this case, a relatively slight change in the temperature greatly alters the efficiency of the process.

Industrial Apparatus for Preparing Ether. The industrial preparation of ether is illustrated by the diagram shown in Fig. 2. This is a simplified representation of the modern equipment which permits the production of an almost unlimited amount of ether from one charge of acid. The operation is as follows. The ether pot is charged with pure concentrated sulfuric acid; ethyl alcohol is then added and the mixture allowed to stand for some time, during which ethylsulfuric acid is formed (reaction 1, p. 34). The pot is then heated by passing steam through the coils which are below the level of the liquid. The temperature is kept at 130°, and alcohol is slowly run in from the alcohol feed tank. The vapor which issues from the ether pot contains alcohol, water, ether, and a small amount of acid fumes (sulfur dioxide). The latter are removed by contact with sodium hydroxide in the caustic scrubber. The vapors then pass through a series of complicated fractionating columns and partial condensers which separate the ether from the alcohol and water. The water and alcohol are separated in another column, and 95 per cent alcohol is recovered. The temperatures of the ether pot and the various fractionating columns are carefully regulated. The process may be run continuously for many weeks. Because of the fractionating columns which separate the ether, alcohol, and water the process is continuously efficient and, unlike the laboratory procedure, does not require recharging with sulfuric acid after considerable water has been formed. Even if the percentage of ether is low in the vapors as they leave the reaction, this ether is continuously separated by the columns and the unchanged alcohol is returned to be once again introduced into the reaction.

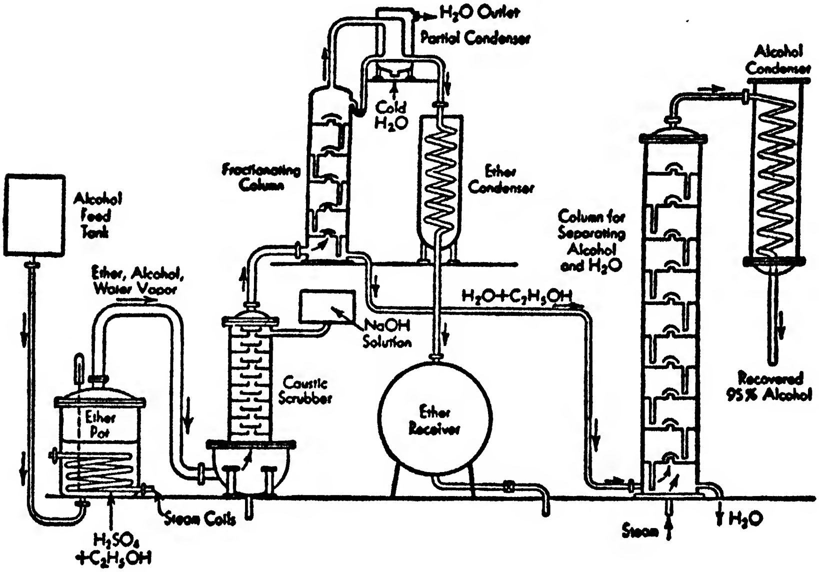


Fig. 2. Diagram of the essential parts of the apparatus used in the industrial preparation of ether. (From data kindly furnished by E. B. Badger and Sons Co.)

Mixed Ethers. Ethers with two different groups are called *mixed ethers.* Such an ether is methyl ethyl ether. It cannot be prepared conveniently by the usual reaction, but instead is prepared by the Williamson synthesis. The equations follow.

$$2C_2H_5OH + 2Na \longrightarrow \underset{\text{Sodium ethoxide}}{2C_2H_5ONa} + H_2$$

$$C_2H_5ONa + \underset{\text{Methyl iodide}}{CH_3I} \longrightarrow C_2H_5OCH_3 + NaI$$

Instead of methyl iodide, dimethyl sulfate may be used.

$$C_2H_5ONa + (CH_3)_2SO_4 \longrightarrow C_2H_5OCH_3 + CH_3OSO_3Na$$

Chemical Reactions of Ethers. Chemically, the ethers are noted for their inertness; they do not react with such reagents as metallic sodium, phosphorus trichloride, or alkalies. They are broken down into two molecules by warming with sulfuric acid or, more rapidly, with aqueous hydrogen iodide.

$$C_2H_5OCH_3 + 2HI \longrightarrow C_2H_5I + CH_3I + H_2O$$

This reaction is often used in determining the structure of ethers.

Ethers of Industrial Importance. Dimethyl ether is manufactured today by the catalytic dehydration of methanol. It finds use as a refrigerant since it can be allowed to come in direct contact with foodstuffs during "quick freezing" without imparting any foreign taste or odor. Diisopropyl ether, $(CH_3)_2CHOCH(CH_3)_2$, (bp 68°) is commercially available, and in many industrial extraction processes it is beginning to replace ethyl ether. It is actually cheaper than ether, and because of its lower volatility it is less hazardous to handle. Higher ethers such as those obtained from the amyl alcohols are now produced. Their chief use is as solvents.

QUESTIONS AND PROBLEMS

1. Write balanced equations for two methods of preparing (*a*) propyl chloride, (*b*) isopropyl bromide, and (*c*) ethyl iodide.

2. Write electronic formulas for methyl bromide, potassium chloride, sodium hydroxide, and sodium ethoxide.

3. Arrange the three alkyl chlorides, *n*-butyl chloride, *sec*-butyl chloride, and *tert*-butyl chloride, in the order of increasing rate of reaction with sodium cyanide.

4. Name the following compounds: $CH_3CH_2OCH_2CH_2CH_3$, $CH_3CH_2CH_2CH_2MgCl$, $CH_3CHBrCH_3$, $NaOCH_2CH_2CH_3$.

5. Write balanced equations for the reactions of *n*-butyl chloride and isopropyl bromide with sodium cyanide, sodium ethoxide, and silver hydroxide.

6. Name the following alcohols: $CH_3CH_2CH_2CH_2CH_2OH$, $CH_3CH_2CHOHCH_2CH_3$, $(CH_3)_2C(OH)C_2H_5$. Arrange these alcohols in the order of increasing rate of reaction with (*a*) hydrochloric acid and (*b*) sodium.

7. How does the electronic theory of valence account for covalences and electrovalences?

8. What factors will affect the rate of the reaction between butyl bromide and (*a*) potassium iodide and (*b*) silver hydroxide?

9. Write balanced equations for two methods of preparing ethyl ether.

10. Compare the reactions of $C_2H_5OC_2H_5$ and $(CH_3)_3COH$ with the following reagents: sodium, phosphorus trichloride, hydrochloric acid, hydrogen iodide.

11. If the reaction between butyl alcohol and hydrobromic acid to form butyl bromide runs to essential completion in 2 hours at 100°, approximately how long would be required at 80°?

12. By what simple chemical or physical tests could you differentiate between: (*a*) *n*-propyl alcohol and *n*-propyl ether, and (*b*) *n*-amyl bromide and *n*-amyl alcohol?

13. List the general formulas for the types of compounds studied so far and include a few fundamental reactions of each.

CHAPTER 3

Saturated or Paraffin Hydrocarbons

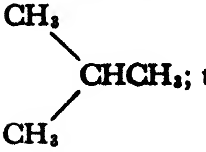
In the preceding chapter we encountered compounds of the type RH (where R is an alkyl group) formed by the action of water on a Grignard reagent; these substances are known as *saturated hydrocarbons.* It will be clear from what has already been learned about the structure of alcohols and alkyl halides that the general formula of members of this class of compounds must be C_nH_{2n+2}. Another common name for the group is *paraffin hydrocarbons;* still another is the *alkanes.* We shall meet in the next chapter classes of substances also composed only of carbon and hydrogen, and hence called *hydrocarbons* but having less hydrogen than the paraffin series, and hence called *unsaturated hydrocarbons.* Petroleum is a mixture of hydrocarbons and the chemistry of these compounds is thus of great importance to industry. In this chapter and the next we shall lay the ground work for a study of two substances now manufactured from petroleum, namely, gasoline and rubber.

The relationship between the compounds we have studied and the corresponding paraffin hydrocarbons is illustrated on the next page.

The alcohols and alkyl halides are often spoken of as *derivatives* of the paraffin hydrocarbons. A derivative of a hydrocarbon is a substance which might be prepared from the hydrocarbon by the replacement of a hydrogen atom by another atom or group. This is a purely formal relationship which is useful in classification. It does not state that the derivatives of the hydrocarbon are prepared in this way.

Alcohol	*Alkyl Iodide*	*Hydrocarbon Alkane*	*Name of Hydrocarbon*
$C_nH_{2n+1}OH$ ROH	$C_nH_{2n+1}I$ RI	C_nH_{2n+2} RH	
CH_3OH	CH_3I	CH_4	Methane
CH_3CH_2OH	CH_3CH_2I	CH_3CH_3	Ethane
$CH_3CH_2CH_2OH$	$CH_3CH_2CH_2I$	$\left.\right\}$ $CH_3CH_2CH_3$	Propane
$CH_3CHOHCH_3$	CH_3CHICH_3		

Isomerism in the Paraffin Series. It will be noticed that only one substance, propane, corresponds to both propyl and isopropyl alcohols. Isomerism in the paraffin hydrocarbons is not met with until we come to the **butanes,** C_4H_{10}. There are two of these, normal or *n*-butane, $CH_3CH_2CH_2CH_3$, and isobutane,



$$\begin{array}{l} CH_3 \\ \quad\diagdown \\ \qquad CHCH_3 \\ \quad\diagup \\ CH_3 \end{array}$$

; they boil at + 0.6° and − 10° respectively. The

SOME NORMAL PARAFFIN HYDROCARBONS

Molecular Formula	*Name*	*Boiling Point*	*Melting Point*	*Density at 20°*
CH_4	Methane	−161°	−184°	—
C_2H_6	Ethane	−88°	—	—
C_3H_8	Propane	−45°	—	—
C_4H_{10}	*n*-Butane	+0.6°	—	0.601 at 0°
C_5H_{12}	*n*-Pentane	36°	−148°	0.631
C_6H_{14}	*n*-Hexane	69°	−94°	0.658
C_7H_{16}	*n*-Heptane	98°	—	0.683
C_8H_{18}	*n*-Octane	126°	−98°	0.702
C_9H_{20}	*n*-Nonane	150°	−51°	0.719
$C_{10}H_{22}$	Decane	174°	−32°	0.747
......	....	....	....	....
$C_{18}H_{38}$	Octadecane	317°	28°	0.777 at 0°
$C_{19}H_{40}$	Nonadecane	330°	32°	0.777 at 0°
$C_{20}H_{42}$	Eicosane	205° (at 15 mm)	36.7°	0.778 at 0°

structural theory predicts three **pentanes,** C_5H_{12}, and three and only three such compounds are known. The student should satisfy himself that no arrangement of the atoms other than those shown below is possible.

ISOMERIC PENTANES (C_5H_{12})

Name	*Formula*	*Boiling Point*
n-Pentane	$CH_3CH_2CH_2CH_2CH_3$	36°
Dimethylethylmethane	$(CH_3)_2CHCH_2CH_3$	28°
Tetramethylmethane	$(CH_3)_4C$	10°

Calculation of the number of possible isomers of the paraffin hydrocarbons shows that the number of isomers increases with startling rapidity as we go up the series. Thus while there are only nine possible isomeric heptanes (all of which are known) there are 366,319 possible isomers with the formula $C_{20}H_{42}$ and 69,491,178,805,831 possible isomers with the formula $C_{40}H_{82}$. Needless to say only a very minute fraction of the total number of possible isomers of the hydrocarbons containing more than nine carbon atoms has been prepared.

Physical Properties. The lower members of the paraffin hydrocarbons are gases, the members above C_4H_{10} are liquids, and above $C_{16}H_{34}$ solids at room temperature. They are all insoluble in water. The boiling points of the *straight-chain compounds* (called the *normal paraffin hydrocarbons*) are given in the table on p. 40 and are plotted in Fig. 3. The boiling points of the normal paraffins increase with increasing molecular weight just as do the boiling points of the alcohols; the rate of increase is greater with the lower members than with the higher (the curve becomes flatter). It is convenient to remember that *n*-pentane (C_5H_{12}) is the simplest member of the series that is liquid at ordinary temperatures. The highest straight-chain member of the series which has been so far prepared is heptacontane $C_{70}H_{142}$, a solid melting at 105°. The largest paraffin hydrocarbon so far synthesized, $C_{94}H_{190}$, has a molecular weight of 1318. It is a chain of seventy-six carbon atoms to which are attached eighteen methyl groups.

Nomenclature of Paraffins. The names of the simple members of the series follow the alcohols: for example, eth-yl alcohol, eth-ane. The five-carbon compound is an exception: instead of the expected "amane" the name *pentane* is used. From this point on, the number of carbon atoms is denoted by the prefix:

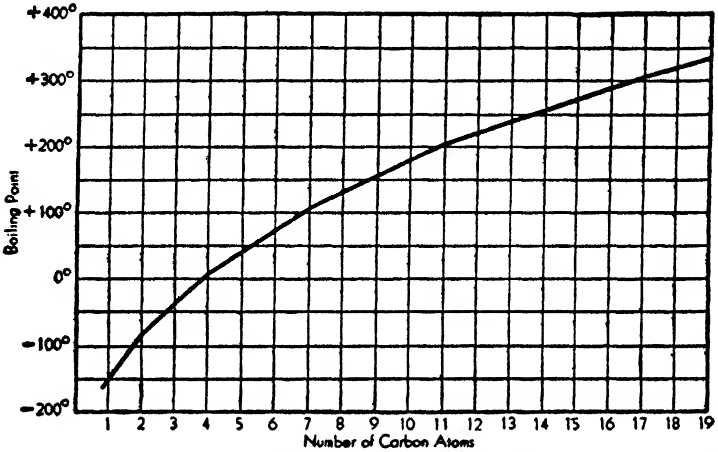
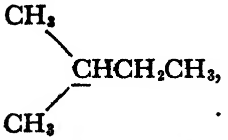


Fig. 3. The boiling points of the normal paraffin hydrocarbons, CH_4 to $C_{19}H_{40}$.

thus, hexane, C_6H_{14}; heptane, C_7H_{16}; octane, C_8H_{18}; nonane, C_9H_{20}; decane, $C_{10}H_{22}$.

In naming complicated hydrocarbons, a system similar to that employed with the alcohols is often used. It will be recalled that methyl alcohol is considered as the parent substance; similarly, in naming the hydrocarbons, methane is chosen as a basis for the nomenclature. A convenient rule to remember is the following: *the most highly substituted carbon atom is considered the center of the molecule* and the alkyl groups attached to it are named. Thus

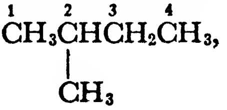

$(CH_3)_2\underline{C}HCH_2CH_3$, dimethylethylmethane

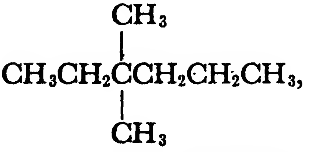
$(CH_3)_2CH\underline{C}(CH_3)_3$, trimethylisopropylmethane

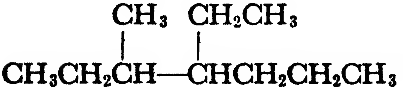
Here we have underlined the central carbon atom to illustrate the method of nomenclature. This is, of course, not usually done.

It is advisable to practice writing and naming a variety of hydrocarbons to be certain that one is familiar with the principles employed.

The Geneva System of Nomenclature. The naming of complex substances presents many difficulties. Methods of naming simple substances are sufficient for the purposes of our elementary study of the subject, but they do not suffice when more complicated compounds are considered. In 1892 a congress of chemists adopted a systematic scheme of nomenclature which has become known as the *Geneva system.* Some of the original rules have undergone modifications at later international chemical meetings, and there are minor variations in usage from country to country, but it is still convenient to refer to the system by its original name.

Paraffin hydrocarbons are named according to the *longest continuous chain;* the name of the hydrocarbon with this number of carbon atoms is modified by noting what alkyl groups are attached to the chain. The chain is numbered and the positions of the substituent alkyl groups are indicated by numbers. For example, the hydrocarbon,  $\overset{1}{CH_3}\underset{\underset{CH_3}{|}}{\overset{2}{CH}}\overset{3}{CH_2}\overset{4}{CH_3}$, is 2-methylbutane;


$CH_3CH_2\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}CH_2CH_2CH_3$, is 3,3-dimethylhexane, and


$CH_3CH_2\overset{\overset{CH_3}{|}}{CH}-\overset{\overset{CH_2CH_3}{|}}{CH}CH_2CH_2CH_3$ is 3-methyl-4-ethylheptane.

The alcohols of the series $C_nH_{2n+1}OH$ are named as derivatives of the hydrocarbons C_nH_{2n+2}. The terminal ending *-ol* is added to the name of the parent hydrocarbon, which is always considered as corresponding to the longest carbon chain carrying the hydroxyl group. The following examples illustrate the naming of alcohols by the Geneva system: $CH_3CHOHCH_2CH_3$ is 2-butanol (the 2 indicates the position of the hydroxyl group),

$\underset{\displaystyle CH_3}{CH_3CHOHCHCH_2CH_3}$ is 3-methyl-2-pentanol. The alkyl halides are named by considering them as chloro, bromo, or iodo derivatives of the paraffin hydrocarbons and indicating the position of the halogen atom by a number; thus, isopropyl bromide, $CH_3CHBrCH_3$ is 2-bromopropane. The system includes all the many types of compounds which are known (e.g., unsaturated hydrocarbons, aldehydes, ketones, acids, cyclic compounds); a hydrocarbon is always considered as the parent substance and a characteristic ending of the name shows the reactive group.

Preparation of Paraffin Hydrocarbons. The preparation of the paraffin hydrocarbons from the corresponding alkyl halides by way of the Grignard reagent (p. 33) amounts to the replacement of a halogen atom by a hydrogen atom. Alkyl halides may also be converted into the corresponding hydrocarbon by direct reduction with "nascent hydrogen" generated by such combinations as zinc and acid, sodium and alcohol, or sodium amalgam and water.

$$C_2H_5Br + \underset{\substack{\text{"Nascent}\\ \text{hydrogen"}}}{2[H]} \longrightarrow C_2H_6 + HBr$$

The higher alkyl iodides may be reduced to hydrocarbons by heating with hydrogen iodide.

$$C_nH_{2n+1}I + HI \longrightarrow C_nH_{2n+2} + I_2$$

Higher members of the series may be prepared by joining two alkyl groups by the Wurtz reaction in which metallic sodium reacts with an alkyl halide (or a mixture of two halides).

$$2CH_3\boxed{I + 2Na} \longrightarrow \underset{\text{Ethane}}{CH_3CH_3} + 2NaI$$

$$CH_3I + 2Na + C_2H_5I \longrightarrow \underset{\text{Propane}}{CH_3CH_2CH_3} + 2NaI$$

If two different alkyl halides are employed there will be always two products besides the desired hydrocarbon. Thus in the example just given, some ethane, CH_3CH_3, and some butane,

$CH_3CH_2CH_2CH_3$, will also be formed. The low yield of the desired product and the necessity of separating it from the other two products limit the usefulness of the Wurtz reaction for joining together two unlike alkyl groups.

Hydrocarbons with fewer hydrogen atoms than the paraffins (unsaturated hydrocarbons) can often be prepared more readily than the saturated compounds. By the addition of further hydrogen (hydrogenation) they can be converted into the corresponding paraffin hydrocarbons. Examples of this will be given in later chapters, together with a consideration of reactions between saturated and unsaturated hydrocarbons which also yield paraffin hydrocarbons; these methods are nowadays the most important reactions for preparing individual members of the paraffin series in large quantities.

REACTIONS OF PARAFFIN HYDROCARBONS

The paraffin hydrocarbons undergo a variety of reactions most of which lead to mixtures of several products. When these mixtures can be used as such or when the quantity of material handled is so large as to justify the expense of elaborate separations, the reactions find extensive industrial applications. Two reactions of the paraffin hydrocarbons, isomerization and decomposition, are fundamental to the manufacture of gasoline and other liquid fuels and we shall discuss them in that connection in Chap. 5. Two other reactions, halogenation and oxidation, we shall discuss briefly here.

Replacement of Hydrogen by Halogen. Chlorine and bromine do not react with the paraffin hydrocarbons at an appreciable rate at room temperature under ordinary conditions. This fact is often used to distinguish between the paraffins and unsaturated hydrocarbons which, as we shall see in the next chapter, combine with bromine rapidly. At temperatures between 100° and 500°, particularly in the presence of certain metallic salts as catalysts or when the reaction mixture is strongly illuminated, *substitution reactions* occur. In these reactions hydrogen atoms are replaced by chlorine or bromine. Such reactions are called *halogenations;* if chlorine is used, *chlorination;* if bromine, *bromination.* The reaction does not stop when a single halogen atom has been introduced for the resulting alkyl halide undergoes further substitution and a mixture of products results. The simplest paraffin, methane, yields four products.

$$CH_4 \xrightarrow[\text{catalyst; high temperature}]{\text{Light or}} CH_3Cl \longrightarrow CH_2Cl_2 \longrightarrow CHCl_3 \longrightarrow CCl_4$$

None of these products is prepared commercially from methane. Although it is possible to convert methane to the completely chlorinated product, carbon tetrachloride, CCl_4; that product, which is used because of its noninflammability for dry cleaning and as a fire extinguisher fluid, is made from carbon disulfide and chlorine.

$$\underset{\substack{\text{Carbon}\\ \text{disulfide}}}{CS_2} + 3Cl_2 \longrightarrow CCl_4 + \underset{\substack{\text{Sulfur}\\ \text{chloride}}}{S_2Cl_2}$$

Oxidation. By comparison with many classes of organic compounds the paraffins are very resistant to attack by the common chemical oxidizing agents. When mixed with atmospheric oxygen and heated, the paraffin hydrocarbons, and other hydrocarbons as well, are oxidized to carbon dioxide and water; the process is known as **combustion** and is the basis for the use of these materials as fuels. There is usually a rather definite temperature above which a hydrocarbon in an excess of air is oxidized so rapidly that we say it *burns.* If the supply of air is insufficient but the temperature remains high, the products will contain carbon monoxide as well as carbon dioxide; with even less air elementary carbon will be produced. In this way *carbon black* and similar materials are prepared from natural gas, which is a mixture of the lower paraffin hydrocarbons.

Exothermic Reactions. The amount of heat evolved when an organic compound is burned can be measured with accuracy. The heat evolved when one gram molecular weight of a compound in the gaseous state is burned to carbon dioxide and liquid water is known as the *heat of combustion,* and is reported in kilogram calories.[1] It is common practice to indicate the heat evolved or absorbed in a reaction on the right-hand side of the equation. Thus we may write for the combustion of gaseous methane:

$$CH_4 + 2O_2 \longrightarrow CO_2 + 2H_2O + 212.8 \text{ kcal}$$

Reactions in which heat is evolved are called *exothermic reactions.* A great many reactions in organic chemistry are of this type, but the amount of heat evolved varies greatly from reaction to reaction. Reactions where heat is absorbed (endothermic) are less common in organic chemistry, and when they do occur the amount of heat absorbed is always relatively small if the reaction runs to completion at room temperature.

QUESTIONS AND PROBLEMS

1. Name the following compounds: $CH_3CH_2CH(CH_3)CH_2CH_3$, $(CH_3)_2CHCHClCH_3$, $(CH_3)_2CHCH(CH_3)_2$, $CH_3CHOHCH_2CH_2C(CH_3)_3$, $CH_3CH_2CHBrCH_2CH_3$, $CH_3CH(CH_2CH_3)_2$, $(CH_3)_2CHC(CH_3)(C_2H_5)_2$.

2. Write balanced equations showing how you could prepare (*a*) *n*-butane and (*b*) *n*-octane from *n*-butyl bromide.

3. Define and illustrate: exothermic reaction, endothermic reaction, heat of combustion, kilogram calorie.

4. What conditions would you use in order to chlorinate *n*-pentane? What products would you expect to obtain from the reaction?

5. If 3.6 g of a certain paraffin hydrocarbon at 100° and 760 mm occupies 153 ml, what is the molecular weight of the hydrocarbon?

6. Define: hydrocarbon, Wurtz reaction, halogenation.

7. Write the structural formulas for: tetraethylmethane; *n*-hexane; isobutane; 3,4-dimethylheptane; di-*n*-propylmethylmethane; 3,3-dimethyl-2-hexanol; 3-bromopentane.

8. By what simple chemical or physical tests could you differentiate between: (*a*) pentane and eicosane (normal $C_{20}H_{42}$), (*b*) *n*-propyl ether and *n*-hexane, (*c*) *n*-amyl alcohol and *n*-octane?

---

[1] The kilogram calorie (kcal) is the quantity of heat required to raise the temperature of 1000 g of water from 15° to 16° C.

9. A substance on analysis was shown to have the composition: C, 85.72; H, 14.28. What type of compound is this and what is its general formula?

10. List the common reactions of: (*a*) paraffins, (*b*) alcohols, (*c*) ethers, (*d*) alkyl halides.

11. Which of the following reactions would you use to prepare CH_3Br and why?

a. $CH_4 + Br_2 \longrightarrow CH_3Br + HBr$

b. $CH_3OH + HBr \longrightarrow CH_3Br + H_2O$

CHAPTER 4

Unsaturated Hydrocarbons

In this chapter we shall consider several classes of hydrocarbons which contain less hydrogen than the corresponding paraffin hydrocarbons. These hydrocarbons combine with bromine and chlorine and, in the presence of suitable catalysts, with hydrogen; therefore they are spoken of as *unsaturated hydrocarbons.*

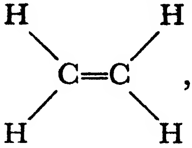
OLEFINS

The simplest unsaturated hydrocarbons are the members of the olefin or ethylene series. Because the products of the action of chlorine on these unsaturated hydrocarbons were oily liquids, the hydrocarbons themselves were called *olefiant* or *oil-making* hydrocarbons. The word *olefiant* was later changed to *olefin.* The members of this series have the general formula C_nH_{2n}; the first member is **ethylene,** C_2H_4, the next **propylene,** C_3H_6. It will be noticed that they contain two less hydrogen atoms than the corresponding members of the methane series (ethane C_2H_6, propane C_3H_8).

The Structure of Ethylene. The olefins combine with bromine or chlorine in such a way that a dibromide or dichloride is formed by the addition of two atoms of the element.

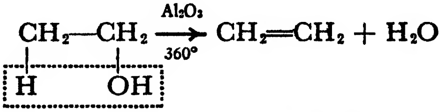
$$\underset{\text{Ethylene}}{C_2H_4} + Br_2 \longrightarrow \underset{\text{Ethylene dibromide}}{C_2H_4Br_2}$$

$$C_2H_4 + Cl_2 \longrightarrow \underset{\text{Ethylene dichloride}}{C_2H_4Cl_2}$$

This is an **addition reaction.** A chemical study of the addition products has shown that they must have the structural formulas CH_2BrCH_2Br and CH_2ClCH_2Cl, respectively. For ethylene itself we write the structure  , in which the double bond between the two carbon atoms indicates the ability to add two monovalent atoms or groups and form compounds containing single linkages. This double bond is sometimes referred to as a *point of unsaturation.* It is also called an ethylenic linkage or ethylenic double bond to distinguish between it and other unsaturated linkages which we shall encounter later.

Just as the covalent single bond in organic compounds corresponds to the sharing of two electrons, the covalent double bond corresponds to the sharing of four electrons. The distance between two doubly linked carbon atoms is, however, less than that between two singly linked carbon atoms, 1.33 Å instead of 1.54 Å, and the double bond does not permit rotation of the two atoms involved in the linkage. One consequence of the lack of free rotation is the existence of isomers of certain ethylenic compounds as will be seen later on p. 195.

Preparation of Olefins. Ethylene is prepared by passing ethyl alcohol vapor through a hot tube containing aluminum oxide or through a tower of coke impregnated with glacial phosphoric acid. These catalysts cause the dehydration of the alcohol.



$$\underset{\displaystyle H}{\underset{|}{CH_2}}-\underset{\displaystyle OH}{\underset{|}{CH_2}} \xrightarrow[360^\circ]{Al_2O_3} CH_2{=}CH_2 + H_2O$$

This is a general and excellent method of preparing a great variety of olefins. Primary, secondary, and tertiary alcohols may be employed and, depending on the nature of the alkyl groups attached to the carbinol carbon atom, different substituted ethylenes will be formed. Olefin formation takes place at much lower temperatures with tertiary alcohols than with primary, as the examples below show. Secondary alcohols, as usual, lie between the two other classes in their behavior.

$$CH_3CH_2CH_2OH \xrightarrow[\text{ca. }300°]{AlPO_4} CH_3CH{=}CH_2 + H_2O$$

$$CH_3CHOHCH_3 \xrightarrow[\text{ca. }250°]{AlPO_4} CH_3CH{=}CH_2 + H_2O$$

$$(CH_3)_3COH \xrightarrow[\text{ca. }150°]{AlPO_4} (CH_3)_2C{=}CH_2 + H_2O$$

An indirect method of dehydrating alcohols is to treat them with sulfuric acid; the alkylsulfuric acid thus formed usually decomposes upon heating with the formation of an olefin and sulfuric acid. This older method, illustrated by the following example, is now largely superseded by the catalytic method.

$$CH_3CH_2OSO_2OH \xrightarrow{\text{Above }150°} CH_2{=}CH_2 + H_2SO_4$$

The alkylsulfuric acid written above is also an intermediate in the formation of ethyl ether from ethyl alcohol (p. 34). This fact is one more illustration of the importance of experimental conditions on the course of organic reactions.

Olefins are also prepared in the laboratory by the action of alcoholic alkali on alkyl halides.

$$CH_3CH_2CH_2Br + KOH \longrightarrow CH_3CH{=}CH_2 + KBr + H_2O$$

Industrially many olefins are obtained by heating the saturated hydrocarbons to a high temperature, particularly in the presence of a catalyst. The process always yields a mixture of products and is not a useful laboratory procedure. Its industrial applications will be considered in Chap. 5.

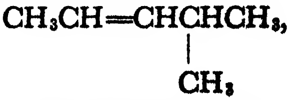
Physical Properties of Isomeric Olefins. The number of isomers is much greater in the olefin than in the paraffin series. This is illustrated by comparing the number of butenes and pentenes with the corresponding butanes and pentanes.

A comparison of the table on p. 52 with the one on p. 40 shows that the boiling points of the olefins are very close to those of the corresponding paraffins. Two hydrogen atoms make very little difference in this physical property. Like all other hydrocarbons the olefins are insoluble in water.

BOILING POINTS OF THE SIMPLER ETHYLENE HYDROCARBONS

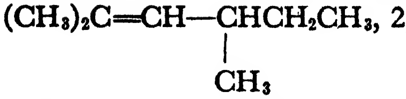
Molecular Formula	*Name*	*Structural Formula*	*Boiling Point*
C_2H_4	Ethylene	$CH_2{=}CH_2$	−104°
C_3H_6	Propylene	$CH_3CH{=}CH_2$	−47°
	Isomeric Butenes		
C_4H_8	Sym. dimethylethylene	$CH_3CH{=}CHCH_3$	+1°
	Unsym. dimethylethylene	$(CH_3)_2C{=}CH$	−6.6°
	Ethylethylene	$CH\ CH_2CH{=}CH_2$	−6.7°
	Isomeric Pentenes		
C_5H_{10}	Sym. methylethylethylene	$CH_3CH{=}CHCH_2CH_3$	+36°
	Unsym. methylethyl-ethylene	$CH_3CH_2(CH_3)C{=}CH_2$	32°
	n-Propylethylene	$CH_3CH_2CH_2CH{=}CH_2$	39°
	Isopropylethylene	$(CH_3)_2CHCH{=}CH_2$	20°
	Trimethylethylene	$(CH_3)_2C{=}CHCH_3$	38°

Nomenclature. The ethylenic hydrocarbons are named according to the Geneva system as follows. The longest unbranched carbon chain which includes the ethylenic linkage is named as in the saturated hydrocarbons, but the ending is changed from *-ane* to *-ene*. The position of substituent alkyl groups is indicated as in the saturated hydrocarbons; the position of the double bond is shown by a number preceding the name. This number indicates the *lower numbered of the two carbon atoms involved in the double linkage.* The numbering is always begun at the end of the chain nearer the double bond. The following examples illustrate the method: $CH_3CH_2CH{=}CH_2$, 1-butene; $CH_3CH{=}CHCH_3$, 2-butene;



$CH_3CH{=}CH\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_3$,

4-methyl-2-pentene; $(CH_3)_2C{=}CH_2$, 2-methyl-1-propene;



$(CH_3)_2C{=}CH{-}\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_3$, 2,4-dimethyl-2-hexene.

The simplest ethylenic hydrocarbons, ethylene and propylene, still carry names that antedate the Geneva system. Many ethylenic hydrocarbons are conveniently named as alkyl derivatives of ethylene. This method of naming is adequately illustrated in the table above.

Ethylene. The first member of the olefin series is a colorless gas with a characteristic sweetish odor. It burns with a luminous, smoky flame. With air or oxygen it forms a highly explosive mixture. It is usually present in illuminating gas to the extent of a few per cent.

Ethylene is obtained today from the gases liberated during the cracking process in gasoline production (p. 72). It is also produced from natural gas, which is a mixture of gaseous paraffins, by cracking under special conditions. The separation of ethylene from the other products is readily accomplished.

Ethylene is used by growers of citrus fruits since exposure of a green-colored fruit to an atmosphere of ethylene develops the highest yellow or orange color. Ethylene also finds use as an anesthetic and in some respects it is superior to ether.

Chemical Properties. The olefins combine with a variety of substances to form addition products which are derivatives of the paraffin hydrocarbons. These reactions are known as *addition reactions*, and the substances which add to the ethylenic linkage are referred to as *addends*. We shall consider next a number of the more important addition reactions of the olefins.

Hydrogenation. The double bond may be saturated with hydrogen by a process known as *catalytic hydrogenation*.

In this process the hydrocarbon, alone or in solution in an inert solvent, is shaken with hydrogen in the presence of highly active forms of platinum or palladium. These catalysts cause the hydrogen to combine with the unsaturated hydrocarbons. Less expensive but also less effective is finely divided nickel whose use generally requires both high temperatures and pressures or a vapor phase reduction. However, a highly active nickel catalyst can be made which will bring about the hydrogenation of many ethylenic hydrocarbons in the cold. With ethylene the reaction may be written as follows:

$$CH_2{=}CH_2 + H_2 \xrightarrow{\text{Catalyst}} CH_3CH_3$$

The catalytic hydrogenation of olefin hydrocarbons provides a method of preparing pure members of the paraffin series.

Addition of Halogens and Hypohalogen Acids. In the absence of a solvent or in inert solvents (carbon tetrachloride, CCl_4, or carbon disulfide, CS_2) and at ordinary temperature chlorine and bromine add to olefins.

$$CH_3CH{=}CH_2 + Br_2 \longrightarrow CH_3CHBrCH_2Br$$

Iodine reacts very slowly with olefins unless the reaction mixture is exposed to intense illumination; then an equilibrium is reached.

$$CH_2{=}CH_2 + I_2 \overset{\text{Light}}{\rightleftharpoons} CH_2ICH_2I$$

In the gas phase at temperatures above 250° and in the presence of small amounts of oxygen, simple olefins react with chlorine by substitution rather than addition. Propylene, for example, furnishes predominantly allyl chloride.

$$CH_2{=}CHCH_3 + Cl_2 \xrightarrow[\substack{\text{Small amounts}\\ \text{of oxygen}}]{250^\circ\text{-}300^\circ} \underset{\substack{\text{Allyl}\\ \text{chloride}}}{CH_2{=}CHCH_2Cl} + HCl$$

Once more the effect of the experimental conditions on the course of an organic reaction is to be noted: with chlorine and simple olefins it is possible by the proper choice of conditions to secure either addition or substitution.

An aqueous solution of bromine or chlorine always contains some hypobromous or hypochlorous acids.

$$Br_2 + H_2O \rightleftharpoons HOBr + HBr$$

These hypohalogen acids also add to the double linkage. Consequently if ethylene is passed into bromine water, addition of bromine and addition of hypobromous acid both take place.

$$CH_2{=}CH_2 + Br_2 \longrightarrow CH_2BrCH_2Br$$
$$CH_2{=}CH_2 + HOBr \longrightarrow CH_2OHCH_2Br$$

By controlling the concentration of the halogen and the acidity, it is possible to make the latter reaction predominate. The preparation of CH_2ClCH_2OH, ethylene chlorohydrin, is now carried out commercially (p. 123).

Addition of Acids. Ethylene is absorbed by warm concentrated sulfuric acid to form ethylsulfuric acid.

$$CH_2{=}CH_2 + H_2SO_4 \longrightarrow CH_3CH_2OSO_3H$$

The same product is formed from ethyl alcohol and sulfuric acid (p. 34). On heating it furnishes ethylene and sulfuric acid (p. 51), and on treatment with water it yields ethyl alcohol and sulfuric acid.

$$CH_3CH_2OSO_3H + H_2O \longrightarrow CH_3CH_2OH + H_2SO_4$$

As a consequence, ethylene and ethyl alcohol are interconvertible.

Higher members of the olefin series react with sulfuric acid at room temperature. The chief product from propylene is *isopropyl*sulfuric acid.

$$CH_3CH{=}CH_2 + H_2SO_4 \longrightarrow CH_3CH(OSO_3H)CH_3$$

The halogen acids also add to olefin hydrocarbons, forming alkyl halides. The reaction proceeds most rapidly with the higher members of the olefin series and more rapidly with hydrogen iodide or bromide than with hydrogen chloride.

$$CH_3CH{=}CH_2 + HI \longrightarrow CH_3CHICH_3$$

The addition of unsymmetrical reagents, like the halogen acids, to unsymmetrical derivatives of ethylene raises a problem concerning the *mode* of addition. Thus, in the examples given above, isopropylsulfuric acid and isopropyl bromide, not propylsulfuric acid and propyl bromide, are formed. The generalization which describes the mode of addition of unsymmetrical reagents to unsaturated hydrocarbons is known as *Markownikoff's rule.* It may be stated as follows: *In the addition of a compound of the type HA*(A = *Cl, Br, I,* OSO_3H, *etc.*) *to an ethylenic hydrocarbon, H adds to the ethylenic carbon atom which already holds the greater* *number of hydrogen atoms.* Careful experiment has shown that in many reactions a small amount of the isomer, formed by the other mode of addition, is also produced, the ratio of the two isomers depending to some extent on the nature of the solvent. It should be carefully noted that *this rule applies only to hydrocarbons.*

When we examine the mode of addition of the hypohalogen acids to unsymmetrical derivatives of ethylene, we find that the halogen atom joins the carbon holding the greater number of hydrogen atoms.

$$CH_3CH{=}CH_2 + HOCl \longrightarrow CH_3CHOHCH_2Cl$$

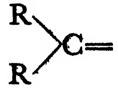
The mode of addition of hydrobromic acid to simple olefin hydrocarbons containing a terminal carbon-carbon double bond may be reversed by the addition of organic peroxides (p. 305). During ordinary manipulations, or better still in the presence of antioxidants (p. 299), isobutylene and hydrogen bromide give tertiary butyl bromide in accordance with Markownikoff's rule. If, however, organic peroxides are present, isobutyl bromide predominates in the product. The following reactions summarize these facts.

$$\underset{\text{Tertiary butyl bromide}}{(CH_3)_3CBr} \xleftarrow[\text{peroxides}]{\text{HBr Absence of}} \underset{\text{Isobutylene}}{(CH_3)_2C{=}CH_2} \xrightarrow[\text{peroxides}]{\text{HBr Presence of}} \underset{\text{Isobutyl bromide}}{(CH_3)_2CHCH_2Br}$$

Oxidation. Olefins are oxidized by potassium permanganate ($KMnO_4$) to compounds containing two hydroxyl groups. The equation [1] for the reaction with ethylene is:

$$CH_2{=}CH_2 + [O] + H_2O \xrightarrow{KMnO_4} \underset{\text{Ethylene glycol}}{CH_2OHCH_2OH}$$

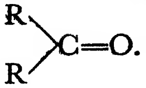
The product is **ethylene glycol**; it is further oxidized to carbon dioxide and water unless the solution is cold and dilute. The final products of oxidation of an olefin depend upon the number and position of the substituents: the group $CH_2{=}$ is oxidized to carbon dioxide and water, the group $RCH{=}$ to an organic acid of the formula RCOOH, and the group



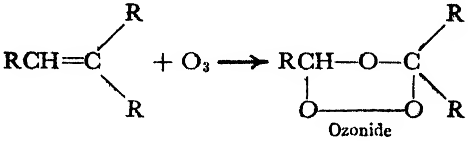
$R_2C{=}$

---

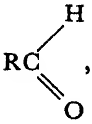
[1] The symbol [O] will be used throughout this book to indicate oxygen from an oxidizing agent; the oxidizing agent is written over the arrow.

to a ketone of the formula  $R_2C=O$. This makes it possible to determine the structure of an olefin by oxidizing and identifying the oxidation products. For example, $CH_3CH_2CH=CH_2$ on oxidation furnishes CH_3CH_2COOH, CO_2, and H_2O; while the isomeric $CH_3CH=CHCH_3$ furnishes two molecules of CH_3COOH.

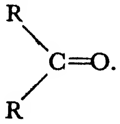
The reaction with ozone, O_3, is an even more valuable method for oxidizing an olefin in such a way as to establish its structure. An olefin reacts with ozone to furnish an ozonide.

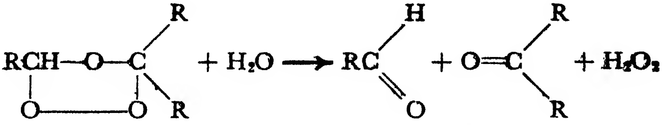


An ozonide will react with water to form hydrogen peroxide and, depending on the number and position of the substituents present in the olefin, aldehydes,

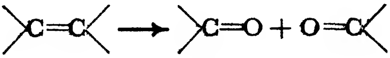


, or ketones,





By identifying the aldehydes or ketones formed, the structure of the olefin is established, for the overall process is



and from the fragments it is easy to deduce the structure of the olefin.

Polymerization. When ethylene as a liquid under very high pressure (1000 atm) is heated to 100° to 400° with small amounts of oxygen, many molecules combine in a long chain. The product has an average molecular weight of 2000 to 20,000, depending on the temperature and pressure. Products of such high molecular weight formed from simple compounds are known as *polymers.* The reaction is called *polymerization.* It may be formulated as:

$$nCH_2{=}CH_2 \xrightarrow[\substack{1000\text{ atm}\\100^\circ\text{–}400^\circ}]{\substack{\text{Small amount}\\\text{of }O_2}} (CH_2CH_2)_n, \quad \text{where } n = 70 \text{ to } 700$$

The product is of importance commercially and is known as *Polythene.* It is a tough solid melting around 118° and has very valuable properties as an insulator which made it of great importance in radar during World War II.

It seems quite clear that in the polymerization a great number of ethylene molecules have joined together in a chain. This type of polymerization is known as *addition polymerization.* It is not certain what is at the ends of the chain, and the molecule is so large that we have difficulty in finding out by ordinary chemical methods. This is a frequent dilemma in the study of polymerization reactions. If we wish to write a formula for the polymerized ethylene we can leave this question unanswered.

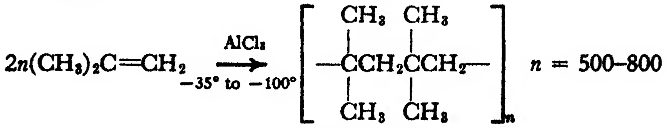
$$?{-}CH_2CH_2(CH_2CH_2)_xCH_2CH_2{-}?$$

Or, we may assume a shift of hydrogen atoms.

$$CH_3CH_2(CH_2CH_2)_xCH{=}CH_2$$

To detect one double bond among 70 to 700 single bonds per molecule would be difficult, but the double bond may not be present in the final molecule since reaction with the little oxygen present may convert it to some saturated compound.

Products similar to polythene have not been produced as yet from the higher olefins. But under a different set of conditions (with aluminum chloride as a catalyst and at temperatures below −35°), isobutylene polymerizes to polyisobutylene, which is a thick liquid or a tough elastic solid depending on its molecular weight.



$$2n(CH_3)_2C{=}CH_2 \xrightarrow[-35^\circ\text{ to }-100^\circ]{AlCl_3} \left[\begin{array}{c} CH_3\quad CH_3 \\ |\qquad\quad | \\ {-}CCH_2CCH_2{-} \\ |\qquad\quad | \\ CH_3\quad CH_3 \end{array}\right]_n \quad n = 500\text{–}800$$

POLYISOBUTYLENE
Molecular weight 25,000 to 40,000

Polymeric substances (i.e., polymers) are frequently obtained when the olefins are heated with powerful catalysts such as aluminum chloride or concentrated sulfuric acid. Such products are often formed as undesirable byproducts in other reactions of hydrocarbons. Unless the conditions of polymerization are carefully controlled, the product consists of such a variety of polymers with different molecular weights that its properties are undesirable. Sticky, gummy, amorphous "tars" are only too readily formed in the laboratory as the chemist knows from sad experience if too powerful reagents are allowed to react too long with most organic substances. These byproducts, which can neither be crystallized nor distilled and have no useful physical properties, are the result of a series of polymerization reactions many of which involve unsaturated compounds.

Other types of polymerization reactions will be encountered later (Chaps. 11, 19).

ACETYLENIC HYDROCARBONS

The acetylenic hydrocarbons have the general formula C_nH_{2n-2}. The first member of the series, acetylene C_2H_2, is by far the most important.

Acetylene has the structure $CH{\equiv}CH$, where the triple bond indicates the ability to add four monovalent atoms or groups as in the reaction with bromine.

$$CH{\equiv}CH + 2Br_2 \longrightarrow CHBr_2CHBr_2$$

The *electronic formula* for acetylene is $H : C : : : C : H$. In three dimensions this corresponds to the union of two tetrahedra by a common face. The distance between the centers of two triply linked carbon atoms is only 1.20 Å. (Compare 1.33 Å for $C{=}C$, and 1.54 Å for $C{-}C$.)

Preparation of Acetylenic Hydrocarbons. Acetylene is easily prepared from calcium carbide, CaC_2, and water.

$$CaC_2 + 2H_2O \longrightarrow CH{\equiv}CH + Ca(OH)_2$$

Since calcium carbide is readily made in the electric furnace from coke and lime, acetylene is one of the cheap organic chemicals available to the industrial chemist.

Acetylene and its homologs may be prepared by eliminating two molecules of halogen acid from a dihalide by means of molten alkali or strong solutions of potassium hydroxide. The dihalide in turn can be made from the corresponding olefin and halogen.

$$CH_3CH{=}CH_2 + Br_2 \longrightarrow CH_3CHBrCH_2Br$$

$$\underset{\text{Propylene dibromide}}{CH_3CHBrCH_2Br} + 2KOH \xrightarrow{\text{Heat}} \underset{\substack{\text{Methyl}\\ \text{acetylene}}}{CH_3C{\equiv}CH} + 2KBr + 2H_2O$$

Acetylene. Acetylene is a colorless gas, insoluble in water, with a characteristic odor. It can be condensed to a liquid which boils at −84° and which is explosive if subjected to a sudden shock. For its transport it is necessary to dissolve the gas under pressure in acetone. In this form it is safe. It burns with a luminous flame when a specially constructed burner is used which allows free access of air.

Acetylene has had a varied industrial history. It was first used at the end of the last century as a lighting gas in competition with coal gas. Acetylene lamps were at one time used as bicycle and automobile lights.

The present industrial use of acetylene is as a cheap raw material from which to prepare other compounds (Chap. 9). The preparation of an artificial rubber from acetylene is discussed in Chap. 5.

Addition Reactions of Acetylene. The triple linkage in acetylene will add four monovalent atoms or groups, much as the double linkage in ethylene adds two such atoms or groups. In a few reactions, only two atoms or groups can be added and a derivative of ethylene is formed. Thus, if acetylene is passed into a water solution of chromous chloride, $CrCl_2$ (a powerful reducing agent), ethylene is formed. Certain other reducing agents enable one to prepare ethylene derivatives from acetylenic hydrocarbons. However, since ethylene and its derivatives are also reactive, usually the addition reactions do not stop at the ethylene stage. The catalytic hydrogenation of acetylene produces ethane if sufficient hydrogen is employed.

$$CH{\equiv}CH + H_2 \xrightarrow{\text{Catalyst}} CH_2{=}CH_2 + H_2 \xrightarrow{\text{Catalyst}} CH_3CH_3$$

With chlorine, tetrachlorethane, $CHCl_2CHCl_2$, is the final product.

$$CH\equiv CH + 2Cl_2 \longrightarrow CHCl_2CHCl_2$$

The halogen acids add to acetylene forming a halogen derivative of ethylene which can then combine further with another molecule; the final product has two halogen atoms on the same carbon atom.

$$\begin{aligned} CH\equiv CH + HCl &\longrightarrow CH_2{=}CHCl \\ CH_2{=}CHCl + HCl &\longrightarrow CH_3CHCl_2 \end{aligned}$$

The addition of acids to homologs of acetylene, like the addition of these same reagents to unsymmetrical olefins, follows Markownikoff's rule (p. 55).

Acetylides. Acetylene and the members of the acetylene series which *contain the grouping* $—C\equiv CH$, enter into two characteristic reactions. When shaken with ammoniacal cuprous or silver solutions, they form precipitates of **metallic acetylides.** These are usually highly explosive in the dry state. The acetylides are related to acetylene as salts are to acids. The metal has replaced a hydrogen atom. The following equations illustrate these reactions.

$$CH\equiv CH + \underset{\substack{\text{As complex}\\ \text{ion}}}{Cu_2Cl_2} + 2NH_4OH \longrightarrow \underset{\substack{\text{Ppt.}\\ \text{copper acetylide}}}{CuC\equiv CCu} + 2NH_4Cl + 2H_2O$$

On treatment with dilute acids, the acetylides regenerate acetylene.

$$AgC\equiv CAg + 2HNO_3 \longrightarrow CH\equiv CH + 2AgNO_3$$

Sodium acetylide, $CH\equiv CNa$, is formed by the action of acetylene on a solution of sodium in liquid ammonia or by passing the gas through molten sodium at 180°. Disodium acetylide, C_2Na_2, can also be formed in this way. The sodium acetylides are colorless solids which are decomposed by water with the formation of acetylene.

The sodium acetylides offer another method of preparing homologs of acetylene. They react with alkyl halides in the following manner, using liquid ammonia as the solvent.

$$CH_3C{\equiv}CH + Na \longrightarrow CH_3C{\equiv}CNa$$

$$CH_3C{\equiv}CNa + CH_3I \longrightarrow \underset{\text{Dimethylacetylene}}{CH_3C{\equiv}CCH_3}$$

Nomenclature. According to the Geneva system acetylenic hydrocarbons are named by changing the ending *-ane* of the saturated hydrocarbon to *-yne;* the position of the unsaturation is indicated as in the olefins by a numeral before the name. They are also named as alkyl derivatives of acetylene. Thus $CH_3C{\equiv}CH$ is **propyne** or **methylacetylene**; it is a gas boiling at −23°. $CH_3C{\equiv}CCH_3$ is **dimethylacetylene** or **2-butyne;** it boils at 28°. $CH_3CH_2C{\equiv}CH$ is **ethylacetylene** or **1-butyne** (bp 14°).

DIOLEFINS

A class of hydrocarbons isomeric with the acetylenic series is the diolefin series, C_nH_{2n-2}. The members of this series contain two double linkages; the simplest member is **allene,** $CH_2{=}C{=}CH_2$, a gas boiling at −32°.

The Butadienes. Among the most interesting and useful members of the diolefin series are the derivatives of 1,3-butadiene, $CH_2{=}CH{-}CH{=}CH_2$. All these compounds contain two double linkages connected by a single bond. *Such a system of alternate single and double linkages* is known as a *conjugated system of double bonds.* Compounds containing conjugated systems undergo a number of special reactions; one of these, the polymerization reaction, will be discussed later in connection with rubber.

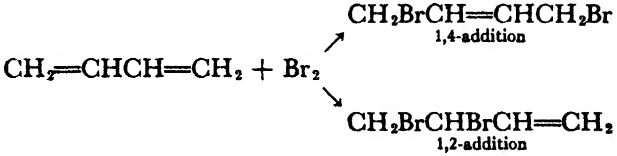
The nomenclature of the diolefins is in accord with the Geneva system. The longest straight chain is named, the ending *-diene* replacing the *-ane* of the saturated hydrocarbon. The position of the two double linkages is indicated by two numerals. Thus $CH_2{=}CH{-}CH{=}CH_2$ is 1,3-butadiene; while $CH_2{=}C{=}CHCH_3$ is 1,2-butadiene.

1,3-Butadiene is a gas which condenses at −4°. **2-Methyl-1,3-butadiene (isoprene)** boils at 34° and **2,3-dimethyl-1,3-butadiene** boils at 70°.

Addition Reactions of Conjugated Dienes. The reactions of conjugated dienes are of extreme interest since they demonstrate the effect of two pairs of double bonds on each other when they are conjugated. Thus, when some of the homologs of butadiene are allowed to react catalytically with hydrogen, and the reaction is stopped after one mole of hydrogen is absorbed, the product obtained indicates a special type of addition.

$$(CH_3)_2C{=}CH{-}CH{=}C(CH_3)_2 + H_2 \xrightarrow{\text{Catalyst}} (CH_3)_2CH{-}CH{=}CH{-}CH(CH_3)_2$$

In this reaction one hydrogen atom has added to each carbon at the end of the conjugated system, and a double bond has formed between the center carbon atoms. This type of addition is known as 1,4-*addition to conjugated systems.* In many addition reactions of such diolefins a mixture of products formed by 1,4-addition to the conjugated system and 1,2-addition to one of the double bonds is obtained. The reaction of 1,3-butadiene with bromine is an example of this.



$$CH_2{=}CHCH{=}CH_2 + Br_2 \begin{cases} \nearrow CH_2BrCH{=}CHCH_2Br \quad \text{1,4-addition} \\ \searrow CH_2BrCHBrCH{=}CH_2 \quad \text{1,2-addition} \end{cases}$$

In other reactions only 1,2-addition may take place. It should be emphasized that 1,4-addition may occur with compounds which have conjugated double bonds, but not with dienes which do not contain the system of alternate single and double linkages.

QUESTIONS AND PROBLEMS

1. A sample of a pure liquid is known to be either 1-pentyne or 1,2-pentadiene. What chemical test could you use to identify the sample?

2. Name the following compounds: $CH_3CH_2CH{=}C(CH_3)_2$, $CH_3CH_2CH_2C{\equiv}CH$, $CH_2{=}C{=}CHCH_2CH_3$, $(CH_3CH_2)_2C{=}C(CH_3)_2$, $CH_2{=}CH{-}CH{=}CHCH_2CH_3$.

3. Write balanced equations for the reactions, if any, between 2-butene and (*a*) bromine, (*b*) hydrogen and a catalyst, (*c*) hypochlorous acid, (*d*) hydrogen bromide, (*e*) sodium hydroxide. Specify the conditions under which each reaction is to be run.

4. What is the peroxide effect in the addition to ethylenic hydrocarbons?

5. How could you convert 1-butanol to (*a*) 2-butanol, (*b*) 2-bromobutane, (*c*) 1-bromobutane, (*d*) 1,2-dibromobutane?

6. How could you prepare (*a*) 1-propyne from isopropyl alcohol, (*b*) butane from *n*-butyl alcohol, and (*c*) 1-propyne from acetylene and methyl alcohol?

7. Define and give examples of polymerization.

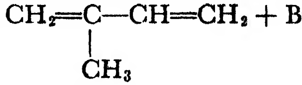
8. A sample of a pure gas is known to be either ethane, ethylene, acetylene, or nitrogen. What chemical tests would you use to identify the gas?

9. What products would you expect to obtain from 1-butyne and (*a*) hydrogen chloride, (*b*) chlorine, (*c*) ammoniacal cuprous chloride?

10. State Markownikoff's rule and show its application to the addition reactions of both ethylenes and acetylenes.

11. Give the structures of: (*a*) 2,3-dimethyl-1,3-butadiene, (*b*) isoprene, (*c*) methylethylacetylene, (*d*) isopropylethylene, (*e*) 2-methyl-2-butene.

12. Define and illustrate: (*a*) addition reaction, (*b*) substitution reaction, (*c*) catalytic hydrogenation, (*d*) acetylides, (*e*) conjugated dienes.

13. Complete the following reactions, indicating when more than one reaction may occur and, if possible, under what conditions: (*a*) $CH_3CHBrCH_2Br + KOH$, (*b*) $(CH_3)_2C{=}CH_2 + HBr$, (*c*) excess CH_3CH_2OH + conc. H_2SO_4 (heated), (*d*)  $CH_2{=}\underset{\overset{|}{CH_3}}{C}{-}CH{=}CH_2 + Br_2$.

14. Define 1,2- and 1,4-addition. Compare the reaction of 1 mole of hydrogen (in the presence of platinum catalyst) with 1 mole of 1,3-hexadiene and with 1 mole of 1,4-hexadiene.

15. Contrast the behavior of primary, secondary, and tertiary alcohols with respect to dehydration and rate of reaction with the halogen acids.

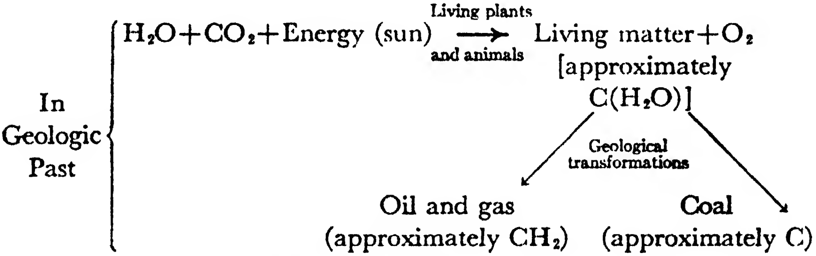
CHAPTER 5

Gasoline and Rubber

Sixty years ago the refining of crude petroleum involved very little chemistry. The most important product was kerosene, then widely used in cities, towns, and villages for burning in lamps as a source of illumination. A simple process of distillation was sufficient to produce this material. Today, gasolines with special characteristics are required for modern combustion engines in automobiles and planes. To produce these products certain rather complicated reactions of hydrocarbons are employed. Furthermore, during World War II a large amount of synthetic rubber was produced from petroleum by a series of complex reactions. In addition, other chemical products, such as the alcohols, may be prepared from petroleum. Therefore the whole subject of the industrial use of petroleum and related substances deserves a special chapter, but the chemical transformations involved can only be understood after the basic knowledge presented in the preceding chapters has been mastered.

Petroleum, natural gas, and coal represent a reservoir of energy which has been stored up in past geologic eras by the reduction of carbon dioxide by living organisms through the use of the sun's energy. (See p. 1.) In the formation of hard coal the reduction has proceeded almost to the point of producing elementary carbon; in petroleum and natural gas it has gone even further to give a mixture of hydrocarbons. Not that the one step precedes the other. At least two types of conversion of vegetable and animal debris were undoubtedly involved in the formation of coal and petroleum.

We can think of the storing of the sun's energy in past geologic ages in terms of the heat evolved when the products we find are burned to carbon dioxide and water. The heat of combustion of starch or cellulose is about 10 kcal per gram of carbon; for pure carbon as graphite the heat of combustion is 7.8 kcal per gram; while for a liquid hydrocarbon the figure is about 13 kcal per gram of carbon. Restated, these figures mean that the principal storage of energy took place when, through the sun's rays, the plants reduced carbon dioxide to starch or its equivalent (the approximate composition of vegetables and animal material). The subsequent changes which either transformed this to coal or gas involved relatively small changes in the stored up energy.



$$\text{Today}\begin{cases} C + O_2 \longrightarrow CO_2 + \text{Heat} \\ CH_2 + \tfrac{3}{2}O_2 \longrightarrow CO_2 + H_2O + \text{Heat} \end{cases}$$

We shall see that, though the energy stored in these various transformation products of reduced carbon dioxide is nearly the same, their molecular structure is so different that quite different chemical reactions can be brought about through their use.

Coal is used as a solid fuel. On destructive distillation it produces coke and a special class of compounds known as *aromatic compounds* which we shall consider later. From coke by the water-gas reaction (steam at a high temperature) carbon monoxide and hydrogen are cheaply manufactured. In Chap. 9 we shall consider how these materials and coal itself can be converted to liquid fuels and such compounds as the alcohols. In this chapter we shall confine our attention to petroleum and natural gas. In the countries where these materials are found they are the raw materials for liquid fuels.

Natural Gas. Natural gas, which occurs in many parts of the United States and elsewhere, is a mixture composed chiefly of methane, together with ethane and the higher members of the paraffin series of hydrocarbons ($C_4H_{10} - C_8H_{18}$). Even those whose boiling points are above room temperature are present in the form of vapor, just as water vapor is present in ordinary air. Natural gas is usually associated with petroleum, and its origins are probably the same.

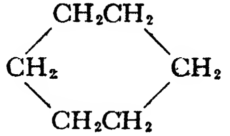
A similar gas, composed chiefly of methane, occurs in coal seams. It is worth pointing out that even today we see evidence of the transformation of vegetable material into a hydrocarbon in the evolution of methane from decaying plants and trees under water, and, hence, in the absence of air. The gas is found bubbling up in certain marshy areas and has been known for a long time as *marsh gas*. Its formation may be approximately formulated as follows:

$$\underset{\substack{\text{Vegetable}\\ \text{material}}}{n(\mathrm{CH_2O})} \xrightarrow[\substack{\text{Absence}\\ \text{of air}}]{\text{Bacteria}} n/2\mathrm{CO_2} + n/2\mathrm{CH_4}$$

Some of the carbon atoms are oxidized and some are reduced.

Petroleum. Petroleum is found in many parts of the world and each field yields a crude oil with its own characteristics. All crude petroleums are complex mixtures of hydrocarbons and contain in addition small amounts of organic compounds containing nitrogen, sulfur, and oxygen. Many theories as to the origin of petroleum have been suggested but no one theory has been conclusively established. It is generally agreed today, however, that petroleum, like coal, represents the transformation of living material formed in past geologic ages. Perhaps the differences between petroleums simply reflect differences in the plant or animal material transformed in the geologic past. For example, the fats and oils (Chap. 8) are nearer in composition to the hydrocarbons than to the starchy and woody parts of plants. If certain groups of plants or animals (perhaps algae or other unicellular organisms) flourished in past geologic periods and produced large quantities of fats and oils, the subsequent changes of this material might have produced petroleum. On the other hand, the same type of plants which yielded coal under one set of conditions may have produced petroleum under another set of conditions.

In addition to the members of the paraffin series most petroleums contain members of the olefin series and often large amounts of a class of compounds isomeric with the olefins but having a cyclic structure. These latter are called *naphthenic hydrocarbons* or *alicyclic hydrocarbons;* they have the general formula C_nH_{2n}. The structural formula of one typical representative, cyclohexane, follows.



Rings of five and six carbon atoms are commonly present; smaller and larger rings are rare (Chap. 21).

Distillation of Petroleum. Quite apart from the differences in chemical composition and structure, the constituents of petroleum differ enormously in their physical properties. At the one extreme are the volatile lower members of the paraffin and olefin series; at the other are substances of such high molecular weight that they decompose before they boil (even under reduced pressure). For practical purposes it is necessary to separate the crude oil into different portions corresponding to the different range of volatility of the constituents. Therefore, the first step in the refining of petroleum is distillation.

The lowest boiling portion (below 70°) is sometimes used in the laboratory as a solvent; it is known as *ligroin* or *petroleum ether.* When obtained from Pennsylvania oil, it is largely composed of pentanes and hexanes. The material which boils between 85° and

200° is usually sold as **gasoline. Kerosene** is the next fraction; it usually boils in the range 200° to 300°; it will not take fire directly, but, if allowed to moisten a wick in a suitable lamp, it will burn with a pleasant luminous flame.

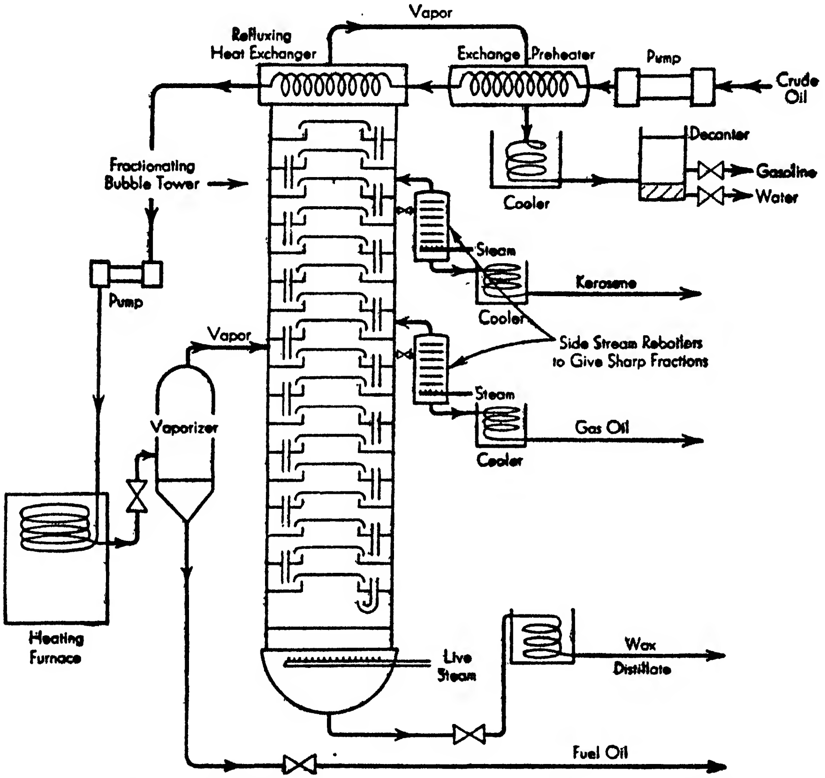


Fig. 4. Diagram of a modern crude oil distillation unit. (It will be noted that the crude oil starts at the upper right hand corner of the diagram and the products are taken off below on the right.)

The residual oil left after the gasoline and kerosene have been distilled is called *topped crude* or *fuel oil*. It is used as fuel. For the most part, fuel oils are blown out from a nozzle in the form of a fine spray mixed with air or steam. This spray is ignited and gives a hot flame. Locomotives and steamships are often fired with crude oil.

Certain kinds of crude petroleum yield on distillation high-boiling oils which are used as **lubricating oils** and a solid, wax-like material, **paraffin**, used in the manufacture of candles. Such oils are said to have a *paraffin base.* From them are also prepared soft greases such as **vaseline,** which is essentially paraffin mixed with some liquid hydrocarbon which has not been removed in the refining. Other varieties of petroleum do not give lubricating oils and paraffin but a thick, black pitch, which is used in roofing and paving; such oils are called *asphaltic.* Pennsylvania petroleum has a paraffin base; Mexican and California oils are for the most part asphaltic. "Liquid petrolatum," or "mineral oil," is a carefully refined, high-boiling distillate obtained from certain oils which do not yield paraffin.

Petroleum Refining. The method of further refining petroleum distillates depends on the kind of objectionable components in the fractions. The undesirable materials are certain olefin hydrocarbons (Chap. 4), which cause gum and tar formation, and sulfur compounds which have bad odors and produce sulfur dioxide when burned.

The elimination of the unsaturated hydrocarbons is generally brought about by treating the petroleum fraction for a short time in the cold with fairly concentrated sulfuric acid. Under specially controlled conditions, the paraffins and cycloparaffins are unaffected. To remove traces of acid, the fraction is agitated with sodium hydroxide solution. Sulfur compounds are removed by special methods.

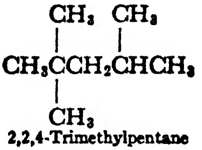
Two other methods of refining are now used. In one the hydrocarbon fraction is extracted with an immiscible solvent which removes the undesirable components. Among the solvents used are liquid sulfur dioxide, furfural (p. 378), and phenol (p. 271). The extraction method is widely used in the refining of lubricating oils and to a less extent for gasoline refining. The other process of refining is to pass the petroleum vapors through a column of natural clay, silica gel, or activated charcoal. In this method the undesirable components are selectively adsorbed from the petroleum mixture.

THE MANUFACTURE OF GASOLINE

With the increase in the number of automobiles the demand for gasoline threatened to exceed the supply available from the distillation of petroleum. About thirty years ago it was discovered that some of the high-boiling fractions could be partially converted to low-boiling fractions by thermal decomposition at high temperatures. This process, known as *cracking*, soon assumed great importance in the industry. Later it was found that some types of hydrocarbons performed better in high-compression engines than others and practical ways of preparing these hydrocarbons were developed. Today, therefore, the manufacture of gasoline involves not only the production of the maximum amount of a low-boiling fraction from petroleum, but the production of a gasoline which will have the maximum content of hydrocarbons of certain structures. This was accomplished by a combination of three processes, *cracking*, *isomerization*, and *alkylation*.

Octane Ratings of Gasoline. An internal combustion engine which has a high-compression ratio is more efficient than an engine with a low one. This has been known for a long time but a limit to the compression was set by the fact that, with the gasolines on the market thirty years ago, excessive knocking occurred if the compression ratio was increased. After a great deal of experimentation it was found in 1922 that such knocking could be largely overcome by adding a small amount of tetraethyllead, $(C_2H_5)_4Pb$, to the gasoline. Gasoline thus treated became known as *ethyl gas*.

In the course of the same investigation it was found, by experimentation with samples of pure hydrocarbons, that certain highly branched compounds caused less knocking than did others. The octane, 2,2,4-trimethylpentane, was arbitrarily chosen as the reference standard and said to have an octane rating of 100; *n*-heptane was given the rating 0, and a scale of octane ratings was thus established. Any gasoline could be compared in a suitable test engine



$$\begin{array}{ccccc} & CH_3 & & CH_3 & \\ & | & & | & \\ CH_3 & C & CH_2 & CH & CH_3 \\ & | & & & \\ & CH_3 & & & \end{array}$$

2,2,4-Trimethylpentane

with mixtures of these two pure hydrocarbons or samples of gasoline containing varying amounts of tetraethyllead which had been previously calibrated against the standard mixture.

The straight-chain hydrocarbons C_4—C_8 have very low octane ratings; the corresponding isomeric branched-chain hydrocarbons have octane ratings which are considerably higher. Aromatic hydrocarbons and the cycloparaffins (naphthenes) have high octane ratings, particularly the former. In view of these facts and the complicated mixture of substances present in petroleum it is not surprising that the low-boiling distillates from the refining of petroleum, called *straight-run gasolines*, from different fields differ widely in their octane rating. Tetraethyllead is added to bring up the octane value, but there is a limit to its effectiveness. Therefore if the hydrocarbons themselves can be converted into branched-chain compounds the octane rating can be raised still more.

Cracking or Thermal Decomposition. When a paraffin hydrocarbon is heated to a high temperature it is broken down into a number of smaller fragments. The process can be illustrated with *n*-butane.

$$CH_3CH_2CH_2CH_3 \xrightarrow{> 400^\circ} \left\{\begin{array}{l} CH_2{=}CH_2 + CH_3CH_3 \\ CH_3CH{=}CH_2 + CH_4 \\ CH_3CH{=}CHCH_3 + H_2 \end{array}\right.$$

With higher members of the series the reaction is even more complex. Thus from a C_{12} hydrocarbon (bp about 210°) there would be obtained saturated and unsaturated hydrocarbons from C_{11} to C_2 inclusive, together with hydrogen and methane. To the extent that C_4 to C_7 hydrocarbons predominated, the boiling point of the mixture would be brought down to the range required for gasoline. The nature of the products depends on (1) the feed stock (i.e., the high-boiling petroleum fraction), (2) the temperature and pressure, and (3) the catalysts. Some cracking processes operate in the vapor phase, some in the liquid phase (under pressure). When no catalyst is employed the process is referred to as *thermal cracking*.

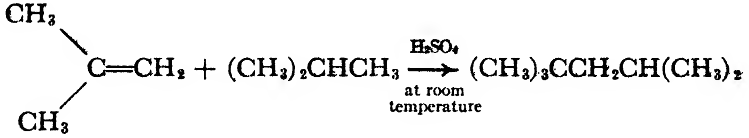
Isomerization and Alkylation. Cracking under suitable conditions, followed by very careful fractional distillation, enables the gasoline manufacturer (petroleum refiner) to prepare on a large scale such hydrocarbons as ethylene, propylene, butane, isobutane, and the butenes. *Isomerization*, heating with aluminum chloride as a catalyst, enables him to shift the isomeric butanes one to the other.

$$CH_3CH_2CH_2CH_3 \overset{AlCl_3}{\rightleftarrows} (CH_3)_3CH$$

Finally, the combination of a paraffin with an olefin—*alkylation*—enables him to synthesize hydrocarbons whose boiling points are in the proper range for gasoline and whose branched-chain structure gives them excellent antiknock properties. By the combination of ethylene and isobutane a so-called neohexane (2,2-dimethylbutane) is prepared. This volatile material, which has a high octane rating (94), is an important constituent of the best aviation gasoline.

$$CH_2{=}CH_2 + (CH_3)_2CHCH_3 \xrightarrow[100^\circ]{ZrCl_4} \underset{\text{Neohexane}}{CH_3CH_2C(CH_3)_3}$$

Another alkylation reaction of great importance industrially is the combination of isobutane and isobutene to form 2,2,4-trimethylpentane (octane rating 100).



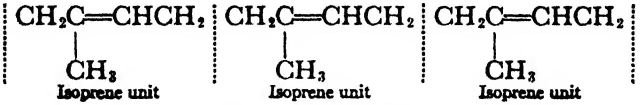
$$(CH_3)_2C{=}CH_2 + (CH_3)_2CHCH_3 \xrightarrow[\text{at room temperature}]{H_2SO_4} (CH_3)_3CCH_2CH(CH_3)_2$$

These examples must suffice to show how, by a combination of cracking, isomerization, and alkylation, the constituents of high-test gasoline can be manufactured.

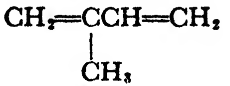
SYNTHETIC RUBBER

A plentiful supply of gasoline with suitable characteristics is essential to the automobile and airplane industry. So too is a supply of rubber. Indeed the introduction of the automobile and the subsequent enormous increase in the number of motor cars caused a revolution in the rubber industry no less than in the petroleum industry. The first phase of this revolution was the cultivation of the rubber tree on plantations in Ceylon and the Straits Settlements. Plantation rubber soon replaced in the world markets the wild rubber from the jungles of South America. The second phase was the development of artificial rubber during World War II when the supply of plantation rubber was threatened and finally cut off by the Japanese. To understand this development it is necessary to know something about the structure of natural rubber.

The Structure of the Rubber Molecule. The naturally occurring hydrocarbon which is raw rubber has the formula $(C_6H_8)_x$. The material is insoluble in water, of course, but soluble in many hydrocarbon solvents. The molecular weight is very large and for a long time was the subject of much discussion. (Only in the last twenty-five years have we learned how to study compounds of high molecular weight.) The best estimates, based on osmotic pressure measurements of benzene solutions, now indicate that from 200 to 4000 C_5H_8 units are united in a long chain in the rubber molecule (molecular weight, 13,600 to 272,000), the size of the molecule depending on the previous treatment of the raw rubber. Oxidation of raw rubber with ozone (p. 57) and subsequent hydrolysis of the ozonide show that the double linkages are placed in the chain as indicated below.



$$\vdots\ CH_2\underset{\underset{\displaystyle CH_3}{|}}{C}{=}CHCH_2\ \vdots\ CH_2\underset{\underset{\displaystyle CH_3}{|}}{C}{=}CHCH_2\ \vdots\ CH_2\underset{\underset{\displaystyle CH_3}{|}}{C}{=}CHCH_2\ \vdots$$



$$CH_2{=}\underset{\underset{\displaystyle CH_3}{|}}{C}CH{=}CH_2$$

Isoprene

It will be clear that such an arrangement of atoms corresponds to the joining together of a series of isoprene molecules (p. 63) in a regular fashion. It is therefore not surprising that years ago it was discovered that rubber on thermal decomposition yielded isoprene, and that this diolefin on standing with metallic sodium yielded a rubberlike material (which was not identical with rubber).

Vulcanization. Natural rubber without further chemical transformation is not a useful substance. While it is elastic, it is not very tough; it cannot be shaped into useful articles and it deteriorates through slow atmospheric oxidation. More than a hundred years ago it was discovered that raw rubber could be converted into a much more durable material by heating with sulfur. This process is called *vulcanization.* A similar change can be brought about by peroxides. The vulcanized rubber is less unsaturated than raw rubber, is of higher molecular weight, and almost certainly has what are called *cross links* between the long hydrocarbon chains of the original molecule. These cross links may be from carbon to carbon or may involve a sulfur atom, or, when peroxides are used, oxygen, or all three. Our knowledge of the molecular structure of vulcanized rubber is far from complete. Indeed in the finished rubber products many varieties of large molecules are probably present.

In the manufacture of tires or similar rubber articles, the raw rubber is milled between warm rollers. This process results in a plastic mass into which sulfur and materials such as zinc oxide and carbon black are incorporated. The mixture is then heated in a mold to temperatures of 100° to 150°. The vulcanization then takes place. The time of the "cure" is enormously reduced by the introduction of small amounts of organic compounds known as *accelerators;* some of these are organic nitrogen compounds (bases) and some are organic sulfur compounds.

From an industrial viewpoint it is of the greatest importance that crude rubber can be "broken down" in the mill to a plastic mass and subsequently "set" to a rigid shape by heating in a mold; this fact alone makes possible the manufacture of rubber goods in a variety of shapes. Vulcanization is not only important because of the change in the properties of the hydrocarbon, but because of the way it allows the manufacturer to manipulate the material. The initial "milling" of the raw rubber probably involves both physical and chemical changes. The oxygen of the air causes a certain amount of oxidation and a degradation of the molecule. The average molecular weight is decreased by the milling. The subsequent vulcanization then unites the smaller molecules into very large ones with "cross linking."

Synthetic Polymeric Hydrocarbons. Strictly speaking, synthetic rubber would be a material identical with natural raw rubber but prepared synthetically. If isoprene could be polymerized under just the right conditions a group of high-molecular-weight substances might be formed identical with that found in natural latex. Actually the high-molecular-weight materials obtainable from isoprene differ considerably in physical properties from raw rubber. And, because of the greater availability of certain other hydrocarbons, no commerical polymer of isoprene is made today. Therefore when we speak of synthetic rubber we mean a rubberlike material or rubber substitute.

Buna Rubber. The synthetic rubber, so called, produced in the United States during World War II was largely Buna S. This is a copolymer. (A copolymer is a material of very large molecular weight formed by the polymerization of two or more different kinds of small molecules, whereas a polymer, like polyethylene, is built up from a single kind of small molecule.) Buna S was first developed in Germany. Butadiene is the chief constituent, about 75 per cent by weight; styrene, $C_6H_5CH{=}CH_2$, is the other. (The grouping C_6H_5 represents a special type of cyclic hydrocarbon structure known as a *phenyl group;* it is derived from the hydrocarbon benzene, C_6H_6, to be considered in detail later. As far as synthetic rubber is concerned, this hydrocarbon residue may be considered as analogous to an alkyl group.) In Buna S there are almost as many double linkages as there are in natural rubber. The material can be vulcanized in the usual manner.

The copolymerization of butadiene and styrene is carried out by making an emulsion of these two hydrocarbons in water with the aid of small amounts of soaplike substances known as *emulsifying agents*. A catalyst is added which is an oxidizing agent, such as a peroxide, and the whole is heated under pressure to prevent the escape of the volatile butadiene. In this way the equivalent of an artificial latex is formed. The emulsion then passes through a column and is subjected to a sort of "steam distillation" which removes the hydrocarbon which has not polymerized. It is then heated with acid which coagulates the synthetic rubber. This final material is easily separated from the aqueous layer and dried as sheet material in a way very similar to that employed in handling the final product from natural latex.

In the more recently developed cold polymerization process the use of a catalyst activator permits the polymerization to be effected at a temperature of about 5° instead of 50° and results in a synthetic rubber of better quality.

Neoprene. The polymerization of a diolefin by itself would seem to be the most direct route to a material similar to natural rubber. Isoprene is not available in sufficient quantity for a starting material, and the polymers of butadiene by itself have not proved as yet to be as suitable as the copolymer just discussed. There are reports, however, that when polymerized by itself, butadiene yields a satisfactory artificial rubber. No such material has been produced industrially in the United States. The first American synthetic rubber, however, was the result of the polymerization of a diolefin closely related to butadiene and isoprene, namely 2-chlorobutadiene or chloroprene. This material can be manufactured from acetylene by the following reactions.

$$2CH{\equiv}CH \xrightarrow[\text{copper salt as catalyst}]{\text{Aqueous solution of}} \underset{\text{Vinylacetylene}}{CH{\equiv}C{-}CH{=}CH_2}$$

$$CH{\equiv}C{-}CH{=}CH_2 + \underset{\text{Gas}}{HCl} \longrightarrow \underset{\text{Chloroprene (bp 60°)}}{CH_2{=}CCl{-}CH{=}CH_2}$$

Chloroprene polymerizes to a rubberlike material more readily than does butadiene or isoprene; the polymerization can be accomplished at room temperature in a short time. The polymerization may be stopped at a stage in which the product has the properties of natural rubber. This material may be mixed with fillers and coloring materials in the same way as natural rubber. The product is then heated for a short time a little above 100° and polymerization proceeds further, yielding a material having the properties of vulcanized rubber. This rubber is more resistant to the action of solvents and other chemicals than ordinary vulcanized rubber. In spite of its relatively high cost the product has wide industrial use. The structure of the long hydrocarbon chain in chloroprene is probably very similar to that in natural rubber, and the last step in the polymerization (the equivalent of vulcanization) may well involve the formation of cross linkages.

ALCOHOLS AND HYDROCARBONS

Alcohols can be prepared from hydrocarbons and hydrocarbons can be prepared from alcohols. Olefins in the presence of sulfuric acid at room temperature yield alcohols, while alcohols heated with a catalyst yield olefins. When we realize that olefins can be formed by the thermal and catalytic decomposition of paraffin hydrocarbons we realize how interchangeable these materials are from an industrial point of view. This was illustrated in the development of the synthetic rubber industry in the United States during World War II. The manufacture of large quantities of butadiene was the bottleneck of the entire effort. Two basic raw materials were available: starch and petroleum or natural gas. From the former by fermentation ethyl alcohol was prepared (p. 19). This can be converted into butadiene in two catalytic steps involving dehydrogenation, dehydration, and combination.

$$2C_2H_5OH \xrightarrow[\substack{100^\circ\text{-}200^\circ \\ \text{two steps}}]{\text{Catalysts}} CH_2{=}CHCH{=}CH_2 + 2H_2O + H_2$$

Ethyl alcohol, however, can be readily prepared from ethylene, and thus from petroleum by cracking reactions.

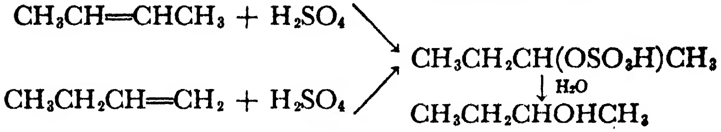
$$CH_2{=}CH_2 + H_2SO_4 \longrightarrow CH_3CH_2OSO_3H \xrightarrow{H_2O} CH_3CH_2OH$$

Students particularly interested in the economics of agriculture will note that as a raw material for the production of ethylene and substances manufactured from ethylene, starch and petroleum are in competition. Which provides the cheapest source will vary from place to place and time to time.

Higher Alcohols from Petroleum. From the higher olefins, other alcohols can be readily prepared commercially. Isopropyl alcohol is manufactured from propylene, and secondary butyl alcohol from the two normal butenes.

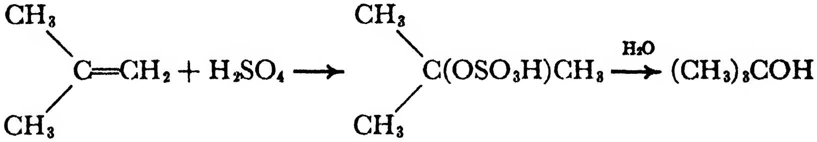
$$CH_2{=}CH_2 + H_2SO_4 \longrightarrow CH_3CH_2OSO_3H \xrightarrow{H_2O} CH_3CH_2OH$$

$$\begin{array}{l} CH_3CH{=}CH_2 + H_2SO_4 \longrightarrow CH_3CH(OSO_3H)CH_3 \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad \downarrow H_2O \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad CH_3CHOHCH_3 \end{array}$$



$$\begin{array}{lcl} CH_3CH{=}CHCH_3 + H_2SO_4 & \searrow & \\ & & CH_3CH_2CH(OSO_3H)CH_3 \\ & & \quad\downarrow H_2O \\ CH_3CH_2CH{=}CH_2 + H_2SO_4 & \nearrow & CH_3CH_2CHOHCH_3 \end{array}$$

Tertiary alcohols result from the branched olefins; isobutylene yields tertiary butyl alcohol.



In all these reactions no attempt is made to isolate the intermediate alkylsulfuric acid; the absorption of the gaseous hydrocarbon and the hydrolysis are carried out in one process.

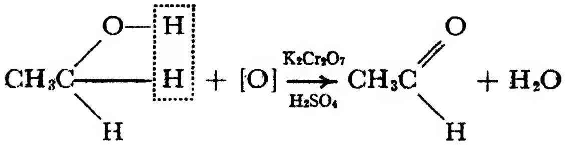
QUESTIONS AND PROBLEMS

1. Compare the storage of solar energy in carbohydrates, coal, and petroleum.
2. Give specific examples of the chemical reactions whereby alcohols can be converted into hydrocarbons and hydrocarbons into alcohols.
3. Describe the distillation of petroleum.
4. What is the structure of the natural rubber molecule?
5. Show the importance of cracking, isomerization, and alkylation in the manufacture of gasoline.
6. Define and illustrate the terms polymer and copolymer.
7. What is the octane rating of a gasoline?
8. What is chloroprene, Buna S, Neoprene?
9. How is rubber vulcanized and what is the chemistry involved?
10. Are natural rubber and synthetic rubber identical? How would you define the term synthetic rubber?

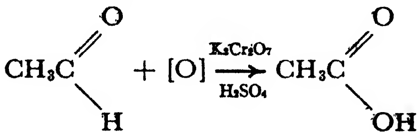
CHAPTER 6

Aldehydes and Ketones

Oxidation of Primary Alcohols. When a primary alcohol is cautiously oxidized, it is possible to isolate a substance known as an *aldehyde*. For example, if ethyl alcohol is slowly added to a mixture of sodium dichromate and sulfuric acid, and the volatile products allowed to distil, we find in the distillate considerable quantities of acetaldehyde, CH_3CHO.

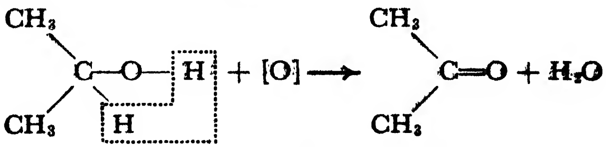


If, however, we arrange the apparatus so that the volatile aldehyde is returned to the reaction flask, the aldehyde is oxidized to the corresponding acid, acetic acid, CH_3COOH.



The organic acids, of which acetic acid is an important example, will be discussed in Chap. 7.

Oxidation of Secondary Alcohols. When a secondary alcohol is oxidized, a ketone is formed.



Here there is little danger that the oxidation will proceed too far; ketones are oxidized only with difficulty and never to a product with the same number of carbon atoms.

It will be noted that both these processes of oxidation consist in the removal of two hydrogen atoms which have been indicated in the formulas. The process is really one of **dehydrogenation;** this term is often applied to it. We may suppose that the function of the oxidizing agent is to supply oxygen to combine with the two hydrogen atoms and form water.

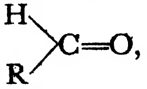
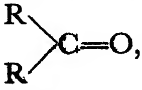
At high temperature in the presence of metallic copper or copper chromite, primary and secondary alcohols spontaneously lose hydrogen and form aldehydes or ketones and gaseous hydrogen.

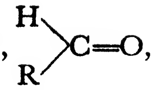
$$RCH_2OH \xrightarrow[300^\circ]{\text{Copper}} RCHO + H_2$$

$$R_2CHOH \xrightarrow[300^\circ]{\text{Copper}} R_2CO + H_2$$

This provides a convenient method of preparing ketones and aldehydes from the corresponding alcohols.

ALDEHYDES AND KETONES

The Carbonyl Group. Aldehydes and ketones both contain the group $>C{=}O$; this is known as the *carbonyl* group. Since they both contain this reactive group, they have many chemical properties in common. The differences between aldehydes and ketones are due to the fact that in the aldehydes,  $\begin{matrix}H\\R\end{matrix}\!\!>C{=}O$, we have one alkyl group and one hydrogen atom attached to the carbonyl group, and in ketones,  $\begin{matrix}R\\R\end{matrix}\!\!>C{=}O$, two alkyl groups. As a result, aldehydes but not ketones are readily oxidized to acids, RCOOH.

It is customary to write the formula of an aldehyde,  as RCHO. Formulas corresponding to RCOH are never used as this might signify that the hydrogen was attached to oxygen.

Physical Properties of Aldehydes. The physical properties of the lower members of the homologous series of aldehydes are given below. The first five all have a peculiar sharp odor. The higher aldehydes have a pleasant odor. Some of them occur in fruits and plants; for example, nonyl aldehyde, $C_8H_{17}CHO$, is found in geranium oil.

Physical Properties of the Simpler Aldehydes

Name	*Formula*	*Boiling Point*	*Solubility Grams per 100 Grams of Water*
Formaldehyde	$HCHO$	−21°	Miscible
Acetaldehyde	CH_3CHO	+20°	Miscible
Propionaldehyde	CH_3CH_2CHO	+50°	20
n-Butyraldehyde	$CH_3CH_2CH_2CHO$	+76°	3.6
Isobutyraldehyde	$(CH_3)_2CHCHO$	+61°	11
n-Valeraldehyde	$CH_3(CH_2)_3CHO$	+103°	

Nomenclature of Aldehydes and Ketones. The aldehydes are named from the acids to which they may be oxidized, as is illustrated by the names in the table. They are also named by the Geneva system, the suffix *-al* being employed. Thus, $CH_3(CH_2)_3CHO$ is pentanal and $(CH_3)_2CHCH_2CHO$ 3-methylbutanal.

The ketones may be classified as simple ketones, RCOR, in which the alkyl groups are the same, and mixed ketones in which they are different, RCOR′. One method of naming ketones is illustrated in the following table. By the Geneva system, the longest chain of carbon atoms is named and the suffix *-one* added, preceded by a number which indicates the position of the carbonyl group. Thus $CH_3COCH_2CH_2CH_3$ is 2-pentanone; $(CH_3)_2CHCOCH_2CH_3$, 2-methyl-3-pentanone.

KETONES

Name	*Formula*	*Boiling Point*	*Solubility Grams per 100 Grams of Water*
Acetone	CH_3COCH_3	56°	Miscible
Methyl ethyl ketone	$CH_3COCH_2CH_3$	80°	25
Diethyl ketone	$CH_3CH_2COCH_2CH_3$	102°	About 20
Methyl *n*-propyl ketone	$CH_3COCH_2CH_2CH_3$	102°	4
Methyl isopropyl ketone	$CH_3COCH(CH_3)_2$	93°	Very slightly soluble
Ethyl *n*-propyl ketone	$CH_3CH_2COCH_2CH_2CH_3$	124°	
Ethyl isopropyl ketone	$CH_3CH_2COCH(CH_3)_2$	115°	

Preparation of Ketones. Aldehydes and ketones are often prepared from the *corresponding alcohols* by oxidation or dehydrogenation, as explained in the first paragraphs of this chapter (p. 80).

1. From Acids. We may also prepare ketones from the *corresponding acids.*

The vapor of the acid is passed through a hot tube containing manganese oxide, MnO, or thorium oxide, ThO_2, as a catalyst. On the surface of the catalyst a reaction takes place yielding the ketone.

$$2RCOOH\text{ (vapor)} \xrightarrow[300°]{MnO} R_2CO + H_2O + CO_2$$

Mixed ketones, for example, methyl ethyl ketone, may be prepared by passing a mixture of the two acids in question over the catalyst. In addition to the mixed ketone, a mixture of the other two possible ketones is always formed. For this reason it is preferable to prepare such mixed ketones by oxidizing the corresponding secondary alcohol, if it can be readily procured.

2. From Dihalides. The hydrolysis of a compound having two halogen atoms on the same carbon atom might be expected to produce a substance having the group $C(OH)_2$. Actually either an aldehyde or ketone is formed. All but a few compounds (see chloral, p. 97) containing two hydroxyl groups on the same carbon atom are unstable, and lose water forming a carbonyl group.

$$CH_3CCl_2CH_3 + H_2O \xrightarrow[\text{catalyst}\ 100^\circ]{\text{Alkaline}} CH_3COCH_3 + 2HCl$$

Preparation of Aldehydes. Similar procedures may be used for the production of aldehydes. By passing the vapors of an acid and formic acid, HCOOH, over a suitable catalyst, considerable aldehyde is formed.

$$RCOOH + HCOOH \xrightarrow[300^\circ]{MnO} RCHO + H_2O + CO_2$$

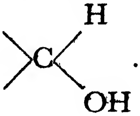
Oxidation of Aldehydes. The chief difference between aldehydes and ketones is that the former are very easily oxidized to an acid while the latter are oxidized only with difficulty. Furthermore, when ketones are oxidized, a carbon-carbon bond is broken, and acids with fewer carbon atoms are the products. The difference in the ease of oxidation is the basis for several tests which enable us to distinguish between the two classes of substances. When aldehydes are warmed with an **ammoniacal solution of silver nitrate,** they precipitate metallic silver which often comes down in the form of a beautiful mirror. The aldehyde is oxidized to the corresponding acid which is present in the alkaline solution as the ammonium salt.

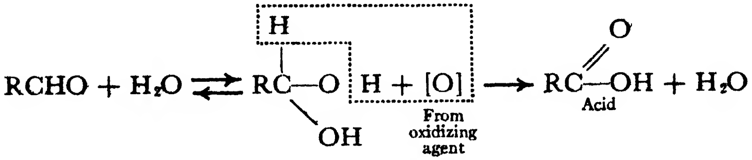
$$RCHO + 2AgOH + NH_4OH \longrightarrow RCOONH_4 + 2Ag + 2H_2O$$

Similarly, when an alkaline solution of copper hydroxide containing sodium tartrate (essentially copper hydroxide in solution) — **Fehling's solution** — is warmed with an aldehyde, red cuprous oxide is precipitated.

$$RCHO + 2Cu(OH)_2 + NaOH \longrightarrow RCOONa + Cu_2O + 3H_2O$$

These tests are very easy to carry out and are frequently employed. Ammoniacal silver nitrate and Fehling's solution are often spoken of as *mild* oxidizing agents, since most organic compounds are not attacked by them.

Mechanism of the Oxidation. The oxidation of aldehydes in solution is another example of dehydrogenation. There is considerable evidence to indicate that the aldehydes are hydrated in water solution; these hydrates, like the primary and secondary alcohols, contain the group  . The following equation represents the course of the oxidation of aldehydes.

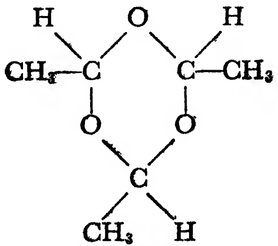


$$RCHO + H_2O \rightleftarrows R\overset{H}{\underset{OH}{C}}—O\,H + [O] \longrightarrow R\overset{O}{\overset{\|}{C}}—OH + H_2O$$

Polymerization of Aldehydes. Aldehydes and ketones differ in still another respect. When an aldehyde is treated with a small amount of mineral acid, it is almost completely *polymerized.*

$$3RCHO \overset{\text{Catalyst}}{\rightleftarrows} (RCHO)_3$$

Unlike the polymerization of ethylene (p. 57), only *three* molecules unite and the reaction is readily reversible. That is to say the polymers can be readily *depolymerized* to acetaldehyde. The polymer of acetaldehyde is known as *paraldehyde.* It is a much higher boiling liquid than acetaldehyde and, unlike acetaldehyde, is insoluble in water. It has none of the characteristic reactions of the aldehydes; for example, it will not reduce Fehling's solution. In the polymer the three aldehyde molecules are joined together in a ring containing alternate carbon and oxygen atoms. Paraldehyde is used as a hypnotic.



Paraldehyde

At low temperatures acetaldehyde is polymerized by dilute sulfuric acid to a crystalline solid known as *metaldehyde*. Like paraldehyde it shows no aldehydic properties. It can be converted into acetaldehyde by distilling with dilute acid. It burns in air with a nonluminous flame and is marketed as a solid fuel for household use in place of "solid alcohol." The trade name for it is "Meta." Metaldehyde is a tetramer, $(CH_3CHO)_4$.

Reversible Reactions. A consideration of the polymerization of an aldehyde is of interest as an example of a reversible reaction. The polymerization, which takes place rapidly at room temperature in the presence of a catalyst, does not run to completion. Instead a state of equilibrium is attained in which measurable quantities of initial material and product are present. For example, when pure acetaldehyde is treated with a few drops of sulfuric acid, it rapidly polymerizes until somewhat more than 95 per cent of the material is present as paraldehyde. In the same way, when pure paraldehyde is treated with a little acid, a few per cent depolymerizes, but no more. We are here dealing with a state of dynamic equilibrium. The reaction appears to stop, but actually the speeds of the polymerization process and the depolymerization reaction are equal; as many molecules are formed in a given time as break up. The composition of the equilibrium mixture is the same whether we start with pure acetaldehyde or paraldehyde.

Importance of the Catalyst. It must be clearly borne in mind that the reaction is reversible *only* in the presence of a suitable catalyst, such as a mineral acid. Pure acetaldehyde or pure paraldehyde may be kept unchanged for a long period of time and may be distilled without decomposition. The rate of the reaction in either direction becomes appreciable only in the presence of a catalyst. For example, to prepare paraldehyde we treat cold acetaldehyde with a few drops of acid, and, after a few minutes, when equilibrium has been established, wash away with water or dilute alkali both the unchanged aldehyde and the catalyst. The paraldehyde can then be dried, distilled, and kept just like any other organic substance.

To convert paraldehyde (bp 124°) into acetaldehyde it is only necessary to add a few drops of mineral acid and slowly distil. Since the acetaldehyde boils at 20°, it rapidly volatilizes and is thus removed from the equilibrium mixture. More paraldehyde then depolymerizes, and this process continues until all the paraldehyde has depolymerized and distilled over in the form of acetaldehyde. This is an excellent example of the completion of a reversible reaction by removing one of the products from an equilibrium mixture which contains appreciable quantities of factors and products.

Polymers of Formaldehyde. Trioxane, $(HCHO)_3$, is the cyclic trimer from formaldehyde which corresponds in structure to paraldehyde. It is a crystalline solid which has no aldehyde properties, but which decomposes on heating to form gaseous formaldehyde.

Formaldehyde also forms solid polymers of unknown molecular weight, $(HCHO)_x$. These are known as *polyoxymethylenes.* They are amorphous solids insoluble in all solvents; they show no aldehydic reactions, and on heating decompose to give formaldehyde. They are formed by evaporating an aqueous solution of the aldehyde and on treating an alcoholic solution with acid. The large molecule present in these polymers is composed of a chain of 40 to 100 formaldehyde units. A portion of this chain may be represented thus:

$$\cdots OCH_2{-}O{-}CH_2{-}O{-}CH_2{-}O{-}CH_2{-}O{-}CH_2{-}O{-}CH_2\cdots$$

Depending on the method of formation, the terminal groups of the long chain are either $-OH$ or $-OCH_3$ (the latter from the methyl alcohol used in the preparation). Acetaldehyde and the higher homologs of formaldehyde do not form such long-chain polymers under the usual conditions.

ADDITION REACTIONS OF THE CARBONYL GROUP

So far, we have stressed the differences between aldehydes and ketones. We shall now consider their many similarities. The carbonyl group, $>C{=}O$, in both substances is very reactive and adds many reagents. Such addition reactions, as we have seen, are characteristic of substances with a double linkage (p. 53). The double linkage in aldehydes and ketones is between carbon and oxygen in contrast with that in ethylene which involves only carbon atoms. The reagents which add to the carbonyl group and to the ethylene linkage are, therefore, for the most part very different.

Hydrogenation. Aldehydes and ketones are both readily hydrogenated to the corresponding primary and secondary alcohols by the use of hydrogen and a catalyst.

$$CH_3CHO + H_2 \xrightarrow{\text{Catalyst}} CH_3CH_2OH$$

$$(CH_3)_2C{=}O + H_2 \xrightarrow{\text{Catalyst}} CH_3CHOHCH_3$$

This is the reversal of the process by which aldehydes and ketones may be prepared, and, at temperatures of about 200° in the presence of copper or nickel, there is a mobile equilibrium; with increasing temperature the dehydrogenation is favored.

$$R_2CHOH \underset{200^\circ\text{–}300^\circ}{\overset{\text{Catalyst}}{\rightleftarrows}} R_2C{=}O + H_2$$

At room temperature, hydrogen and a suitable catalyst will hydrogenate aldehydes and ketones practically completely; above 200° the reverse reaction is evident. The aldehydes, ketones, and alcohols undergo other reversible reactions at still higher temperatures so that the dehydrogenation process (unlike the hydrogenation) is never quantitative.

Reduction. Hydrogen may also be added to the carbonyl group by using some reagent which liberates "nascent hydrogen." For example, zinc and acid, sodium and alcohol, or sodium amalgam and water are often employed. We shall use the symbol [H] for the hydrogen which comes from such reducing agents. These reagents usually reduce aldehydes and ketones to alcohols.

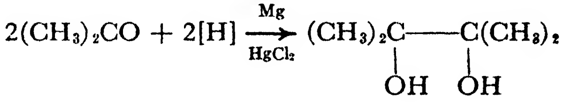
$$R_2CO + 2[H] \longrightarrow R_2CHOH$$

An effective reagent which is specific for the reduction of the carbonyl group of aldehydes and ketones is aluminum isopropoxide.

$$3RCHO + Al[OCH(CH_3)_2]_3 \longrightarrow (RCH_2O)_3Al + 3CH_3COCH_3$$

$$(RCH_2O)_3Al \xrightarrow{H_2SO_4} 3RCH_2OH + Al_2(SO_4)_3$$

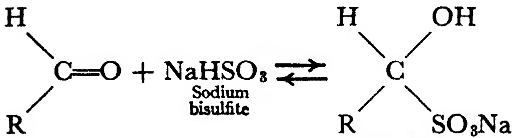
Dimolecular Reduction. Ketones can be also reduced to 1,2-dihydroxy compounds known as *pinacols;* this type of reduction involves the joining of two molecules and is called *dimolecular reduction.* It is accomplished by metals in alkaline solution; amalgamated magnesium is particularly effective.



$$2(CH_3)_2CO + 2[H] \xrightarrow[HgCl_2]{Mg} (CH_3)_2\underset{\displaystyle OH}{\underset{|}{C}}\text{——}\underset{\displaystyle OH}{\underset{|}{C}}(CH_3)_2$$

The simplest representative, whose preparation from acetone is shown by the equation above, is called *pinacol.* Here, as elsewhere in organic chemistry, the name of the earliest known representative of a class of compounds has become the general name for the class.

Bisulfite Reaction. Ketones which contain one methyl group adjacent to the carbonyl group, and all aldehydes, combine with sodium bisulfite to form solid crystalline compounds soluble in water but insoluble in an excess of sodium bisulfite solution.



Crystalline solid
"bisulfite addition product"

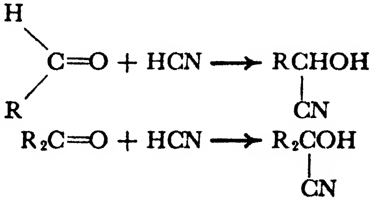
It is still unsettled whether in the bisulfite addition compound the sulfite group is linked to carbon through oxygen or sulfur.

Purification of Aldehydes and Methyl Ketones. On shaking an aldehyde with sodium bisulfite solution and cooling, a crystalline mass of the bisulfite addition product is formed which can be filtered. This reaction is utilized for purifying aldehydes and methyl ketones. The reaction is reversible, but the equilibrium is such that most of the material is present as the addition product; by using sufficient excess of bisulfite practically all the aldehyde can be converted into the desired product, which can be further purified by recrystallization. To regenerate the aldehyde the addition product is warmed in water solution with a reagent which will react with sodium bisulfite. By removing the bisulfite in this way, the equilibrium is reversed completely and the aldehyde is set free. Two reagents which are used for this purpose are sodium carbonate and dilute hydrochloric acid. The reaction between a bisulfite addition product and sodium carbonate is shown in the equation which follows; the student should work out the corresponding equation for hydrochloric acid.

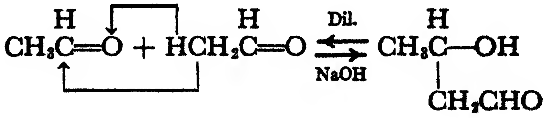
$$\underset{\displaystyle SO_3Na}{\underset{|}{RCHOH}} + \underset{(in\ H_2O)}{Na_2CO_3} \longrightarrow RCHO + Na_2SO_3 + NaHCO_3$$

The aldehyde is obtained from the water solution by distilling or extracting with an organic solvent. Exactly the same procedure can be used for purifying ketones which contain a methyl group. Other ketones do not form bisulfite addition products.

Addition of Hydrocyanic Acid. Hydrocyanic acid combines with aldehydes and ketones; the hydrogen atom attaches itself to the oxygen atom and the CN group to the carbon atom. The product, often called a cyanohydrin, is of interest as an intermediary in the preparation of hydroxy acids (p. 177).



Aldol Condensation. The addition reactions of the carbonyl group include a reaction in which one molecule of an aldehyde adds to the carbonyl group of another molecule. Such a reaction is called an *aldol condensation.* It is reversible and is brought about by the action of dilute alkali. We shall see that this reaction is fundamental to the biological transformations of the sugars (p. 251).



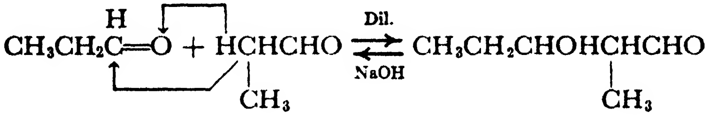
$$CH_3\overset{H}{C}{=}O + HCH_2\overset{H}{C}{=}O \underset{NaOH}{\overset{Dil.}{\rightleftharpoons}} CH_3\overset{H}{\underset{\displaystyle CH_2CHO}{\underset{|}{C}}}{-}OH$$

(The formula for the product has been written with a crooked chain to show the analogy between this reaction and other addition reactions of the carbonyl group.) The product formed from acetaldehyde is called *aldol*, $CH_3CHOHCH_2CHO$.

Aldol when heated in the presence of a catalyst is dehydrated to form an unsaturated aldehyde, crotonaldehyde, which can be reduced catalytically to *n*-butyl alcohol.

$$CH_3CHOHCH_2CHO \xrightarrow[\text{Catalyst}]{\text{Heat}} CH_3CH{=}CHCHO \xrightarrow[\text{Catalyst}]{H_2} CH_3CH_2CH_2CH_2OH$$

When the higher aldehydes are treated with dilute alkali, an aldol condensation takes place, but always in such a way that a hydrogen atom on the *carbon atom immediately adjacent to the carbonyl group* is involved. Thus, propionaldehyde reacts as follows:



$$\overset{H}{CH_3CH_2C{=}O} + \underset{CH_3}{HCHCHO} \underset{\text{NaOH}}{\overset{\text{Dil.}}{\rightleftharpoons}} CH_3CH_2CHOH\underset{CH_3}{C}HCHO$$

If there is no hydrogen atom on the carbon atom next the carbonyl group, no aldol condensation takes place. Thus trimethylacetaldehyde, $(CH_3)_3CCHO$, forms no aldol when treated with dilute alkali.

When warmed with concentrated solutions of sodium hydroxide, all aldehydes which undergo the aldol condensation form brown sticky materials insoluble in water known as *resins*. These are probably produced by repeated aldol condensations until a very large molecule is formed. Ketones do not form resins under the same conditions.

Condensation of Ketones. Ketones undergo a self-condensation similar to the aldol condensation. For example, acetone in the presence of an alkali yields **diacetone alcohol.**

$$(CH_3)_2C{=}O + CH_3COCH_3 \overset{Ba(OH)_2}{\rightleftharpoons} \underset{\text{Diacetone alcohol}}{(CH_3)_2COHCH_2COCH_3}$$

In this reaction the equilibrium is unfavorable for the product; only a few per cent of diacetone alcohol is formed when liquid acetone is treated with solid barium hydroxide. However, this difficulty is obviated in the manufacture of diacetone alcohol by a special device. The solid catalyst, $Ba(OH)_2$, is placed in a porous container above boiling acetone. The vapors are condensed in such a way that the liquid is returned to the boiler continuously by passing through the porous vessel which holds the catalyst. In its passage through the solid catalyst the liquid acetone is converted to diacetone alcohol as far as the equilibrium conditions permit (a few per cent). The diacetone alcohol being much less volatile than the acetone does not volatilize and accumulates in the boiler; since no catalyst is present, the concentration of product may greatly exceed the equilibrium conditions. In fact, in this way nearly all the acetone may be converted into diacetone alcohol. It is interesting that this product, though perfectly stable when pure, immediately decomposes when treated with alkali, forming the equilibrium mixture which is largely acetone. The apparatus used in this preparation (Fig. 5) is known as a *Soxhlet extractor* and is employed whenever a liquid is to be passed continuously through a solid as in the extraction of solid fatty material by ether.

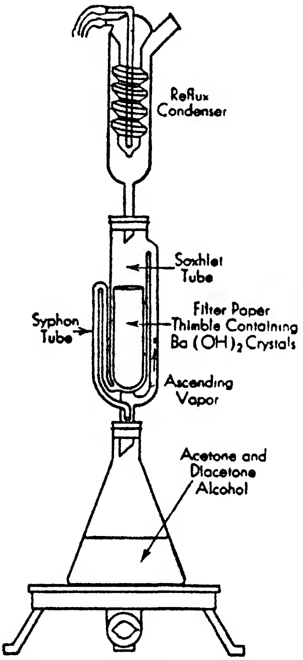
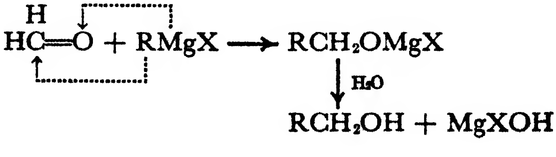


Fig. 5. Soxhlet extraction apparatus used in the conversion of acetone to diacetone alcohol.

Reaction with the Grignard Reagent. Both aldehydes and ketones combine with the Grignard reagent. The first product of the reaction is a magnesium compound which is easily hydrolyzed by water or decomposed by acids, yielding an alcohol. In this manner *aldehydes yield primary or secondary alcohols and ketones tertiary alcohols.* The reactions are illustrated by the following examples.

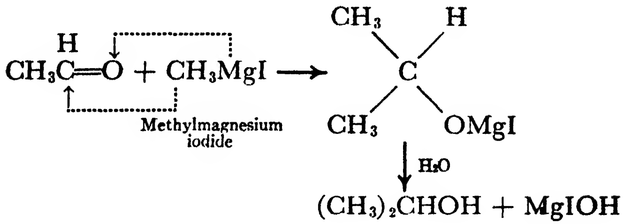
1. Synthesis of a Primary Alcohol. If *formaldehyde* (as a gas or sometimes as the solid polymer) is added to a Grignard reagent, the decomposition of the product yields a primary alcohol.



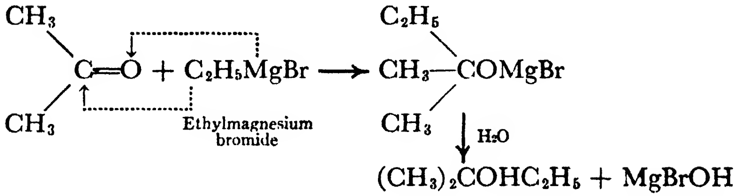
$$\overset{H}{HC}{=}O + RMgX \longrightarrow RCH_2OMgX$$

$$RCH_2OMgX \xrightarrow{H_2O} RCH_2OH + MgXOH$$

2. Synthesis of a Secondary Alcohol.

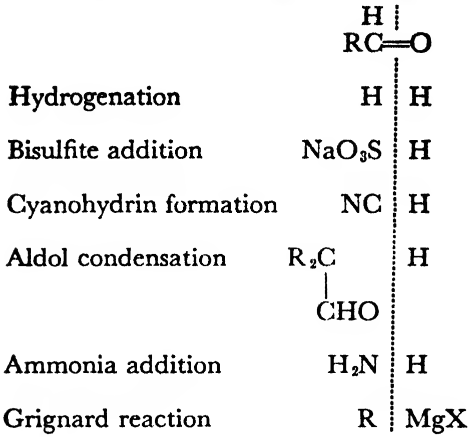


3. Synthesis of a Tertiary Alcohol.



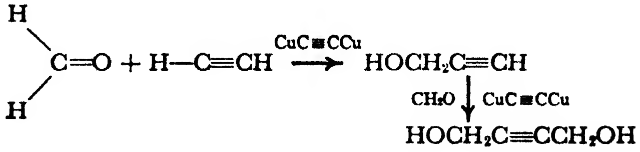
Since a variety of primary, secondary, and tertiary alcohols can thus be prepared, these three reactions are of the greatest importance. It will be noted that in these reactions the magnesium atom together with the halogen atom attaches itself to oxygen, and the alkyl group goes to the carbon atom. These reactions proceed rapidly at room temperature in ether solution. They are usually carried out by preparing the Grignard reagent in ether solution as described in Chap. 2, and then slowly adding the aldehyde or ketone. The reaction mixture is then treated with ice-cold ammonium chloride solution or acid, which hydrolyzes the addition product and keeps the basic magnesium salt (MgXOH) in solution.

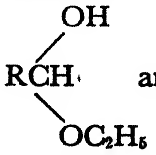
A Summary of the Addition Reactions. In all the addition reactions of the carbonyl group except hydrogenation, we have been dealing with the addition of unsymmetrical reagents. It is important to remember the way in which such reagents add. A very simple rule holds: *A hydrogen atom or a metal adds to the oxygen, the residue adds to the carbon.* The diagram on p. 94 illustrates the addition reactions of aldehydes (all of these also take place with methyl ketones).

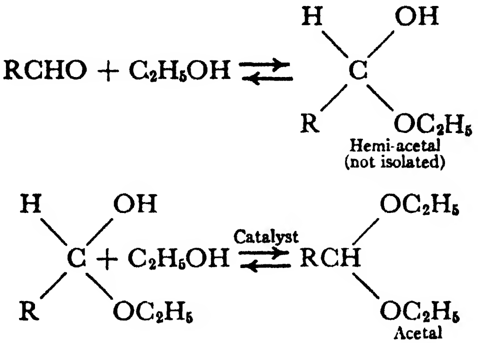


The *addition of ammonia* has been included in this diagram because there is evidence that aldehydes do combine with ammonia to give products of the type $RCHOHNH_2$ (called an *aldehyde ammonia*); but this reaction is usually followed by other reactions yielding complex products.

In the presence of copper acetylide as a catalyst, acetylene will add to carbonyl compounds as H—C≡CH. The reaction with formaldehyde will serve as an illustration.

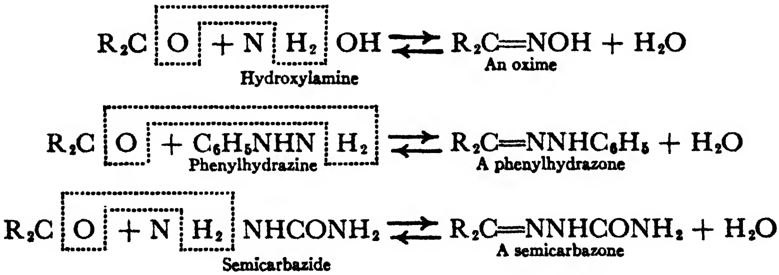


Reaction of Aldehydes with Alcohols. Alcohol and water might be added to the diagram given above since the addition compounds of the type $RCH(OH)_2$ and  $RCH(OH)(OC_2H_5)$ are probably formed in aqueous and alcoholic solutions of aldehydes. However, except for a few chloroaldehydes (p. 97) the products are too unstable to isolate. If an aldehyde is treated with an alcohol in the presence of calcium chloride or a trace of acid, a reaction takes place which probably proceeds through the primary addition product of the aldehyde and alcohol. The final product is known as an *acetal*, the intermediate as a *hemi-acetal*.



The acetals are hydrolyzed by boiling with aqueous acids; they are insensitive to bases.

Condensation with Ammonia Derivatives. It has been found that aldehydes and ketones react with derivatives of ammonia to form unsaturated compounds which in many instances are crystalline solids. If **hydroxylamine,** NH_2OH, is used, the compounds are called *oximes*, and if **phenylhydrazine,** $C_6H_5NHNH_2$, is used, the compounds are known as *phenylhydrazones*. With **semicarbazide,** $NH_2NHCONH_2$, **semicarbazones** are formed.



$$R_2C\boxed{O} + N\boxed{H_2}OH \rightleftharpoons R_2C{=}NOH + H_2O$$

Hydroxylamine — An oxime

$$R_2C\boxed{O} + C_6H_5NHN\boxed{H_2} \rightleftharpoons R_2C{=}NNHC_6H_5 + H_2O$$

Phenylhydrazine — A phenylhydrazone

$$R_2C\boxed{O} + N\boxed{H_2}NHCONH_2 \rightleftharpoons R_2C{=}NNHCONH_2 + H_2O$$

Semicarbazide — A semicarbazone

Similar reactions occur with aldehydes and the products are known by the same general names.

Identification of Aldehydes and Ketones. The identification of very small amounts of liquids is always a difficult matter in the laboratory. The identification of small amounts of solids is relatively easy if the solids have a melting point between room temperature and 200°. The simple aldehydes and ketones are all liquids, and the problem of identifying them therefore resolves itself into the problem of converting them into crystalline solids with sharp melting points. This is mostly done by means of one of the three condensation reactions just described. In fact, hydroxylamine, phenylhydrazine, and semicarbazide are often called *carbonyl group reagents* because they form crystalline condensation products with most aldehydes and ketones. For the simplest aldehydes and ketones, the last two reagents are used since the oximes of low molecular weight are liquid. The phenylhydrazones and semicarbazones formed from practically all aldehydes and ketones are crystalline solids with a sharp melting point.

Tests for Aldehydes. The fuchsine test and the reaction with ammoniacal silver nitrate are often used for distinguishing aldehydes from ketones. The fuchsine test consists of adding a solution of the material to a solution of *fuchsine* (magenta) which has been barely decolorized with sulfur dioxide; such a solution is known as *Schiff's reagent.* If an aldehyde is present, a bright pink color soon appears. Ketones do not give this test and do not reduce ammoniacal silver nitrate (p. 84).

REACTIONS INVOLVING HALOGEN

Replacement of Carbonyl Oxygen. The carbonyl oxygen in simple aldehydes and ketones may be replaced by the action of phosphorus pentachloride.

$$RCHO + PCl_5 \longrightarrow RCHCl_2 + POCl_3$$
$$R_2CO + PCl_5 \longrightarrow R_2CCl_2 + POCl_3$$

The dichloro compounds thus produced undergo hydrolysis on boiling with alkali and regenerate the carbonyl compound.

Replacement of Hydrogen by Halogen. By the action of chlorine or bromine on a ketone, one or more hydrogen atoms adjacent to the carbonyl group are readily replaced by halogen.

$$CH_3COCH_3 + Br_2 \longrightarrow \underset{\text{Monobromoacetone}}{CH_2BrCOCH_3} + HBr$$

The hydrogen atom replaced is the same one that is active in the aldol condensation. We thus see that as a general rule the hydrogen atoms on the *carbon adjacent to the carbonyl group* are active. This carbon atom is often called the *alpha* carbon atom since by one method of nomenclature the position of the substituent in aldehydes or ketones is denoted by Greek letters, thus; $\overset{\gamma}{C}H_3\overset{\beta}{C}H_2\overset{\alpha}{C}HBrCHO$ is known as *α-bromobutyraldehyde.*

Chloral. Trichloroacetaldehyde, commonly called *chloral*, can be prepared by treating acetaldehyde with chlorine water or by the action of chlorine on ethyl alcohol. In the latter reaction, the chlorine first oxidizes the alcohol to acetaldehyde and then chlorinates this substance. Chloral is an oily liquid which boils at 97° and has the unusual property of combining with a molecule of water, forming the crystalline solid, **chloral hydrate,** $CCl_3CH(OH)_2$. This finds a limited use in medicine as a hypnotic.

The Haloform Reaction. Chloral is rapidly decomposed on treatment with aqueous sodium hydroxide, yielding chloroform, $CHCl_3$, and sodium formate.

$$CCl_3\boxed{CHO + NaO}H \longrightarrow CHCl_3 + HCOONa$$

A similar reaction takes place with trichloroacetone, CCl_3COCH_3; here sodium acetate is one of the products.

$$CCl_3\boxed{COCH_3 + NaO}H \longrightarrow CHCl_3 + CH_3COONa$$

Sodium hypochlorite acts on *acetaldehyde or any methyl ketone* to form chloroform. It also acts on substances which are readily *oxidized to acetaldehyde or a methyl ketone*, since it is both an oxidizing agent and a chlorinating agent. The reactions proceed very rapidly and no intermediates can be isolated under these conditions.

Chloroform from alcohol:

$$\begin{aligned}
CH_3CH_2OH + NaOCl &\longrightarrow CH_3CHO + NaCl + H_2O\\
CH_3CHO + 3NaOCl &\longrightarrow CCl_3CHO + 3NaOH\\
CCl_3CHO + NaOH &\longrightarrow CHCl_3 + HCOONa
\end{aligned}$$

Chloroform from acetone:

$$CH_3COCH_3 + 3NaOCl \longrightarrow CH_3COCCl_3 + 3NaOH$$
$$CH_3COCCl_3 + NaOH \longrightarrow CH_3COONa + CHCl_3$$

The product of these reactions, chloroform, is an excellent noninflammable solvent which also finds limited use as an anesthetic.

A similar reaction occurs if sodium hypobromite (NaOBr) or sodium hypoiodite (NaOI) is used in place of the hypochlorite; the halogen-containing products are **bromoform,** $CHBr_3$, or **iodoform,** CHI_3. The latter is a yellow solid which melts at 120° and has a characteristic odor. It was used in the early development of antiseptic surgery as a dressing for wounds and is still used to some extent for this purpose.

The Iodoform Test for Ethyl Alcohol. Generally in the laboratory, sodium hypoiodite is prepared by treating an aqueous solution of iodine in an iodide with sodium hydroxide. Such a solution gives an immediate precipitate of iodoform with acetone, and when warmed with ethyl alcohol gives a similar precipitate. Since methyl alcohol does not form iodoform when treated with sodium hypoiodite, this test is often used *to distinguish ethyl from methyl alcohol.* Acetone, acetaldehyde, isopropyl alcohol and any substance which is a methyl ketone or is oxidized to a methyl ketone by hypoiodite will also give the test.

A FEW INDUSTRIALLY IMPORTANT ALDEHYDES AND KETONES

A number of aldehydes and ketones are commercially available. Of these the most important are **formaldehyde, acetaldehyde,** and **acetone.** They were long prepared from methyl alcohol, ethyl alcohol, and acetic acid respectively. New and even cheaper methods of producing the last two have been discovered. The importance of acetaldehyde lies in the fact that from it a great variety of compounds may be prepared. We will postpone a discussion of this development until the next chapter.

Formaldehyde. This aldehyde is prepared by the oxidation of methyl alcohol by air in the presence of metallic silver or copper at a temperature of about 300°. The reaction is carried out by passing a mixture of the vapors of methyl alcohol and air through a tube containing copper gauze kept at the desired temperature. The issuing gases containing formaldehyde, water, and unchanged methyl alcohol are passed through water which dissolves the organic material. A 40 per cent water solution of formaldehyde is sold as **formalin.**

,Large quantities of formaldehyde are prepared industrially for use as an antiseptic, as a starting point for the manufacture of other organic compounds, and for the preparation of synthetic resins (p. 317).[1] Formaldehyde solutions are used in preserving and hardening biological specimens. **Paraformaldehyde** (the polymer) is often used as a convenient source of the gas. Such solid paraformaldehyde is often heated in a little burner in order to disinfect a sickroom from contagious disease. Formaldehyde gas has a certain disinfecting action and kills the lower forms of life. This is one of the important uses of formaldehyde.

Unique Properties of Formaldehyde. As the first member of the series, formaldehyde has certain peculiarities. It differs from the other aldehydes in that on warming with concentrated sodium hydroxide it yields no resin, but undergoes the following reaction.

$$2HCHO + NaOH \longrightarrow CH_3OH + HCOONa$$

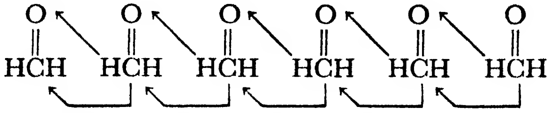
Reactions such as this where one molecule is oxidized at the expense of the other are known as *disproportionation* reactions. This particular reaction is known as the **Cannizzaro** reaction; it is characteristic of those *aldehydes which have no hydrogen in the alpha position,* as R_3CCHO.

When a formaldehyde solution is kept slightly alkaline and allowed to stand, a condensation peculiar to formaldehyde takes place. A mixture of compounds known as *sugars* (carbohydrates) is formed. These are polyhydroxyaldehydes and ketones and contain five and six carbon atoms in a straight chain (Chap. 13).

---

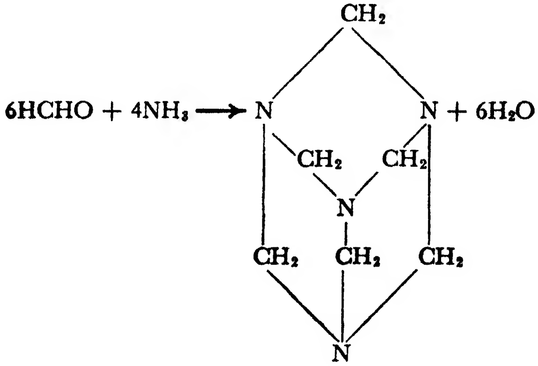
[1] In 1940 the United States production of formalin was 90,000 tons; in 1947 it was 307,000 tons.

The actual product of the self-condensation of formaldehyde is a complex mixture, but the reaction may be illustrated by the following equation.

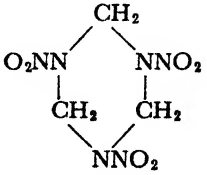


$$\longrightarrow CH_2OHCHOHCHOHCHOHCHOHCHO$$

Hexamethylene tetramine, $(CH_2)_6N_4$, **hexamine,** is a complex substance obtained by evaporating a mixture of an aqueous solution of formaldehyde and ammonia.



The compound is a crystalline solid which is used in medicine under the name **urotropin.** On nitration it furnishes the powerful high explosive RDX.



Acetone. Acetone is the ketone most commonly met. Until 1927, it was prepared by the destructive distillation of calcium acetate which was obtained from the destructive distillation of wood.

It is now largely prepared by a special type of fermentation and is a byproduct of the butyl alcohol industry (p. 21). A large amount of acetone is also made by the oxidation of isopropyl alcohol, which is obtained from petroleum (p. 78).

The chief use of acetone industrially is as a solvent, since it dissolves many organic substances which dissolve with difficulty even in alcohol. The rapid growth of acetone as a commercial solvent may be illustrated by the fact that, while 6500 tons of acetone were manufactured in 1927, more than 198,000 tons were produced in 1947.

A COMPARISON OF ALDEHYDES AND KETONES

The following table summarizes the more important reactions of aldehydes and ketones. Formaldehyde is given a separate place, since as the first member of the series it has no alkyl group attached to the carbonyl group and has certain unique properties.

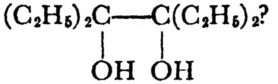
	Fehling's Solution	*Fuchsine Test*	$NaHSO_3$	*RMgX Yields*	
Formaldehyde	Oxidized	Positive	Addition product	Primary alcohol	Polymers of high mol. wt
Acetaldehyde and other aldehydes	Oxidized	Positive	Addition product	Secondary alcohol	Trimolecular polymers
Acetone and other ketones	No action	Negative	Addition product if CH_3COR	Tertiary alcohol	No polymer

QUESTIONS AND PROBLEMS

1. Write structural formulas for 3-heptanone, 2-methylbutanal, diethyl ketoxime, 2,3-dimethylheptanal, 3-methyl-4-octanone, acetaldehyde phenylhydrazone, butanone semicarbazone.

2. A sample of an organic liquid is either hexanal, methyl butyl ketone, butyric acid, or 1-chlorohexane. What chemical tests would you use to identify the liquid?

3. Write balanced equations for the following reactions: (*a*) methyl ethyl ketone and hydroxylamine, (*b*) hexanal and semicarbazide, (*c*) 2-ethylhexanal and phenylhydrazine.

4. How would you reduce $(CH_3)_2C{=}CHCHO$ to $(CH_3)_2C{=}CHCH_2OH$, and $C_2H_5COC_2H_5$ to  $(C_2H_5)_2\underset{\substack{|\\ OH}}{C}-\underset{\substack{|\\ OH}}{C}(C_2H_5)_2$?

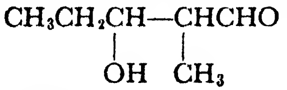
5. Indicate the reactions you would use to prepare (*a*) dipropyl ketone and (*b*) dibutyl ketone from butyl alcohol.

6. Compare the behavior of pentanal, 2-pentanone, and 3-pentanone with (*a*) sodium bisulfite, (*b*) dilute sodium hydroxide, (*c*) hydrogen cyanide, (*d*) ammoniacal silver nitrate, (*e*) Fehling's solution.

7. Write balanced equations for the following reactions: (*a*) CH_3MgI and CH_3COCH_3, (*b*) $(CH_3)_2CHMgBr$ and CH_3CH_2CHO, (*c*) $CH_3CH_2CH_2MgBr$ and CH_2O, (*d*) CH_3CH_2MgBr and $CH_3COCH_2CH_3$, (*e*) CH_3CH_2MgBr and H_2O.

8. How are formaldehyde and acetone prepared industrially, and what are their more important uses?

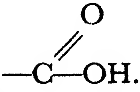
9. Define and illustrate the following terms: *acetal, hemiacetal, Cannizzaro reaction, haloform reaction, aldol condensation.*

10. Write equations (showing for each reaction the experimental conditions to be used) for preparing: (*a*) $CH_3CH_2CH_2CHO$ from $CH_3CH_2CH_2CH_2OH$, (*b*) CH_3CHO from paraldehyde, (*c*)  $CH_3CH_2\underset{\substack{|\\ OH}}{CH}-\underset{\substack{|\\ CH_3}}{C}HCHO$ from CH_3CH_2CHO, (*d*) CHI_3 from CH_3COCH_3.

11. Outline a procedure for separating by chemical means a mixture of hexanal and ethyl propyl ketone. Each substance is to be recovered after the separation.

CHAPTER 7

Organic Acids

In the preceding chapter we saw that the oxidation of an aldehyde, RCHO, furnishes the corresponding acid, RCOOH. All the members of the homologous series of *fatty acids*, except the first, may be represented by the general formula RCOOH; the first member, formic acid, HCOOH, has a hydrogen atom attached to the *carboxyl group*,  $-\overset{\overset{\displaystyle O}{/\!/}}{C}-OH$. The name fatty acid arose from the fact that two of the higher members of the series, palmitic and stearic acids, were prepared from animal fats. These two acids and the other higher fatty acids containing even numbers of carbon atoms are still obtained from the naturally occurring fats and oils (Chap. 8).

The Formation of Salts. The hydrogen atom of the carboxyl group is acidic; dilute water solutions of organic acids color blue litmus red, evolve hydrogen when acted on by metals, and are neutralized by metallic hydroxides forming salts. In terms of the electrolytic theory of dissociation we write the following ionic equilibrium.

$$RCOOH \rightleftarrows RCOO^- + H^+$$

Most organic acids are relatively weak, i.e., the degree of the dissociation even in dilute solution is small. For example, in a tenth normal solution of acetic acid, only a few per cent of the molecules are dissociated. However, the organic acids are strong enough to displace the very weak carbonic acid from its salts. Thus sodium salts may be made from sodium hydroxide, sodium carbonate, or sodium bicarbonate.

$$RCOOH + NaOH \longrightarrow RCOONa + H_2O$$
$$2RCOOH + Na_2CO_3 \longrightarrow 2RCOONa + H_2O + CO_2$$
$$RCOOH + NaHCO_3 \longrightarrow RCOONa + H_2O + CO_2$$

Formic acid is prepared industrially from sodium formate, which in turn is made by heating sodium hydroxide and carbon monoxide.

$$CO + NaOH \xrightarrow[\text{6–10 atm}]{200^\circ} HCOONa$$

To prepare the acid, the salt is heated carefully with the calculated amount of sulfuric acid. If formic acid itself is heated with sulfuric acid it undergoes dehydration; the reaction is a convenient laboratory source of carbon monoxide.

$$HCOOH \xrightarrow[H_2SO_4]{60^\circ\text{–}80^\circ} H_2O + CO$$

Formic acid is a stronger acid than the other aliphatic acids and, unlike its homologs, is readily oxidized. Because of these two properties it finds considerable use in industrial operations, particularly in the textile industry.

$$HCOOH + [O] \longrightarrow H_2O + CO_2$$

Preparation of Acids from Salts. The salts of the fatty acids are nonvolatile, crystalline solids and are usually soluble in water. The acids are prepared from them by treating with sulfuric acid. If the acid is sufficiently volatile to be distilled, the dry salt and concentrated sulfuric acid are employed. The higher acids which distil only at high temperatures are more readily obtained from their salts by adding the mineral acid to an aqueous solution and extracting with ether. The organic acid, but not the salt, is soluble in the ether layer. This is an excellent illustration of the use of an immiscible solvent in separating an organic substance (the acid) from an aqueous solution containing inorganic material (Na_2SO_4, H_2SO_4). The ether is easily removed by evaporation.

$$RCOONa + H_2SO_4 \xrightarrow[\text{Distil or extract}]{} RCOOH + NaHSO_4$$

Acetic acid is obtained as a dilute aqueous solution, vinegar, by the fermentation of weak aqueous solutions of alcohol. The anhydrous acid, known as *glacial acetic acid* because of its high melting point, 16.6°, is not prepared by concentrating vinegar but by a variety of industrial processes described in Chap. 9. The acid is widely used in industry when a weak acid is required, and its esters are extensively used as solvents. Acetic acid is one of the important chemicals of commerce; the total production, synthetic and recovered, in 1947 was over 830,000 tons.

Physical Properties. There is a gradual change in boiling point and solubility in water as we proceed from one member of the homologous series to the next higher straight-chain compound. The acids above butyric are only slightly soluble in water, and the solubility decreases as the hydrocarbon portions of the molecule become more predominant with the increase in the

Name	*Formula*	*Boiling Point*	*Melting Point*	*Density at 20°*	*Solubility Grams per 100 Grams of Water at 20°*
Formic acid	$HCOOH$	101°	8°	1.220	Miscible in all proportions
Acetic acid	CH_3COOH	118°	17°	1.049	
Propionic acid	CH_3CH_2COOH	141°	−22°	0.992	
n-Butyric acid	$CH_3CH_2CH_2COOH$	164°	−8°	0.959	
Isobutyric acid	$(CH_3)_2CHCOOH$	154°	−47°	0.949	20
n-Valeric	$CH_3CH_2CH_2CH_2COOH$	187°	−18°	0.942	4
n-Caproic	$CH_3CH_2CH_2CH_2CH_2COOH$	202°	−1.5°	0.929	Less than 1
n-Heptoic	$CH_3(CH_2)_5COOH$	223°	−10°	0.918	Less than 1
Caprylic	$CH_3(CH_2)_6COOH$	237°	16°	0.914	Less than 1
n-Nonylic	$CH_3(CH_2)_7COOH$	253°	12.5°		
Capric	$CH_3(CH_2)_8COOH$	268°	31°		Practically insoluble
Undecylic	$CH_3(CH_2)_9COOH$		28.5°		
Lauric	$CH_3(CH_2)_{10}COOH$		43°		
Tridecylic	$CH_3(CH_2)_{11}COOH$		42.5°		
Myristic	$CH_3(CH_2)_{12}COOH$		53.8°		
Pentadecylic	$CH_3(CH_2)_{13}COOH$		53°		
Palmitic	$CH_3(CH_2)_{14}COOH$		64°		
Margaric	$CH_3(CH_2)_{15}COOH$		61°		
Stearic	$CH_3(CH_2)_{16}COOH$		69°		

number of carbon atoms. The acids are all very soluble in alcohol, ether, benzene, and chloroform and even the lower members may be extracted from their water solutions by the last three solvents.

Some of the physical properties of the series are given in the table on the previous page.

It will be noted that the melting points of the straight-chain acids show no regular increase but vary up and down; the melting point of an acid containing an even number of carbon atoms is higher than that of the preceding one in the series. The straight-chain acid with a total of nine carbon atoms melts at 12.5°, and all those above this are solid at room temperature. The odor of the acids above propionic is very disagreeable unless they are so nonvolatile as to be practically odorless. Rancid butter owes its disagreeable smell to butyric acid.

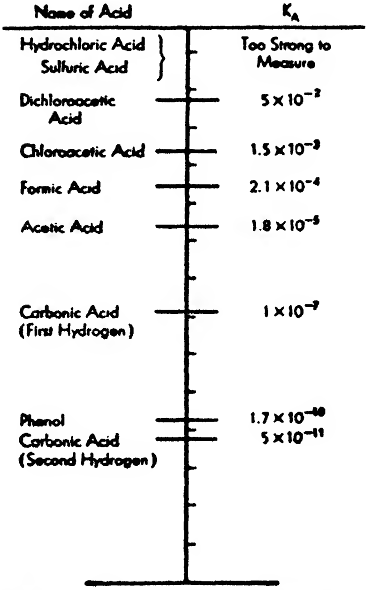


Fig. 6. The relative strengths of some common acids. The strongest acids are at the top of the scale; each scale unit corresponds to a ten-fold change in the acid dissociation constant.

Dissociation Constants. Those who are familiar with the quantitative aspects of the theory of electrolytic dissociation will recall that the strength of acids may be expressed in terms of a dissociation constant K_A which is defined as follows:

$$K_A = \text{Conc. of hydrogen ion} \times \left(\frac{\text{Conc. of acid ion}}{\text{Conc. of undissoc. acid}} \right)$$

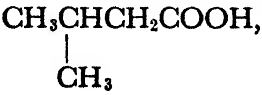
It is evident that, when the quotient inside the parentheses has a value of one, the value of K_A is equal to the concentration of the hydrogen ion. This condition is easily realized with weak acids by preparing a solution which contains one mole of the acid and one mole of a soluble salt of the acid. Since the free acid is only very slightly dissociated, the concentration of the undissociated acid is practically the same as the total concentration. The salt, on the other hand, is completely ionized and the concentration of the acid ion is therefore equal to the total concentration of the salt. Consequently, one may visualize the dissociation constant of a weak acid by thinking of it as being equal to the acidity (the hydrogen ion concentration) of a mixture of the acid and its soluble salt in equal molar amounts. The dissociation constants of some of the fatty acids are as follows:

$$\text{Formic, } K_A = 2.14 \times 10^{-4}$$
$$\text{Acetic, } K_A = 1.86 \times 10^{-5}$$
$$n\text{-Butyric, } K_A = 1.6 \times 10^{-5}$$

It will be recalled that the hydrogen ion concentration of pure water $= 1 \times 10^{-7}$. The dissociation constants of the first and second hydrogens of carbonic acid are about 1×10^{-7} and 5×10^{-11}, respectively. The diagram in Fig. 6 shows graphically the relative acidities of some common acids; several acids are included which will be considered later (phenol, p. 271, chloroacetic acid, p. 223).

Nomenclature. A great many of the fatty acids having a straight chain are found in nature, and were isolated before chemical nomenclature had been put on a rational basis; for this reason they have trivial names. In a systematic fashion, acids may be named as derivatives of acetic acid or by the Geneva system. The former method is illustrated by trimethylacetic acid, $(CH_3)_3CCOOH$. This is a convenient method for relatively simple acids.

In the Geneva system, the acid is named according to the longest chain of carbon atoms which it contains, *counting the carbon of the carboxyl group*. The suffix *-oic* is then added to the name of the paraffin hydrocarbon corresponding to this chain; branches are named and numbered as in the hydrocarbons. The numbering is always started *on* the carboxyl group. The following examples will make this method clear: pentanoic acid, $CH_3CH_2CH_2CH_2COOH$; $CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2COOH$, 3-methylbutanoic acid.



$$CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2COOH$$

GENERAL METHODS OF PREPARING ACIDS

The important members of the fatty acid series are prepared industrially by special methods or from special sources. When we wish to prepare any of the other fatty acids in the laboratory we use an alcohol as our starting material.

Oxidation of a Primary Alcohol. If we have a primary alcohol with the same number of carbon atoms, the problem is easy. The oxidation of a primary alcohol yields an acid with the same number of carbon atoms.

$$RCH_2OH + 2[O] \longrightarrow RCOOH + H_2O$$

An illustration of this is the oxidation of ethyl alcohol by air in the presence of "mother of vinegar." In the laboratory a mixture of potassium dichromate and sulfuric acid is often employed as the oxidizing agent.

$$CH_3CH_2OH + 2[O] \xrightarrow{K_2Cr_2O_7} CH_3COOH + H_2O$$

It will be noted that RCH_2OH is a general formula for any primary alcohol and RCOOH for the corresponding acid. The alcohol which corresponds to formic acid, HCOOH, is methyl alcohol, CH_3OH.

Since aldehydes are intermediate products in the oxidation of primary alcohols to acids, we can use aldehydes if they are readily available in the synthesis of acids.

Acids from Lower Alcohols. If we have the problem of preparing an acid with one more carbon atom than the alcohol at hand, a simple oxidation will not avail. There are two ways of accomplishing this synthesis, however. Both start with the alkyl halide RX and yield the same acid RCOOH. They are illustrated below by the synthesis of propionic acid from ethyl bromide.

1. Grignard Synthesis of Acids. In this process dry carbon dioxide is passed into the ethereal solution of the Grignard reagent, or the Grignard reagent is poured onto Dry Ice. Then the reaction mixture is decomposed with dilute hydrochloric or sulfuric acid, which sets free the organic acid.

$$CH_3CH_2Br + Mg \xrightarrow[\text{ether}]{\text{Dry}} CH_3CH_2MgBr$$

$$CH_3CH_2MgBr + CO_2 \longrightarrow CH_3CH_2COOMgBr$$

$$CH_3CH_2COOMgBr + HCl \longrightarrow CH_3CH_2COOH + MgBrCl$$

The organic acid is extracted with ether and is obtained by evaporating this solvent. This process is a good laboratory method of preparing many acids and has been widely employed since the discovery of the Grignard reaction.

2. Nitrile Synthesis of Acids. The older process of preparing acids involves the preparation of a **nitrile,** RCN. This substance has the carbon atom of the cyanide group directly bound to the alkyl group. It is an organic cyanide and may be regarded as an ester of hydrocyanic acid. The nitriles are formed by boiling an alcoholic solution of the alkyl halide with sodium cyanide (p. 29).

$$C_2H_5Br + NaCN \longrightarrow C_2H_5CN + NaBr$$

The nitriles are hydrolyzed on boiling with dilute alkalies.

$$CH_3CH_2CN + NaOH + H_2O \xrightarrow{\text{Boil}} CH_3CH_2COONa + NH_3$$

The product is the sodium salt from which the free acid may readily be prepared (p. 104).

$$CH_3CH_2COONa + HCl \longrightarrow CH_3CH_2COOH + NaCl$$

The hydrolysis of nitriles to acids may also be accomplished with strong mineral acids.

$$CH_3CH_2CN + H_2SO_4 + 2H_2O \longrightarrow CH_3CH_2COOH + NH_4HSO_4$$

SOME GENERAL REACTIONS OF ACIDS

The acidic reaction of the carboxyl group is perhaps the most characteristic property of organic acids. Certain other reactions, however, are important. They are illustrated by the following general equations, where RCOOH stands for acetic acid or a higher homolog.

1. Replacement of OH by halogen; formation of acid chlorides.

$$3RCOOH + PCl_3 \longrightarrow 3RCOCl + P(OH)_3$$

2. Replacement of OH by OR; formation of esters.

$$RCO\boxed{OH + H}OR \rightleftharpoons RCOOR + H_2O$$

The preparation of aldehydes and ketones from acids was described on pp. 83 and 84.

Two other reactions of much less importance may be mentioned. In both the carboxyl group is eliminated as carbon dioxide.

3. Formation of a paraffin hydrocarbon RH.

$$RCOONa + NaOH \xrightarrow[300^\circ]{\text{Fused}} RH + Na_2CO_3$$

$$\text{e.g., } CH_3COONa + NaOH \longrightarrow CH_4 + Na_2CO_3$$

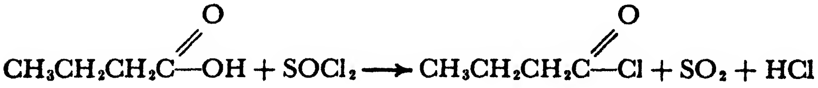
4. Formation of a hydrocarbon RR by electrolysis of the sodium salt, RCOONa.

$$2RCOO^- \text{ (minus two electrons at anode)} \longrightarrow RR + 2CO_2$$

$$\text{e.g., } 2CH_3COO^- \longrightarrow CH_3CH_3 + 2CO_2 + 2 \text{ electrons}$$

ACID CHLORIDES

When an acid is treated with phosphorus trichloride (PCl_3), the OH group of the carboxyl group is replaced by chlorine. Phosphorus pentachloride and thionyl chloride ($SOCl_2$) are also used in replacing the OH group of acids. The action of the latter is illustrated by the preparation of butyryl chloride.



$$CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}{-}OH + SOCl_2 \longrightarrow CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}{-}Cl + SO_2 + HCl$$

An acid chloride is also called an *acyl chloride.* It has the general formula RCOCl, and is named by slightly changing the name of the acid; thus, acet-yl chloride and propion-yl chloride. Formyl chloride, HCOCl, is unknown; attempts to prepare it yield only hydrogen chloride and carbon monoxide. Acetyl chloride is a low-boiling liquid (52°), which fumes in moist air and is very irritating to the mucous membrane. Acid bromides and acid iodides are known but are of no importance.

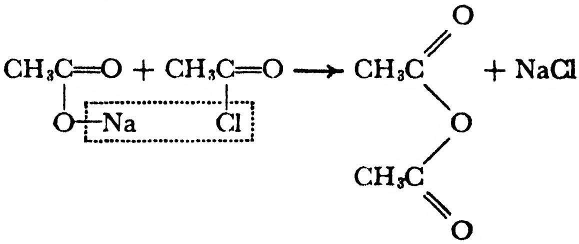
Reactions of Acid Chlorides. Acyl chlorides are much more reactive than alkyl halides. Acetyl chloride reacts violently with water, alcohol, and ammonia at room temperature.

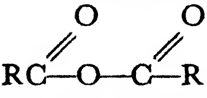
Hydrolysis $CH_3COCl + H_2O \longrightarrow CH_3COOH + HCl$
Alcoholysis $CH_3COCl + C_2H_5OH \longrightarrow CH_3COOC_2H_5 + HCl$
Ammonolysis $CH_3COCl + 2NH_3 \longrightarrow CH_3CONH_2 + NH_4Cl$

The product of the second reaction is an **ester**; the substance formed in the last reaction is an **amide.** These reactions show how the acid chlorides are useful in preparing other compounds.

ACID ANHYDRIDES

When anhydrous sodium acetate and acetyl chloride are heated together, a reaction takes place and **acetic anhydride,** $(CH_3CO)_2O$, is formed.



This compound is a representative of the acid anhydrides  $R\overset{O}{\overset{/\!/}{C}}—O—\overset{O}{\overset{/\!/}{C}}—R$ or $(RCO)_2O$. The acid anhydrides are formally related to acids as the ethers are to alcohols. There is little resemblance in properties, however, between the two classes. The anhydride of formic acid is unknown; all attempts to prepare it yield carbon monoxide. As the name indicates, the anhydrides react with water, regenerating acids; they also react with alcohols, forming esters.

$$(RCO)_2O + H_2O \longrightarrow 2RCOOH$$
$$(CH_3CO)_2O + C_2H_5OH \longrightarrow CH_3COOC_2H_5 + CH_3COOH$$

Acetic Anhydride. Acetic anhydride is prepared in the laboratory from sodium acetate and acetyl chloride. Industrially it is made by the action of sulfur chloride (S_2Cl_2) on acetic acid or sodium acetate, by heating acetic acid vapor to very high temperatures in the presence of a catalyst under special conditions whereby provision is made for removing the water formed in the process and by the reaction of the highly unsaturated compound *ketene*, $CH_2{=}C{=}O$, with acetic acid.

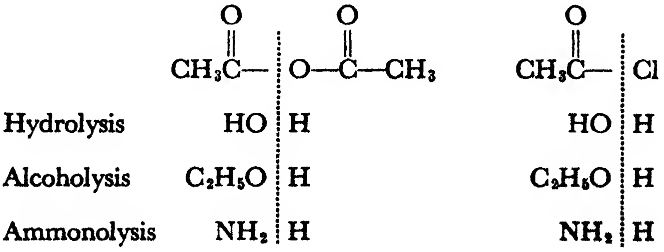
$$CH_2{=}C{=}O + CH_3COOH \longrightarrow (CH_3CO)_2O$$

Ketene itself is obtained by the thermal decomposition of acetone.

$$CH_3COCH_3 \xrightarrow{650^\circ\text{-}700^\circ} CH_2{=}C{=}O + CH_4$$

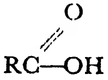
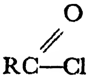
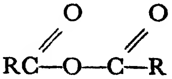
Acetic anhydride is a liquid boiling at 140°; it has a very irritating odor. Its importance depends on the fact that it reacts with many substances forming acetyl derivatives, that is, compounds containing the acetyl group $CH_3CO—$. Large quantities of acetic anhydride are manufactured for the production of cellulose acetate, one of the artificial silks now widely used (p. 214). During 1935 over 116,000,000 lb. of acetic anhydride was produced; in 1947 the production had increased to 632,000,000 lb.

Acetylating Agents. Acetyl chloride and acetic anhydride are spoken of as *acetylating agents* because they will react with many substances to form acetyl derivatives. This is illustrated by the following diagram of the reactions with water, alcohol, and ammonia.



ACYL GROUPS AND ALKYL GROUPS

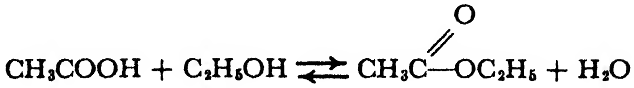
The acyl group RCO— may be regarded as the hypothetical group formed from an acid by removal of the OH group. The acyl groups should not be confused with the acid ion $RCOO^-$. For example, the acetyl group $\mathrm{CH_3}\overset{\mathrm{O}}{\overset{/\!/}{\mathrm{C}}}\text{—}$ is quite different from the acetate ion CH_3COO^-.

Compounds Having an Alkyl Group		Compounds Having an Acyl Group	
Class Name	*General Formula*	*Class Name*	*General Formula*
Alcohol	ROH	Acid	 $\mathrm{R}\overset{\mathrm{O}}{\overset{/\!/}{\mathrm{C}}}\mathrm{—OH}$
Alkyl chloride	RCl	Acyl chloride	 $\mathrm{R}\overset{\mathrm{O}}{\overset{/\!/}{\mathrm{C}}}\mathrm{—Cl}$
Ether	ROR	Acid anhydride	 $\mathrm{R}\overset{\mathrm{O}}{\overset{/\!/}{\mathrm{C}}}\mathrm{—O—}\overset{\mathrm{O}}{\overset{/\!/}{\mathrm{C}}}\mathrm{—R}$

The table above may serve as a general review of some of the types of compounds thus far studied. The contrast between the *acyl* and corresponding *alkyl* compounds should be carefully studied; they bear a formal resemblance to each other, but their chemical and physical properties are very different.

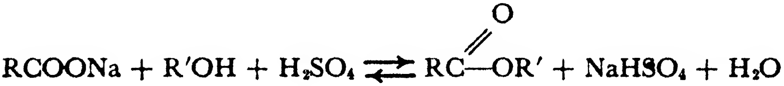
ESTERS OF ORGANIC ACIDS

Esterification. When an alcohol and an acid are brought together, the hydroxyl group of the acid and the hydrogen atom of the alcohol unite to form water: the new compound is called an *ester*. The reaction is known as *esterification*. It may be illustrated by the formation of ethyl acetate from acetic acid and ethyl alcohol.

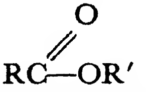


$$CH_3COOH + C_2H_5OH \rightleftharpoons CH_3\overset{O}{\overset{/\!/}{C}}\text{—}OC_2H_5 + H_2O$$

The reaction does not go to completion, and, at room temperature in the absence of a catalyst, equilibrium is attained very slowly. Therefore, it is common practice to heat the mixture to the boiling point of the alcohol and to add a little sulfuric acid or hydrochloric acid as a catalyst. Another method of accomplishing the same end is to heat the alcohol with equivalent quantities of sulfuric acid and the sodium salt of the acid. The sulfuric acid fulfils two functions: that of liberating the organic acid from the salt, and catalyzing the reaction.



$$RCOONa + R'OH + H_2SO_4 \rightleftharpoons R\overset{O}{\overset{/\!/}{C}}\text{—}OR' + NaHSO_4 + H_2O$$



The esters of organic acids except formic have the general formula $R\overset{O}{\overset{/\!/}{C}}\text{—}OR'$ ($RCOOR'$) where R and R′ may be the same or different alkyl groups; the esters of formic acid have the general formula HCOOR. There is, therefore, a homologous series for each acid, the alkyl groups becoming increasingly larger. Thus, we have methyl formate, $HCOOCH_3$; ethyl formate, $HCOOC_2H_5$; propyl formate, $HCOOC_3H_7$ (two isomers), etc. Similar series may be written with acetic acid, propionic acid, and all the other fatty acids.

In the table on p. 115 are listed some of the commoner esters which can be prepared from the alcohols and acids already considered. They are all liquids which float on water.

The esters have a very pleasant, fruity odor, each different from that of the others. It is particularly interesting that although butyric and valeric acids have very disagreeable odors, their esters are sweet-smelling substances. The characteristic fragrance of many fruits and flowers is due to the presence of

SOME COMMON ESTERS

Name	*Formula*	*Boiling Point*
Methyl formate	$HCOOCH_3$	32°
Ethyl formate	$HCOOCH_2CH_3$	54°
Methyl acetate	CH_3COOCH_3	57°
Ethyl acetate	$CH_3COOCH_2CH_3$	77°
n-Butyl acetate	$CH_3COOCH_2CH_2CH_2CH_3$	127°
n-Amyl acetate	$CH_3COOCH_2CH_2CH_2CH_2CH_3$	148°
Isoamyl acetate	$CH_3COOCH_2CH_2CH(CH_3)_2$	143°
Methyl propionate	$CH_3CH_2COOCH_3$	80°
Ethyl propionate	$CH_3CH_2COOCH_2CH_3$	99°

various esters. Thus, amyl acetate, $CH_3COOC_5H_{11}$, has a pear-like odor and the odor of methyl butyrate, $C_3H_7COOCH_3$, is reminiscent of pineapple. A number of the simple esters are manufactured for use in artificial perfumes and flavors. The most important use of esters is as solvents, especially in the manufacture of quick-drying automobile lacquers (p. 213).

The fats and oils which occur in animals and plants are esters of an alcohol with three hydroxyl groups and acids of high molecular weight. They are of great importance, not only as food, but as the raw material used in manufacturing soap, candle stock, and glycerin (Chap. 8).

Other Methods of Preparing Esters. In addition to the esterification of acids, esters may also be prepared by (1) the reaction between an acid chloride and an alcohol (p. 111); (2) the reaction between an acid anhydride and an alcohol (p. 111); and the reaction between the silver salt of an acid and an alkyl halide.

$$CH_3COOAg + C_2H_5Br \longrightarrow CH_3COOC_2H_5 + AgBr$$

Esterification and Hydrolysis. An Equilibrium. The interaction of an alcohol and acid does not go to completion as do many organic reactions. If we start with 1 mole of acetic acid (60 g) and 1 mole of ethyl alcohol (46 g), we find that, try as we will, we cannot get a reaction mixture containing more than about 66 per cent of 1 mole of ethyl acetate. On the other hand, if we were to start with ethyl acetate and heat it with 1 mole of water for a long time, we would find that the reaction apparently stopped when the mixture contained about 66 per cent of unchanged ester. Thus, whether we start with alcohol and acid or with water and ester, *the final composition of the reaction mixture is the same.* We have already seen (p. 86) that this is typical of a reversible reaction. The reverse of esterification is called *hydrolysis.*

The Composition of the Equilibrium Mixture. The composition of the final reaction mixture, the equilibrium mixture, is approximately expressed by what is often called the *mass law.* This is given by the following equation in which the symbols [ester], [H_2O], etc., refer to concentrations expressed as moles per liter, or better as mole fractions.

$$\frac{[\text{Ester}] \times [H_2O]}{[\text{Alcohol}] \times [\text{Acid}]} = K \text{ (the equilibrium constant)}$$

For example, in the preparation of ethyl acetate, experiments show that the equilibrium mixture contains about 0.6 mole of ester, if we start with one mole of acid and one of alcohol (a total of 2 moles). Therefore, the mole fraction of ester is $\frac{0.6}{2} = 0.3$ and of water the same (for each molecule of ester formed, one of water is also formed). The concentrations of alcohol and acid are $\frac{0.4}{2} = 0.2$ each. These numbers substituted in the equation give:

$$\frac{0.3 \times 0.3}{0.2 \times 0.2} = 2.25 = K$$

Experiment shows that whatever relative amounts of acetic acid and ethyl alcohol are employed, the composition of the equilibrium mixture is such that K has *approximately* this value.

Practical Applications of the Mass Law. It is an easy matter to calculate the composition of an equilibrium mixture if we know the value of K and the relative amounts of alcohol and acid at the start. Without going through the calculations, it is evident from an inspection of the mass law equation that if we use a large excess of alcohol, the yield of ester per mole of acid will be increased. For this reason, if we wish to prepare the ethyl ester of an expensive acid we use a considerable excess of the alcohol.

It is also evident that if we remove a certain amount of one of the products (water or ester), a further amount will be formed so that the composition of the mixture will conform to the mass law expression. This can be realized very often in practice and is sometimes referred to as *upsetting the equilibrium*. For example, if the alcohol, ester, and acid boil much higher than water, it is often possible to distil the latter from the reaction mixture. This is also accomplished by making use of an azeotropic mixture (p. 21). Some solvent such as benzene is added to the acid and alcohol. On distillation at a relatively low temperature, a mixture of water and benzene is separated from the reaction mixture. In this way the yield of the process may be much greater than otherwise would be possible. It should be noted that these methods are only effective if they are carried out under such conditions (temperature and catalyst) that the rate of the reactions is rapid and more product will be rapidly formed as some is removed.

Reaction Rates and Equilibria. Probably the student has studied reversible reactions and the application of the mass law to them in the ionic reactions of inorganic chemistry. If so he is accustomed to thinking that equilibria are established very rapidly if not instantaneously. This is true when the reaction involves ions alone. In organic chemistry, however, the reactions in both directions are usually very slow under ordinary conditions and require a catalyst.

The factors affecting the rate of a reaction must not be confused with the factors affecting the composition of the equilibrium mixture. Whether we are considering the forward or back reaction of a reversible reaction, or a reaction which runs to completion, we find that a rise of temperature always increases the rate. (As a general rule the rate of reactions involving liquids or solutions approximately doubles with every 10° increase.) We further find that it is almost always possible to increase the rate by the use of some catalyst. And finally we know that increasing the concentration of the reactants (other factors being constant) increases the rate.

On the other hand, the **composition of the equilibrium mixture is not affected by the absence or presence of a catalyst.** Thus we may speed up enormously the time in which equilibrium conditions are attained by finding the right catalyst, but *at constant temperature* we cannot shift the equilibrium by virtue of any catalyst.

Mechanism of Esterification and Hydrolysis. It is obvious that two schematic representations of the esterification reaction may be written depending upon whether the acid or the alcohol loses a hydroxyl group. The water formed during esterification must arise from one of the following paths.

$$RCO\boxed{OH + H}OC_2H_5 \quad \text{or} \quad RCOO\boxed{H + HO}C_2H_5$$

The first mechanism was shown to be correct by esterifying an organic acid with methyl alcohol containing an abnormal amount of the heavy oxygen isotope (atomic weight, 18). The water obtained from this experiment had the normal density, showing that the oxygen atoms in the water were a mixture of the isotopes in the usual normal manner. This in turn proved that the oxygen in the water did not originate from the alcohol but rather from the acid; thus:

$$RCO\boxed{OH + H}OC_2H_5 \longrightarrow RCOOC_2H_5 + H_2O$$

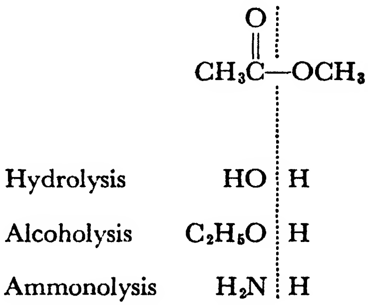
This is an illustration of how it is sometimes possible to establish the mechanism of a reaction by "tagging" one of the atoms.

Saponification of Esters. If we heat an ester with water, the hydrolysis is slow unless an acid or base is present to accelerate the process. In the absence of an acid or base, the reaction eventually reaches an equilibrium, and only about a third of the ester is hydrolyzed. If an equivalent amount of base is employed, however, the acid formed is neutralized and hence removed from the equilibrium. The process thus goes to completion. It is a special instance of hydrolysis and is called *saponification.*

$$CH_3COOC_2H_5 + NaOH \longrightarrow CH_3COONa + C_2H_5OH$$

Rates of Esterification and Hydrolysis. It has been found that the rate of formation of esters (under given conditions) depends on the structure of the acid and alcohol. Primary alcohols react most rapidly, tertiary least rapidly, with secondary in between. It will be noted this is the *reverse* of the order met with in alkyl halide formation; this is explained by the fact that in alkyl halide formation the hydroxyl of the alcohol is necessarily involved and in esterification the hydroxyl of the acid is eliminated (as demonstrated above). It is often difficult to esterify tertiary alcohols by the direct method. Acids of the general formula R_3CCOOH are also difficult to esterify directly. In general, branching the chain next to the carboxyl group causes the acid to esterify more slowly. Branching the chain of the alcohol has the same effect. The value of the equilibrium constant is relatively little affected by changes in the structure of the alcohol and acid. In esterification and hydrolysis, rates rather than the composition of the equilibrium mixture determine the characteristic chemical behavior of alcohols and acids.

Reactions of Esters with Alcohols and Ammonia. Like the acid chlorides and acid anhydrides, the esters can undergo alcoholysis and ammonolysis as well as hydrolysis. This is illustrated with methyl acetate in the following diagram:



$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}\text{—}OCH_3$$

Hydrolysis $HO \vdots H$

Alcoholysis $C_2H_5O \vdots H$

Ammonolysis $H_2N \vdots H$

The reaction with ammonia is a method of preparing amides (p. 151). The alcoholysis reaction is also known as *ester interchange.* It takes place extremely slowly in the absence of a catalyst but rapidly if a trace of sodium alkoxide is added to the mixture. The reaction does not go to practical completion unless there is a very large excess of one of the alcohols, or unless some provision is made for removing one of the products.

$$RCOOR' + R''OH \rightleftharpoons RCOOR'' + R'OH$$

Reduction of Esters to Alcohols. Esters are reduced to primary alcohols in good yields by the action of sodium and alcohol or by sodium and moist ether. The following equation for the preparation of *n*-hexyl alcohol from the ethyl ester of *n*-caproic acid illustrates the method.

$$CH_3(CH_2)_4COOC_2H_5 + 4[H] \xrightarrow{Na + C_2H_5OH} CH_3(CH_2)_4CH_2OH + C_2H_5OH$$

Esters may also be reduced catalytically with excellent results. The ester is shaken with hydrogen at elevated temperature and high pressure in the presence of a mixed catalyst of copper and chromium oxide (copper chromite).

$$RCH_2COOC_2H_5 + 2H_2 \xrightarrow[250°]{\text{Catalyst; 2000-3000 lb}} RCH_2CH_2OH + C_2H_5OH$$

This process is convenient; industrially it is preferable to the sodium reduction because it is cheaper and less hazardous. A number of higher alcohols, which once were rare, are now manufactured in quantity by catalytic reduction.

ESTERS OF INORGANIC OXYGEN ACIDS

The alcohols react with the inorganic oxygen acids, nitrous, nitric, and sulfuric acids, to form esters. The formation of these esters and their hydrolysis are much more rapid than the corresponding reactions with the organic acids.

The esters of nitrous acid are prepared by treating an alcohol and sodium nitrite with sulfuric acid. Ethyl nitrite, C_2H_5ONO, bp 17°, is sold in alcoholic solution as "sweet spirits of nitre." *n*-Butyl nitrite boils at 75°; amyl nitrite at 99°. Both esters serve in the laboratory as sources of nitrous acid which can be used in organic solvents. In the same way methyl nitrate and ethyl nitrate, which are prepared from the alcohols by treatment with a mixture of nitric and sulfuric acids, serve as sources of nitric acid which can be used in organic solvents. The volatile esters of nitrous acid find use in medicine. The corresponding esters of nitric acid are powerful, and dangerously sensitive, explosives.

Since sulfuric acid is an acid with two hydrogen atoms, it can form two types of esters just as it can form two classes of salts. **Ethylsulfuric acid,** $C_2H_5OSO_3H$, is both an ester and an acid. **Ethyl sulfate,** $C_2H_5OSO_2OC_2H_5$, and **methyl sulfate,** $CH_3OSO_2OCH_3$, are examples of neutral esters of sulfuric acid.

Ethylsulfuric acid (or ethyl hydrogen sulfate) is an oily liquid. It is usually prepared as needed by mixing sulfuric acid and alcohol; the reaction mixture contains water, some unchanged alcohol and sulfuric acid, and the desired ethylsulfuric acid. Since the substance is both an acid and an ester, it has the characteristic properties of both classes. It forms salts when cautiously treated with bases and is hydrolyzed to alcohol and sulfuric acid when heated with water.

QUESTIONS AND PROBLEMS

1. Write structural formulas for: (*a*) trimethylacetic acid, (*b*) ethyl formate, (*c*) propanoic acid, (*d*) methyl acetate, (*e*) 3,3-dimethylpentanoic acid.

2. What chemical tests would you use to decide whether a sample of a liquid was an acid, an acid chloride, an acid anhydride, or an alkyl chloride?

3. How would you prepare (*a*) butyric acid and (*b*) pentanoic acid from 1-butanol?

4. Define and illustrate the following terms: acyl group, carboxyl group, alkyl group.

5. In preparing the ester RCOOR′ from the acid RCOOH and the alcohol R′OH, why does one add a small amount of mineral acid and heat the reaction mixture?

6. Write balanced equations for two methods of preparing propionyl chloride from propionic acid.

7. Write structural formulas for: (*a*) propionic anhydride, (*b*) butyryl chloride, (*c*) 2-ethylhexanoic acid.

8. What products would you expect to obtain from the reaction between propionyl chloride and (*a*) ethanol, (*b*) water, and (*c*) ammonia?

9. What is the meaning of the term *reversible equilibrium?* What is the effect on such a process of (*a*) raising the temperature, (*b*) adding a catalyst, and (*c*) removing a product?

10. Write balanced equations for the reaction between ethyl propionate and (*a*) hydrogen, (*b*) ammonia, (*c*) water.

CHAPTER 8

Polyhydric Alcohols: Fats and Oils

In previous chapters we have seen that many classes of organic compounds are characterized by having a certain reactive group in the molecule. Such reactive groups as the hydroxyl group of alcohols, the carboxyl group of acids, and the carbonyl group of aldehydes and ketones are known as *functional groups.* Up to this point we have considered only compounds which have one such functional group. Many important organic compounds, however, contain several functional groups and are known as *polyfunctional compounds.* We begin their study in this chapter. This study is simplified by the fact that, usually, each functional group reacts exactly as it would if it occurred alone. Thus the reactions of complicated substances may be predicted in many instances from a knowledge of simple compounds. Exceptions to this rule will be noted.

As an introduction to the study of polyfunctional compounds we shall consider those substances which contain several hydroxyl groups in the molecule. These are known as the *polyhydric alcohols.* Two compounds of this class, ethylene glycol, $C_2H_4(OH)_2$, and glycerin (glycerol), $C_3H_5(OH)_3$, are of great importance; the first because of its cheap commercial production from ethylene, and the other because it is the alcohol which is combined with complex organic acids in animal fats and vegetable oils.

The simplest polyhydric alcohols are the **glycols;** these are compounds having the general formula $C_nH_{2n}(OH)_2$. They are derivatives of the saturated hydrocarbons in which two hydrogens have been replaced by hydroxyl groups. Compounds containing two hydroxyl groups on the *same* carbon atom, e.g., $RCH(OH)_2$, are not included in this class. We have previously noted (p. 94) that attempts to prepare such a compound usually fail because of the elimination of water and the formation of an aldehyde or ketone. Therefore, the first member of the glycol series is **ethylene glycol,** CH_2OHCH_2OH, which has two hydroxyl groups on adjacent carbon atoms.

GLYCOLS

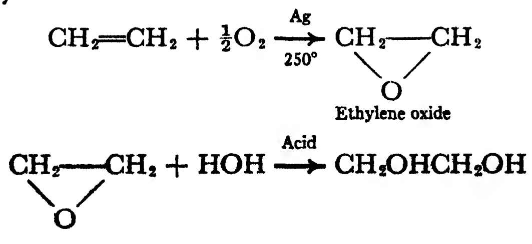
Preparation of Ethylene Glycol. Just as an alcohol may be prepared from an alkyl halide, so a glycol may be prepared from the corresponding dihalide. Thus by the action of silver hydroxide on ethylene dibromide, ethylene glycol is formed.

$$CH_2BrCH_2Br + 2AgOH \longrightarrow CH_2OHCH_2OH + 2AgBr$$

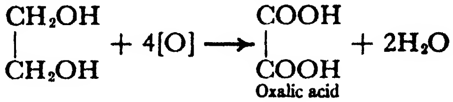
Ethylene glycol is prepared commercially from ethylene by two different processes. In one, hypochlorous acid is added to ethylene and the product, **ethylene chlorohydrin** (p. 54), is heated with sodium bicarbonate solution at 70° to 80° for 4 to 6 hours. Under these conditions the chlorine atom is replaced by a hydroxyl group.

$$\underset{\substack{\text{Ethylene}\\ \text{chlorohydrin}}}{CH_2ClCH_2OH} + NaHCO_3 \longrightarrow CH_2OHCH_2OH + NaCl + CO_2$$

In the other, ethylene is oxidized to ethylene oxide and the oxide is heated with water in the presence of a small amount of acid as a catalyst.



Reactions, Properties, and Uses of Ethylene Glycol. The chemical reactions of ethylene glycol correspond to the fact that it has two primary hydroxyl groups. For example, it may be oxidized to the corresponding acid, oxalic acid (p. 167), which contains two carboxyl groups.

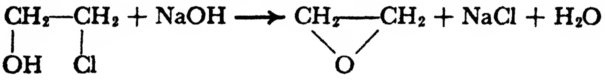


$$\begin{array}{l} CH_2OH \\ | \\ CH_2OH \end{array} + 4[O] \longrightarrow \underset{\text{Oxalic acid}}{\begin{array}{l} COOH \\ | \\ COOH \end{array}} + 2H_2O$$

Similarly, the reactions of ethylene glycol with the halogen acids and with the fatty acids are those to be expected of a molecule containing two primary hydroxyl groups.

Ethylene glycol is a slightly sweet, mobile liquid, miscible with water in all proportions, but only slightly miscible with ether. It boils at 197° and solidifies at $-11.5°$. Ethylene glycol has been used extensively as a solvent and as a substance to be added to the water in the radiators of automobiles to prevent freezing under winter conditions. It is also used in the preparation of certain resins (p. 172).

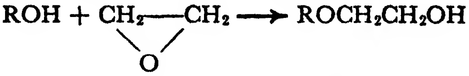
Ethylene Oxide. The cyclic ether ethylene oxide is the source of many industrially important substances which are closely related to ethylene glycol. Ethylene oxide, as noted above, can be prepared from ethylene and converted to ethylene glycol. The oxide can also be prepared from ethylene chlorohydrin.



$$\underset{OH}{CH_2}—\underset{Cl}{CH_2} + NaOH \longrightarrow \underset{\diagdown\ O\ \diagup}{CH_2—CH_2} + NaCl + H_2O$$

Ethylene oxide is soluble in water and boils at 13°. Mixed with 9 parts of carbon dioxide, it forms an important fumigant for foodstuffs and books because of the ease with which it can be removed by exposure to air.

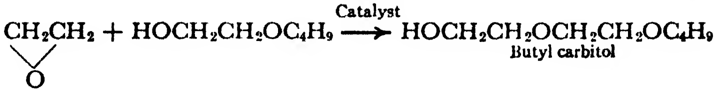
Alcohols react with ethylene oxide in the presence of small amounts of catalyst to furnish monoalkyl ethers of ethylene glycol.



$$ROH + \underset{\diagdown\ O\ \diagup}{CH_2—CH_2} \longrightarrow ROCH_2CH_2OH$$

The monomethyl ether of ethylene glycol, $CH_2OHCH_2OCH_3$, the monobutyl ether, $CH_2OHCH_2OC_4H_9$, and similar compounds are readily prepared in this way. They are marketed under the name of *Cellosolve*. Thus the monomethyl ether is called **Methyl cellosolve,** and the monobutyl ether is called **Butyl cellosolve.** The former boils at 124°, the latter at 170.6°. These substances are useful solvents because they are at one and the same time both alcohols and ethers, and for this reason readily dissolve a great variety of organic compounds. They are also miscible with water up to and including Butyl cellosolve.

Closely related to the *cellosolves* are the ethers of diethylene glycol, $CH_2OHCH_2OCH_2CH_2OH$; they are known as the *carbitols*. The carbitols are prepared by the action of ethylene oxide on the monoethers of ethylene glycol.



$$\underset{\text{O}}{CH_2CH_2} + HOCH_2CH_2OC_4H_9 \xrightarrow{\text{Catalyst}} \underset{\text{Butyl carbitol}}{HOCH_2CH_2OCH_2CH_2OC_4H_9}$$

Butyl carbitol, boiling at 222°, is particularly interesting as it is an excellent solvent and is completely miscible with water. It can be used for preparing homogeneous solutions containing both water and complex organic compounds insoluble in water.

Other Glycols. Two other glycols are worthy of mention. **Propylene glycol,** $CH_3CHOHCH_2OH$, can be prepared from propylene by exactly the same reactions as are used in the preparation of ethylene glycol from ethylene. It resembles ethylene glycol in its physical properties but differs from it chemically in that it is a *secondary* as well as a primary alcohol. **Trimethylene glycol,** $CH_2OHCH_2CH_2OH$, is a byproduct of the preparation of glycerol from fats. It is a viscous liquid boiling at 214° and miscible with water in all proportions. The corresponding dibromide, trimethylene dibromide, $BrCH_2CH_2CH_2Br$, may be prepared from it by the action of hydrobromic acid.

Pinacols (p. 89), which are formed by the dimolecular reduction of ketones, are tetrasubstituted ethylene glycols. Both in their mode of preparation and reactions they are not typical representatives of dihydroxy compounds.

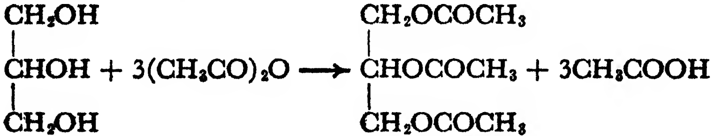
GLYCEROL

Glycerol or, as it is often called, *glycerin*, is a trihydroxy derivative of propane having the formula $CH_2OHCHOHCH_2OH$. It is formed whenever an animal fat or a vegetable oil is boiled with sodium hydroxide. If we take a typical animal fat, such as tallow from the beef animal, and boil it with sodium hydroxide, it changes into a thick mass which with sufficient water will form a clear solution. On adding sulfuric acid to this solution we obtain a precipitate which consists of a mixture of two acids of the fatty acid series, namely, palmitic acid, $C_{15}H_{31}COOH$, and stearic acid, $C_{17}H_{35}COOH$. Since these acids are insoluble in water, they separate when the solution of their sodium salts is made acid. If we evaporate the water solution, we find that after distilling all the water a viscous high-boiling liquid remains together with sodium sulfate. This liquid is **glycerol.** It can be purified by distillation under diminished pressure.

The industrial preparation of glycerol is essentially that just outlined. It is thus a byproduct of the manufacture of the fatty acids or their salts—the soaps. It has also been manufactured by the fermentation of sugar by yeast under special conditions and can be made from petroleum. It has been sold as an anti-freeze for automobile radiators. It is used in the manufacture of cosmetics, dentifrices, and in the preparation of inks and mucilages.

Physical and Chemical Properties. Glycerol is a viscous, nontoxic, colorless liquid with a sweetish taste. It is miscible in all proportions with water. When pure it can be made to solidify by cooling; the crystals melt at 17°. The liquid is prone to supercool and it is often extremely difficult to start crystallization. The usual samples of glycerol contain varying proportions of water since glycerol is hygroscopic. It boils at 290°. If kept long at its boiling point, it undergoes partial decomposition, and is therefore best purified by distillation under diminished pressure.

Glycerol contains two primary and one secondary hydroxyl group. The presence of three hydroxyl groups in the molecule is established by the fact that, when acylated, three acyl groups are introduced. As an example of this the preparation of the triacetate may be given.



$$\begin{array}{lcl} CH_2OH & & CH_2OCOCH_3 \\ | & & | \\ CHOH + 3(CH_3CO)_2O & \longrightarrow & CHOCOCH_3 + 3CH_3COOH \\ | & & | \\ CH_2OH & & CH_2OCOCH_3 \end{array}$$

Glycerol triacetate (triacetin)

Nitroglycerin and Dynamite. The trinitrate of glycerol is called nitroglycerin. This ester, an oily liquid which solidifies at 12°, has the formula $CH_2(ONO_2)CH(ONO_2)CH_2(ONO_2)$. It is a powerful explosive which is very sensitive to shock and dangerous to transport. Nobel discovered in 1867 that if nitroglycerin was absorbed by some inert porous material such as kieselguhr (silica), a powerful but relatively safe explosive was formed. This was *dynamite.* Dynamite today is commonly manufactured by using wood pulp or sawdust as the solid absorbent materials and adding ammonium nitrate.

Nitroglycerin is prepared by the action of concentrated nitric and sulfuric acids on glycerol. The temperature must be carefully controlled.

$$C_3H_5(OH)_3 + 3HNO_3 \overset{H_2SO_4}{\rightleftharpoons} C_3H_5(ONO_2)_3 + 3H_2O$$

Higher Polyhydric Alcohols. Alcohols having four, five, and six hydroxyl groups are known. Many of these are found in nature. **Erythritol,** $CH_2OH(CHOH)_2CH_2OH$, occurs, usually as an ester, in many lichens and fungi. The tetranitrate of erythritol is used in medicine for certain cardiac disturbances. **Arabitol, xylitol,** and **adonitol** are pentahydric alcohols. They all may be represented by the formula $CH_2OH(CHOH)_3CH_2OH$. The hexahydric alcohols, **mannitol, dulcitol,** and **sorbitol,** $CH_2OH(CHOH)_4CH_2OH$, also occur in nature.

In general the higher polyhydric alcohols are sweet, crystalline compounds, readily soluble in water. Their reactions are those which would be predicted from a knowledge of the simpler polyhydric alcohols. Thus on acylation with acetic anhydride, the pentahydric alcohols form pentaacetates, the hexahydric alcohols, hexaacetates. The close relationship of these higher polyhydric alcohols to the sugars will be evident later (Chap. 13).

FATS AND OILS

One of the three main categories of foodstuffs is that of the fats and oils. Having considered the chemistry of glycerol we are in a position to attack this complicated subject. The organic chemist often speaks of fats and oils meaning thereby the esters of glycerol, some of which are liquid at room temperature and known as vegetable oils. Mineral oils which are petroleum products are entirely different. The biochemist thinks of the fats and oils as a subdivision of a wide class of substances with common solubilities known as the **lipids.** Some examples of other members of this class will be noted later.

The Acids Obtained from Fats and Oils. When tallow is hydrolyzed by the action of sodium hydroxide, a mixture of acids which consist predominantly of stearic and palmitic acids is obtained. If we examine in a similar way other animal fats and oils, we always find glycerol and a mixture of acids as the products of saponification. The more important of these acids are listed below in the table, together with their physical properties.

THE ACIDS WHICH OCCUR COMMONLY IN FATS AND OILS

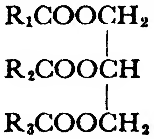
Name	*Formula*	*Structure*	*Melting Point*
Palmitic acid	$C_{15}H_{31}COOH$	$CH_3(CH_2)_{14}COOH$	63°
Stearic acid	$C_{17}H_{35}COOH$	$CH_3(CH_2)_{16}COOH$	69°
Oleic acid	$C_{17}H_{33}COOH$	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$	14°
Linoleic acid	$C_{17}H_{31}COOH$	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	<0°
Linolenic acid	$C_{17}H_{29}COOH$	$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	<0°

The last three acids are unsaturated acids which contain the same carbon skeleton (seventeen carbon atoms and a carboxyl group) as stearic acid. Four separate homologous series of acids with different general formulas are represented. Palmitic and stearic acids, which belong to the fatty acid series, have the general formula $C_nH_{2n+1}COOH$; oleic acid has the formula

$C_nH_{2n-1}COOH$, linoleic the formula $C_nH_{2n-3}COOH$, and linolenic the formula $C_nH_{2n-5}COOH$.

Glycerides. The esters of an acid with glycerol are called *glycerides*. They may be simple glycerides, that is, glycerol esterified with three molecules of the same acid; or they may be mixed glycerides in which one molecule of glycerol has been esterified with two, or even three, different acids.

The general formula of a glyceride is:



$$\begin{array}{l} R_1COOCH_2 \\ \quad\quad\quad\quad | \\ R_2COOCH \\ \quad\quad\quad\quad | \\ R_3COOCH_2 \end{array}$$

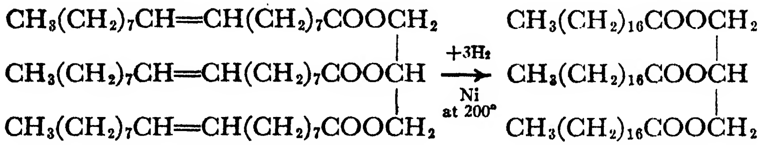
If $R_1 = R_2 = R_3$ we have a simple glyceride, for example, tristearin ($R = C_{17}H_{35}$). If the R's are different we have a mixed glyceride. The fats and oils are largely composed of mixed glycerides.

The melting points of some simple glycerides are given below.

	Melting Point
Tripalmitin	60°
Tristearin	71°
Triolein	17°
Trilinolein	Oil below 0°

Both the simple and mixed glycerides of the saturated acids, like the free acids themselves, melt at a much higher temperature than the glycerides of the unsaturated acids. Thus, the relatively low melting point of a vegetable oil, in comparison to that of an animal fat, is due to the fact that the former contains unsaturated glycerides. The essential difference between tallow and cottonseed oil is the absence of a few hydrogen atoms in the latter.

Hydrogenation of Vegetable Oils. A large industry exists which transforms vegetable oils into solid fats. The chemistry of this process is extremely simple. It is based on the reaction known as *catalytic hydrogenation* which we have already considered (p. 53). The following reaction illustrates the transformation of triolein to tristearin.



$$\begin{array}{lcl} CH_3(CH_2)_7CH{=}CH(CH_2)_7COOCH_2 & & CH_3(CH_2)_{16}COOCH_2 \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad | & & \qquad\qquad\qquad\quad | \\ CH_3(CH_2)_7CH{=}CH(CH_2)_7COOCH & \xrightarrow[\text{Ni at } 200^\circ]{+3H_2} & CH_3(CH_2)_{16}COOCH \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad | & & \qquad\qquad\qquad\quad | \\ CH_3(CH_2)_7CH{=}CH(CH_2)_7COOCH_2 & & CH_3(CH_2)_{16}COOCH_2 \end{array}$$

The hydrogenation of vegetable oils is controlled in order to yield the type of product desired. Thus, if a synthetic lard is wanted for cooking purposes, the reduction is stopped when partially complete; otherwise a material comparable to tallow is obtained. The term *hardening* is sometimes given to this process of hydrogenating a vegetable oil.

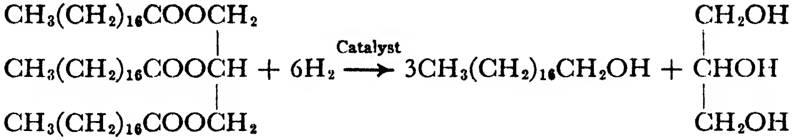
THE ACIDS OBTAINED BY SAPONIFICATION OF SOME FATS AND OILS

Name	*Stearic and Palmitic*	*Oleic*	*Linoleic*	*Other Acids*
	Per cent	Per cent	Per cent	Per cent
Tallow	75	25	0	0
Butterfat (There is some tributyrin in this fat.)	53	39	0	8
Olive oil	25	70	5	0
Cottonseed oil	25	25	47	3
Linseed oil	8	18	30	44*
Soybean oil	7	33	52	8
Tung oil	5	13		82†

*Contains about 30 per cent of linolenic acid.

† Contains about 73 per cent of eleostearic acid, $C_{17}H_{29}COOH$, which is isomeric with linolenic acid.

If the reduction is carried past the formation of saturated glycerides, these glycerides, since they are esters, undergo reduction to alcohols (see p. 119). This reduction furnishes glycerol and the long-chain alcohols corresponding to the acids present in the glycerides. It is an important source of the C_{12}, C_{16}, and C_{18} alcohols.



$$\begin{array}{lcr} CH_3(CH_2)_{16}COOCH_2 & & CH_2OH \\ \qquad\qquad\qquad\quad | & & | \quad \\ CH_3(CH_2)_{16}COOCH + 6H_2 & \xrightarrow{\text{Catalyst}} 3CH_3(CH_2)_{16}CH_2OH + & CHOH \\ \qquad\qquad\qquad\quad | & & | \quad \\ CH_3(CH_2)_{16}COOCH_2 & & CH_2OH \end{array}$$

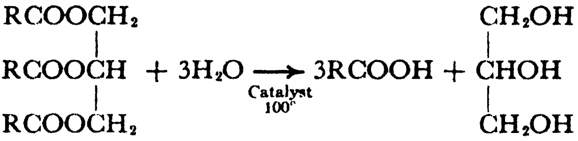
If a suitable catalyst is used, glycerides of the unsaturated acids can be reduced to glycerol and long-chain unsaturated alcohols.

Butter. Butter differs from most other fats in that it contains the glycerides of a large number of different acids. Among these acids is butyric acid. When butter has stood for some time it slowly becomes rancid because of the liberation of free butyric acid by the hydrolysis of the glyceride. Although only a very small per cent of the glyceride may be decomposed, the butter is quite unfit for use because of the disagreeable smell of butyric acid. The butyric acid may be removed by washing the butter with an aqueous solution of sodium bicarbonate, or by blowing steam through the molten butter which volatilizes the butyric acid. Butter thus freed from butyric acid is called *renovated butter.* In order to restore to it some of the characteristic flavor and consistency of natural butter, it is usually churned with skim milk under such conditions that it separates in more or less of a conglomerate containing considerable amounts of water.

Oleomargarine and various vegetable butters and other butter substitutes are mixtures of vegetable oil and animal fats or partially hydrogenated vegetable oils of such consistency as to resemble butter. To simulate the mechanical structure of butter and its characteristic flavor such substances are often agitated with milk before being put on the market. They must be artificially colored. In many states, to prevent fraud, there are special laws covering the sale of oleomargarine and other special butters.

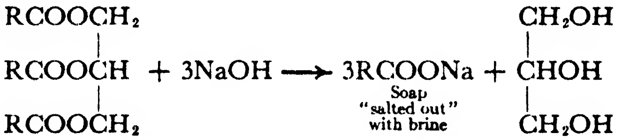
Candle Stock. A mixture of palmitic and stearic acids is prepared industrially and sold under the name of *stearin.* It is waxlike solid, used for the manufacture of candles and sometimes called *candle stock.* For the preparation of this substance animal fats or hydrogenated oil must obviously be used, since only the high-melting acids obtained from saturated glycerides yield a solid material suitable for candles.

Hydrolysis of Fats. The hydrolysis of fats to produce the free acids is brought about by heating with a catalyst and water. The catalyst used is usually either a small amount of lime or a complex organic acid known as *Twitchell's reagent.* The reaction goes to completion, probably because the acids are insoluble and separate from the mixture and because a large excess of water is used. The solution from which the insoluble acids have been separated is distilled and glycerol is obtained.



$$\begin{array}{l}\mathrm{RCOOCH_2}\\ \quad|\\ \mathrm{RCOOCH}\\ \quad|\\ \mathrm{RCOOCH_2}\end{array} + 3\mathrm{H_2O} \xrightarrow[\text{Catalyst } 100^\circ]{} 3\mathrm{RCOOH} + \begin{array}{l}\mathrm{CH_2OH}\\ |\\ \mathrm{CHOH}\\ |\\ \mathrm{CH_2OH}\end{array}$$

Manufacture of Soap. Soap is prepared by heating animal fats and vegetable oils with sodium hydroxide. When the reaction is complete, salt is added, which causes the complete separation of the sodium salts of the fatty acids: these are lighter than water, float on the surface, and are removed. The glycerol in the residual brine may be obtained by distillation.



$$\begin{array}{l}\mathrm{RCOOCH_2}\\ \quad|\\ \mathrm{RCOOCH}\\ \quad|\\ \mathrm{RCOOCH_2}\end{array} + 3\mathrm{NaOH} \longrightarrow \underset{\substack{\text{Soap}\\ \text{“salted out”}\\ \text{with brine}}}{3\mathrm{RCOONa}} + \begin{array}{l}\mathrm{CH_2OH}\\ |\\ \mathrm{CHOH}\\ |\\ \mathrm{CH_2OH}\end{array}$$

The soaps which come on the market are the sodium salts of the fatty acids mixed with a number of other materials which give them odor, color, and better cleansing properties. The hydrogenated vegetable oils are much used in soap manufacture. A satisfactory soap cannot be made from an oil like cottonseed oil itself, but after hydrogenation the oil is the equivalent of tallow.

Rosin is also used in the manufacture of soaps. It is the amorphous yellow residue left after the distillation of *spirits of turpentine* from the sap of coniferous trees. It is an organic acid (or acid anhydride) of high molecular weight (p. 354) and, therefore, reacts with bases to form salts. Solutions of sodium "rosinate" have cleansing power and produce lather like soap solutions. Many cheap laundry soaps contain much rosin. Shaving soap usually contains some rosin to produce good lather; it also contains glycerol and gum to prevent too rapid drying.

Detergents and Their Mode of Action. In recent years many other materials have become available which have the cleansing action of the ordinary soaps but which are quite different in structure. The alkali salts of the alkylsulfuric acids having ten or more carbon atoms in the molecule are detergents. Sodium laurylsulfate, $CH_3(CH_2)_{10}CH_2OSO_3Na$, is representative. The alcohols used are obtained by the hydrogenation of the fats and oils (p. 130). The sodium alkylsulfates may be used in slightly acid solutions (which would precipitate the fatty acids from ordinary soaps), and in salt water and hard water since the calcium and magnesium alkylsulfates are soluble.

Later we shall encounter some other types of detergents (pp. 161, 269). Now we can consider in simplified terms the way in which detergents work. Detergents lower the surface tension of water. Their water solutions, therefore, will more readily than pure water wet the particles of dirt which are to be removed. The detergents all contain one group which confers water solubility, a hydrophilic group, and one which has just the opposite effect, a hydrophobic group. In the ordinary soaps the hydrophilic group is carboxyl, while the hydrophobic group is the long alkyl group; in the sodium alkylsulfates the hydrophilic group is sulfate, while the hydrophobic group is again the long-chain alkyl. In water the detergents emulsify oil, grease, and dirt, presumably by surrounding these individual foreign particles in such a way that the hydrophobic end of the detergent is near the emulsified particle and the hydrophilic end of the detergent is in the water.

DRYING OILS

Drying of Oil Paints Is Oxidation. Linseed oil and certain other vegetable oils, such as tung and soybean oil, slowly absorb oxygen from the air and change to hard transparent solids. This property is particularly manifested if a thin layer of the oil is spread on some surface such as wood which is exposed to the air. This oxidation of linseed oil is commonly and quite erroneously called *drying*. It is the basic chemical reaction in the so-called drying of oil paints.

The linseed oil as it comes from the flax seed (called *raw linseed oil*) absorbs oxygen very slowly; paint made from it would be too slow drying for most purposes. If linseed oil is heated to 200° in the presence of certain heavy metal salts it undergoes a chemical change as a result of which it will absorb oxygen much more rapidly at room temperature. Oil which has been thus treated is called *boiled linseed oil* and is the material used in the manufacture of practically all oil paints.

Our knowledge of the chemistry of the drying of linseed oil is very meager. The ability of an oil to combine with oxygen seems to be connected with the presence of glycerides of highly unsaturated acids such as linolenic acid. We always find a high percentage of such glycerides in oils which have drying properties. It is probable that the oxygen of the air combines with some of the unsaturated linkages and that a polymerization somewhat analogous to the polymerization of ethylene then takes place. If this is true, dried paint is a polymerized, oxidized glyceride of linolenic acid.

Oil Paints. Oil paints are suspensions of very finely divided pigments in linseed oil. The pigments are for the most part inorganic compounds such as basic lead carbonate (white lead), lead oxide (red lead), etc. When an especially quick-drying oil paint is desired the oil is sometimes diluted with spirits of turpentine which really dries in the sense that it evaporates and leaves a thin coating of the material behind; this then "dries" by absorbing oxygen in the usual manner. Certain substances called *driers* are sometimes added to the paint. They act catalytically to accelerate the oxidation process.

Oilcloth is made by covering cloth with boiled linseed oil and letting it dry. Linoleum is a "dried" mixture of linseed oil and cork which have been pressed together. Tung oil is also used for the same purpose.

There is a great distinction between oil paints, which we have just been discussing, and various other forms of paint or paintlike substances, such as shellac, varnishes, and lacquers. These latter substances are solutions of organic materials in volatile solvents, and their drying is due to the evaporation of the solvent, the organic material being left behind as a thin coating. For many purposes lacquers of various sorts are now replacing oil paints. Automobiles, for example, and many other metal surfaces are painted with a lacquer prepared from cellulose (Chap. 13.)

Analysis of Fats and Oils. Certain convenient methods of analysis are frequently employed in studying fats and oils. By saponifying a weighed sample of the material with potassium hydroxide, the **saponification number** may be obtained. It is defined as the number of milligrams of potassium hydroxide required to saponify 1 g of fat. The saponification number reflects the average molecular weight of the glycerides present in the sample. A large saponification number indicates the presence of glycerides of the lower fatty acids.

The degree of unsaturation of a fat or oil can be determined by allowing a known weight of the material to react with iodine in a solution of mercuric chloride in alcohol. The amount of halogen which combines with the double linkages of the various unsaturated glycerides can be readily determined. It should be noted carefully, however, that the direct combination of iodine with double linkages is very slow; addition proceeds in this instance at a convenient rate because of the special reagent employed. The results are expressed as the **iodine number,** *which is the number of grams of iodine combining with 100 g of fat.* This number is obviously greater the more unsaturated glycerides are present. Typical saponification and iodine numbers are given in the table below.

Fat or Oil	*Saponification Number*	*Iodine Number*
Butter	220–241	22–37
Cottonseed oil	191–195	104–114
Olive oil	190–195	77–91
Linseed oil	190–195	175–202
Lard	193–203	48–64
Tallow	191–195	35–40

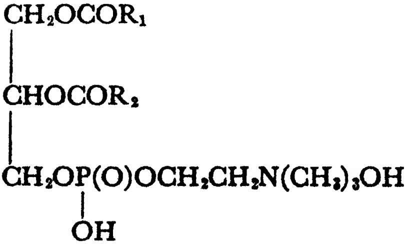
Reichert-Meissl Number. Butter contains a relatively large amount of the glycerides of the lower fatty acids; artificial butters and renovated butters contain much less. It is, therefore, important to have a method of determining the percentage of the glycerides of the lower fatty acids in a sample of butter or other fat. This is done by saponifying 5 g of the fat, acidifying with sulfuric acid, and distilling the aqueous solution until a definite volume of distillate is collected. The lower fatty acids are volatile with steam and are largely in the distillate. The number of cubic centimeters of $0.1N$ potassium hydroxide required to neutralize this distillate is the Reichert-Meissl number of the fat.

In addition to the tests we have described, the analyst makes use of a variety of specific tests, such as color reactions, given by individual fats and oils. A pure fat or oil, it must be realized, is not a pure compound, but a complex mixture of glycerides. Different pure samples of the same fat or oil will not give identical numerical values in the tests, but the values for a given fat or oil will fall in a definite range. Consequently the analyst's task is an art.

PHOSPHOLIPIDS

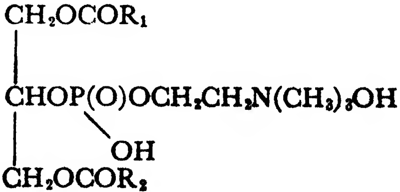
The class of compounds known to the biochemist as the lipids includes, in addition to the fats and oils, all nonvolatile constituents of plant and animal cells which are insoluble in water and soluble in ether and similar solvents. Very closely related to the fats chemically are the phospholipids or phosphatides. They occur widely distributed in animal and plant cells but usually in small amounts. They may be regarded as fats in which one acyl group has been replaced by a complex phosphoric acid. Like the fats, they usually are present in nature as a mixture of several compounds containing different closely related acyl groups (e.g., stearyl and palmityl). For this reason probably no representative of the phosphatides has been obtained in a pure state.

The **lecithins** (α and β) are the commonest phosphatides. Their structures are usually represented by the following formulas, where R_1CO and R_2CO represent the acyl groups of the higher fatty acids.



$$\begin{array}{l}
CH_2OCOR_1 \\
| \\
CHOCOR_2 \\
| \\
CH_2OP(O)OCH_2CH_2N(CH_3)_3OH \\
\quad\;\; | \\
\quad\; OH
\end{array}$$

α-Lecithin



$$\begin{array}{l}
CH_2OCOR_1 \\
| \\
CHOP(O)OCH_2CH_2N(CH_3)_3OH \\
| \qquad \backslash \\
| \qquad\; OH \\
CH_2OCOR_2
\end{array}$$

β-Lecithin

On hydrolysis the lecithins yield glycerol, a mixture of fatty acids (composed of stearic, palmitic, and oleic acids), phosphoric acid, and the quaternary base, choline, $CH_2OHCH_2N(CH_3)_3OH$ (p. 164). Large amounts of lecithins are found in egg yolk, liver, and brain; they are believed to be involved in the formation and oxidation of the fats.

Two other phospholipids which have been isolated are *cephalin* (or *kephalin*) and *sphingomyelin.* Only the former is a glyceride and yields glycerol on hydrolysis; both contain fatty acid residues, phosphoric acid, and a basic nitrogen-containing substance. The **cerebrosides** are a group of compounds of unknown structure which on hydrolysis produce fatty acids, the basic nitrogen containing compound found in sphingomyelin, and the sugar galactose (p. 202). Because of the solubility of these substances in ether they are classed as lipids; they are found particularly in the brain.

Complex monohydric alcohols with many carbon rings in the structure are found widely distributed in plant and animal tissues. These are the **sterols;** though classified, together with the fats and phospholipids, as lipids by the biochemist, they are so dissimilar in structure as to require a separate consideration (Chap. 21).

WAXES

Among the lipids are included the waxes which are mixtures of the higher homologs of ethyl alcohol and their esters with the higher fatty acids. Waxes are primarily plant products; associated with them in some plants in small amounts are hydrocarbons of the paraffin series with twenty-nine to thirty-five carbon atoms. Waxes may be distinguished from the fats by the fact that when boiled with sodium hydroxide they are not transformed into water-soluble products. (The higher alcohols are, of course, insoluble in water and aqueous sodium hydroxide.) Together with sterols they are the "unsaponifiable portion" left when a chloroform or ether extract of plant or animal tissue is hydrolyzed with alkali. (The esters of the higher alcohols present in the waxes are converted to the higher alcohols themselves by this treatment, of course.)

The alcohols, $C_{30}H_{61}OH$, **myricyl alcohol,** and $C_{26}H_{53}OH$, **ceryl alcohol,** are frequently found in waxes. **Beeswax** is largely myricyl palmitate, $C_{15}H_{31}COOC_{30}H_{61}$. It is widely used in the manufacture of polishes and in pharmaceutical preparations. **Chinese insect wax** is obtained from a deposit made by a parasitical insect on certain trees in Asia. It is largely ceryl cerotate, $C_{25}H_{51}COOC_{26}H_{53}$. (Cerotic acid is $C_{25}H_{51}COOH$.) **Carnauba wax** has an exceptionally high melting point (83° to 86°). It is extracted from the leaves of a Brazilian palm. It is largely $C_{25}H_{51}COOC_{30}H_{61}$.

QUESTIONS AND PROBLEMS

1. Write balanced equations for the preparation of ethylene oxide and for its reaction with water and ethyl alcohol.

2. Upon what chemical reactions does the "drying" of such oils as linseed oil depend?

3. Define and give examples of functional groups.

4. Write balanced equations for the reaction between (*a*) butyric anhydride and glycerol, (*b*) acetic anhydride and mannitol.

5. What experiments would you use to distinguish (*a*) cottonseed oil from a mixture of tallow and linseed oil, (*b*) butter from a mixture of cottonseed oil and lard, (*c*) cottonseed oil from a sample of a mineral oil, and (*d*) beeswax from beef tallow?

6. Define and illustrate the terms (*a*) polyfunctional compound, (*b*) detergent, (*c*) dynamite, (*d*) glycol, (*e*) lipid.

7. Write equations for the conversion of (*a*) triolein to tristearin, (*b*) triolein to octadecyl alcohol.

8. Compare the structural formulas and the chemical and physical properties of the following five naturally occurring materials: tristearin, lecithin, arabitol, triolein, myricyl palmitate.

9. Describe briefly the manufacture of soap. Compare the structure of soap with the structures of some other detergents.

10. A chloroform extract of a certain natural product was known to contain fats, free fatty acids, and solid ketones. Devise a simple scheme for isolating the ketones.

CHAPTER 9

Industrial and Laboratory Syntheses

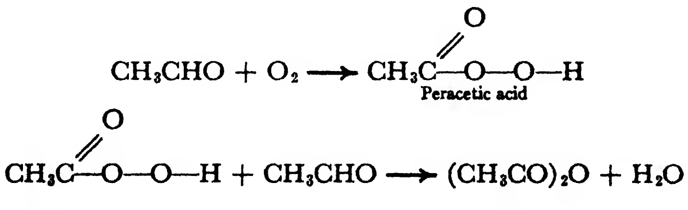
IMPORTANT INDUSTRIAL SYNTHESES

We have already considered several important industrial methods of preparing organic compounds. We are now in a position to survey the overall picture of the industrial sources of the simpler aliphatic compounds such as the alcohols, the acids, and the carbonyl compounds. Basically the cheap sources of raw materials are (1) carbohydrates, (2) petroleum, (3) natural gas, and (4) coke. Since there are many methods of going from almost all these sources to the individually important aliphatic compounds, the choice of the method to be employed is a matter of cost rather than chemistry. An important element in this cost is the transportation either of the raw material or the finished product. For this reason one process suitable in an area where petroleum or natural gas occurs plentifully (and hence is very cheap) is replaced by another process in a locality where coal is much cheaper than oil or gas. Still another raw material may be used if both electricity and coal are cheap. Carbohydrates are usually a more expensive source of carbon compounds than either petroleum, gas, or coal; but ethyl alcohol has been prepared in the United States by the fermentation of molasses from Cuba in competition with ethyl alcohol from natural gas. Where the products must be used in beverages or foods, of course, other considerations than cost come into play.

Synthetic Acetaldehyde. Cheap acetaldehyde is a substance of great industrial importance although relatively small quantities of it are sold as such. It is instead converted on the spot into such substances as ethyl alcohol, acetic acid, acetic anhydride, aldol, ethyl acetate, and acetone. Acetaldehyde can be prepared from acetylene, from ethyl alcohol (and this from either ethylene or carbohydrates), and by oxidation of petroleum hydrocarbons such as propylene, propane, ethane, and butane. Using an excess of hydrocarbon vapor and air at 500°, considerable amounts of acetaldehyde, formaldehyde, and methyl alcohol are formed. Methane is but little affected under these conditions. The United States production of acetaldehyde in 1947 exceeded 210,000 tons.

Acetic Anhydride from Acetaldehyde. The oxidation of acetaldehyde to acetic acid or its reduction to ethyl alcohol requires no special comment (the latter process cannot at present compete with other ways of preparing alcohol). The transformation of acetaldehyde to acetic anhydride, however, involves a new reaction.

By oxidizing acetaldehyde with air in a dilute solution in an unreactive volatile solvent such as carbon tetrachloride or benzene, a mixture of acetic acid and acetic anhydride is formed directly. The reaction appears to involve the formation of a *per*-acid (an unstable acyl derivative of hydrogen peroxide). This peracetic acid then reacts with acetaldehyde to give acetic anhydride and water.



$$CH_3CHO + O_2 \longrightarrow \underset{\text{Peracetic acid}}{CH_3\overset{\overset{O}{/\!\!/}}{C}—O—O—H}$$

$$CH_3\overset{\overset{O}{/\!\!/}}{C}—O—O—H + CH_3CHO \longrightarrow (CH_3CO)_2O + H_2O$$

The products of the reaction, acetic anhydride and water, of course react to form acetic acid. But, in the presence of a diluent, the rate of hydration of acetic anhydride is low because the concentration of the two reactants is low. Therefore, only a portion of the anhydride is converted into the acid before the mixture is separated by distillation. The volatile diluent, unchanged aldehyde, and water are removed continuously by distillation;

the acetic acid and anhydride are then separated by distillation. The dehydration of acetic acid is an endothermic reaction and takes place only at very high temperatures; the oxidation of acetaldehyde is a strongly exothermic reaction. Through the intermediary of a peracid the two reactions — oxidation and dehydration — are in a sense *coupled* together so that the overall reaction proceeds to completion only slightly above room temperature.

Sources of Acetylene. Acetylene is prepared in enormous quantities from calcium carbide and water (p. 59). Calcium carbide in turn is manufactured by heating lime and coal (or coke) in an electric furnace. Hence acetylene is a very cheap substance where hydroelectric power is available. Very recently large-scale experiments have been in progress looking to the production of acetylene by the thermal cracking of the simple paraffin hydrocarbons at very high temperatures (1000° to 1500°). Not only ethane and propane, but methane itself forms acetylene at these very high temperatures. The thermal exposure must be very short or the acetylene will undergo other reactions; hydrogen is the other product.

$$C_2H_6 \xrightarrow{1500^\circ} HC\equiv CH + 2H_2$$

$$2CH_4 \xrightarrow{1500^\circ} HC\equiv CH + 3H_2$$

Syntheses Based on Acetylene. Acetylene is a remarkably versatile raw material for chemical syntheses. When the hydrocarbon is passed into a vigorously agitated suspension of mercuric sulfate in dilute sulfuric acid, acetaldehyde is formed.

$$CH\equiv CH + H_2O \xrightarrow[H_2SO_4]{HgSO_4} CH_3CHO$$

Under different experimental conditions the reaction between acetylene and water furnishes acetone.

$$2CH\equiv CH + 3H_2O \xrightarrow{ZnO} CH_3COCH_3 + CO_2 + 2H_2$$

Acetylene will add to carbonyl compounds as H— and —C≡CH. This reaction with formaldehyde permits the synthesis of butadiene.

$$2H_2C{=}O + CH{\equiv}CH \xrightarrow[\text{acetylide catalyst}]{\text{Metallic}} HOCH_2C{\equiv}CCH_2OH$$

$$HOCH_2C{\equiv}CCH_2OH \xrightarrow[\text{Ni}]{H_2} HOCH_2CH_2CH_2CH_2OH \longrightarrow CH_2{=}CH{-}CH{=}CH_2$$

The versatility of acetylene, however, results chiefly from the fact that a variety of organic compounds of the general type H—A, where A is some element other than carbon or H is acidic, will add to it.

$$CH{\equiv}CH + HA \longrightarrow CH_2{=}CHA$$

The products contain the group $CH_2{=}CH{-}$, known as the *vinyl* group, and the reaction is known as *vinylation.* As examples we may cite the addition of hydrogen chloride and bromide which leads to the corresponding vinyl halides;

$$CH{\equiv}CH + HCl \longrightarrow CH_2{=}CHCl$$

the addition of alcohols which furnishes vinyl ethers;

$$CH{\equiv}CH + CH_3OH \xrightarrow{NaOCH_3} \underset{\text{Vinyl methyl ether}}{CH_2{=}CHOCH_3}$$

and the addition of aliphatic acids which leads to vinyl esters.

$$CH{\equiv}CH + CH_3COOH \xrightarrow{Zn(OCOCH_3)_2} \underset{\text{Vinyl acetate}}{CH_3COOCH{=}CH_2}$$

The reaction between acetic acid and acetylene can be controlled so that two moles of the acid add. The product, ethylidene diacetate, yields acetic anhydride and acetaldehyde on distillation.

$$CH{\equiv}CH + 2CH_3COOH \longrightarrow \underset{\text{Ethylidene diacetate}}{CH_3CH(OCOCH_3)_2}$$

$$CH_3CH(OCOCH_3)_2 \xrightarrow{\text{Distil}} CH_3CHO + (CH_3CO)_2O$$

VINYL POLYMERS

Compounds containing the vinyl group polymerize readily to large molecules similar to those formed by the polymerization of ethylene (p. 57). As we have just seen, a wide variety of vinyl compounds are available from acetylene. The polymers of these compounds have many industrial uses. Polyvinyl chloride and bromide are amorphous solids which are insoluble in all the common solvents. Polyvinyl acetate, often known as *vinylite*, is used in the preparation of artificial resins, varnishes, and lacquers. The acetate groups may be removed by hydrolysis yielding polyvinyl alcohol; in this compound the group $—CHOHCH_2—$ is repeated many times as is the isoprene unit in the rubber molecule (p. 74). Although the molecular weight is large, the presence of so many hydroxyl groups makes polyvinyl alcohol soluble in water. By copolymerizing two different vinyl compounds the range of vinyl polymers is greatly extended; thus *saran* is a copolymer of vinyl chloride and vinylidene chloride, $CH_2{=}CCl_2$.

Vinyl Alcohol, the parent substance of the polyvinyl alcohol mentioned above, is unknown. All attempts to prepare a substance with the formula $CH_2{=}CHOH$ lead instead to acetaldehyde, which one can imagine is formed by the shift of a hydrogen atom from oxygen to carbon. The synthesis of acetaldehyde from acetylene, described on p. 141, presumably involves the addition of water to acetylene to furnish vinyl alcohol which then isomerizes to acetaldehyde. Compounds containing the grouping $—CH{=}CHOH$ are rare; attempts to prepare them usually result in the formation of the isomeric substance of the structure $—CH_2CO$.

Allyl Alcohol. The vinyl group is also present in a series of closely related substances, allyl alcohol, acrolein, and acrylic acid. A few compounds containing the allyl group occur in nature; acrolein is present in the acrid fumes produced by burning fat, but the chief interest in the group centers around the nitrile and the esters of acrylic acid. These are readily polymerized by light, heat, and peroxides. By carefully controlling the reaction, clear colorless resins are obtained which are known as **acryloids.** These resins have excellent optical properties and can be molded into lenses, prisms, and sheets which are used to make laminated safety glass.

$CH_2{=}CHCH_2OH$	$CH_2{=}CHCHO$	$CH_2{=}CHCN$	$CH_2{=}CHCOOH$
Allyl alcohol	Acrolein	Acrylonitrile	Acrylic acid

Industrially, acrylic esters are prepared from ethylene chlorohydrin (p. 123) by conversion to ethylene cyanohydrin and subsequent esterification and dehydration.

$$CH_2OHCH_2Cl + NaCN \longrightarrow \underset{\text{Ethylene cyanohydrin}}{CH_2OHCH_2CN}$$

$$CH_2OHCH_2CN + CH_3OH \xrightarrow{H_2SO_4} \underset{\text{Methyl acrylate}}{CH_2{=}CHCOOCH_3} + NH_3$$

Acrylic esters can also be made from acetylene, carbon monoxide, and the appropriate alcohol.

$$CH{\equiv}CH + CO + CH_3OH \xrightarrow{\text{Catalyst}} CH_2{=}CHCOOCH_3$$

Dehydration of ethylene cyanohydrin furnishes acrylonitrile. The polymer made from this material and known as Orlon is a fiber comparable in its properties to Nylon (p. 173).

SYNTHESES FROM CARBON MONOXIDE

The discussion up to this point has dealt with syntheses from coal or coke via acetylene. We now shall consider some important syntheses that start from carbon monoxide, which is prepared from coke by the water gas reaction.

$$H_2O + C\ (\text{coke}) \xrightarrow{1000^\circ} CO + H_2$$

Methane is a very cheap source of carbon in many parts of this country and hence is a promising source of carbon monoxide. At high temperatures with steam, methane forms carbon monoxide and hydrogen.

$$CH_4 + H_2O \xrightarrow[800^\circ\text{–}1000^\circ]{\text{Catalyst}} CO + 3H_2$$

In Europe, however, where there are no petroleum and natural gas deposits, coke from coal is of course the source of carbon monoxide.

Industrial Synthesis of Methyl Alcohol. A very large fraction of the methyl alcohol now prepared industrially is the product of the hydrogenation of carbon monoxide.

$$CO + 2H_2 \xrightarrow[\substack{300^\circ\text{–}400^\circ \\ \text{High pressure (200 atm)}}]{\text{Catalyst}} CH_3OH$$

Other Products from Carbon Monoxide. With a suitable catalyst, methyl alcohol and carbon monoxide under pressure yield acetic acid. Therefore this acid as well as methyl alcohol can be synthesized industrially from coal via carbon monoxide.

$$CH_3OH + CO \xrightarrow[\text{High pressure; above } 300^\circ]{\text{Catalyst}} CH_3COOH$$

It has been found that, in addition to methyl alcohol, higher alcohols, such as propyl and isobutyl alcohols, are obtained in the catalytic hydrogenation of carbon monoxide. These products are probably formed by the interaction of two alcohol molecules with loss of water.

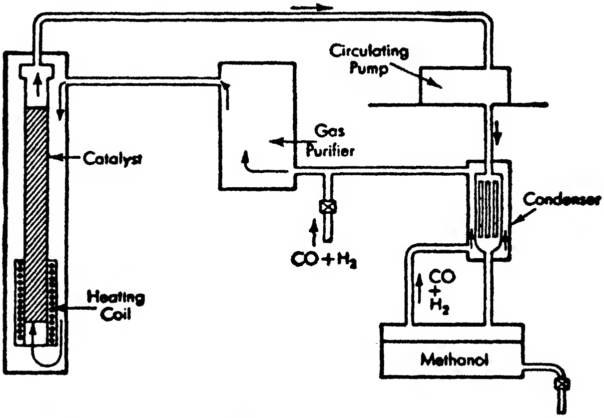


Fig. 7. Diagram showing the essential features of an apparatus for the synthesis of methyl alcohol from carbon monoxide and hydrogen.

Such a process could repeat itself until a long-chain alcohol was formed. The following hypothetical mechanism would lead to the formation of higher alcohols.

$$CH_3OH + HCH_2OH \xrightarrow[\text{High pressure; } 300^\circ]{\text{Catalyst}} CH_3CH_2OH + H_2O$$

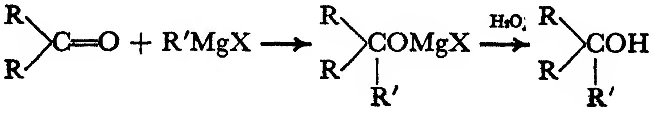
$$CH_3CH_2OH + HCH_2OH \longrightarrow CH_3CH_2CH_2OH + H_2O$$

The hydrogenation of carbon monoxide may be carried out in the presence of catalysts which so favor the formation of longer chain compounds that these become the major product. These alcohols on dehydration yield unsaturated hydrocarbons which can be hydrogenated or alkylated to give the desired components of modern gasoline. In this way liquid fuels can be prepared commercially from coal or natural gas via carbon monoxide. The original process, known as the Fischer-Tropsch method, was developed before World War II in Germany where it was used to prepare gasoline from coal since the supply of petroleum was so limited.

LABORATORY SYNTHESES

An important part of the work of the organic chemist is the synthesis of organic compounds in the laboratory. Before the relations between the structure of hydrocarbons and their anti-knock properties (p. 271) could be worked out, it was necessary for the chemist to synthesize the hydrocarbons for study. Several thousand organic compounds were synthesized for testing in the program of research on antimalarial drugs (Chap. 23). The actual syntheses which engage the attention of organic chemists today are for the most part far too complex to be considered here. The methods employed can be illustrated, however, by some simple examples. And, since the reactions of one class of compounds constitute the methods of preparing other classes of compounds from them, the student will find that one of the best methods of reviewing these reactions is by working out simple syntheses. A few examples of syntheses follow.

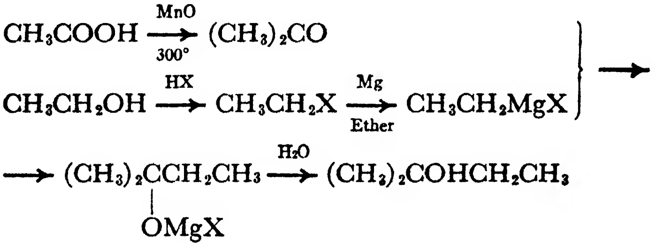
Synthesis of a Tertiary Alcohol. The synthesis of dimethylethylcarbinol, 2-methyl-2-butanol, will serve as an example. The first step is to write the structural formula; the second is to recall the methods available for preparing tertiary alcohols. The action of a Grignard reagent on a ketone comes to mind.



$$R_2C{=}O + R'MgX \longrightarrow R_2C(R')OMgX \xrightarrow{H_2O} R_2C(R')OH$$

What Grignard reagent, what ketone? Consideration of the formula of dimethylethylcarbinol, $(CH_3)_2COHC_2H_5$, shows that the Grignard reagent could be ethylmagnesium bromide, C_2H_5MgBr; the ketone, acetone, CH_3COCH_3.

Even the beginner in organic chemistry is now on familiar ground. Ethylmagnesium bromide can be prepared from ethyl bromide which in turn is made from ethyl alcohol. Acetone, if not available, could be prepared from acetic acid by the catalytic process. If we imagine that circumstances force the chemist to start with such simple substances as acetic acid, ethyl alcohol and inorganic material, the steps in the synthesis may be represented as follows.

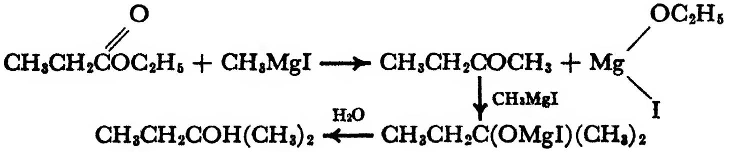


$$\left.\begin{array}{l} CH_3COOH \xrightarrow[300^\circ]{MnO} (CH_3)_2CO \\ CH_3CH_2OH \xrightarrow{HX} CH_3CH_2X \xrightarrow[Ether]{Mg} CH_3CH_2MgX \end{array}\right\} \longrightarrow$$

$$\longrightarrow (CH_3)_2\underset{\displaystyle \overset{|}{OMgX}}{C}CH_2CH_3 \xrightarrow{H_2O} (CH_3)_2COHCH_2CH_3$$

It often happens that there is more than one possible route to the desired goal, but usually one route is shorter and better than the others. In the example above we might have elected to treat methyl ethyl ketone with methylmagnesium iodide; methyl ethyl ketone, however, being a mixed ketone, is less readily prepared than acetone.

Tertiary Alcohols from Esters. In addition to the method previously given for preparing tertiary alcohols, it will be well to mention another useful method. This consists in treating an ester with a Grignard reagent (a ketone is formed as an intermediate but rarely can be isolated). The method is illustrated by the preparation of dimethylethylcarbinol from ethyl propionate and two moles of methylmagnesium iodide.

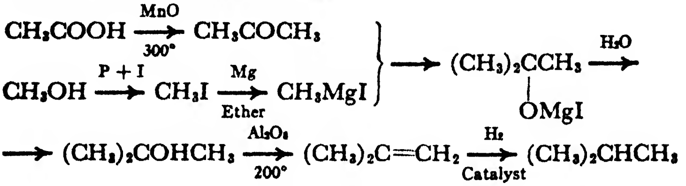


$$CH_3CH_2\overset{\displaystyle O /\!\!/}{C}OC_2H_5 + CH_3MgI \longrightarrow CH_3CH_2COCH_3 + Mg\begin{array}{l} \diagup OC_2H_5 \\ \diagdown I \end{array}$$

$$CH_3CH_2COCH_3 \xrightarrow{CH_3MgI} CH_3CH_2C(OMgI)(CH_3)_2 \xrightarrow{H_2O} CH_3CH_2COH(CH_3)_2$$

Synthesis of a Paraffin. The synthesis of isobutane from the common reagents of the laboratory is indicated below.

Problem: Prepare $(CH_3)_2CHCH_3$.



$$\left.\begin{array}{l} CH_3COOH \xrightarrow[300^\circ]{MnO} CH_3COCH_3 \\ CH_3OH \xrightarrow{P + I} CH_3I \xrightarrow[Ether]{Mg} CH_3MgI \end{array}\right\} \longrightarrow (CH_3)_2\underset{\substack{| \\ OMgI}}{C}CH_3 \xrightarrow{H_2O}$$

$$\longrightarrow (CH_3)_2COHCH_3 \xrightarrow[200^\circ]{Al_2O_3} (CH_3)_2C{=}CH_2 \xrightarrow[Catalyst]{H_2} (CH_3)_2CHCH_3$$

The student should note the mental process by which, working *backward step by step*, such a synthesis can be evolved. These backward steps may be summarized as follows: Isobutane is a saturated hydrocarbon; saturated hydrocarbons can be made by (1) the reduction of unsaturated hydrocarbons and (2) from the Grignard reagent and water. Different routes will be traveled according to whether the first or second method is chosen. The first route has been selected in the example above. The unsaturated hydrocarbon is best prepared by loss of water from the corresponding alcohol, which is either tertiary butyl alcohol, $(CH_3)_3COH$, or the primary alcohol, $(CH_3)_2CHCH_2OH$. Tertiary alcohols in turn are made by the action of the Grignard reagent on ketones. This problem then resolves itself into the preparation of acetone and methylmagnesium iodide.

Lengthening a Carbon Chain. Among the many problems which the organic chemist has to solve in synthetic work is that of making compounds having more carbon atoms than the one from which he starts. The following diagrams show how this can be done when one wants an alcohol or an acid.

Problem: Synthesize RCH_2OH *from* ROH.

$$\begin{tikzcd} ROH \arrow[r, "HX", "\text{or } P+I"'] & RX \arrow[r, "Mg", "Ether"'] & RMgX \arrow[r, "HCHO"] & RCH_2OMgX \arrow[d, "H_2O"] \\ & & & RCH_2OH \end{tikzcd}$$

Problem: Synthesize an acid RCOOH *from an alcohol* ROH.

$$ROH \xrightarrow[\text{or } P+I]{HX} RX \xrightarrow[Ether]{Mg} RMgX \xrightarrow{CO_2} RCOOMgX \xrightarrow[\text{(acidify)}]{} RCOOH$$

Alternative method.

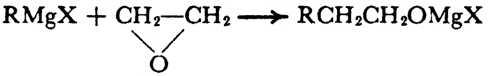
$$ROH \xrightarrow[\text{or } P + I]{HX} RX \xrightarrow{KCN} RCN \xrightarrow{NaOH} RCOONa \xrightarrow{HX} RCOOH$$

Problem: Synthesize an acid RCH_2COOH *from an acid* $RCOOH$.

$$\begin{tikzcd}
RCOOH \arrow[r, "C_2H_5OH"] & RCOOC_2H_5 \arrow[r, "{[H]}", "Na + C_2H_5OH"'] & RCH_2OH \arrow[r, "P + I"] & RCH_2I \arrow[d, "Mg"] \\
 & & RCH_2COOH & RCH_2MgI \arrow[l, "CO_2"']
\end{tikzcd}$$

Alternative for last two steps, prepare RCH_2CN *and hydrolyze.*

Two carbon atoms may be added in a single reaction by treating a Grignard reagent with ethylene oxide.



$$RMgX + CH_2{-}CH_2(O) \longrightarrow RCH_2CH_2OMgX$$

$$RCH_2CH_2OMgX + H_2O \longrightarrow RCH_2CH_2OH + MgXOH$$

Limitations of the Reactions. These synthetic methods which we have generalized above by the use of the symbol R for an alkyl group, *are subject to serious limitations in practice.* A consideration of these limitations is the province of an advanced course in organic chemistry. As an example of such limitations, we may mention the fact that certain highly branched ketones, such as $(CH_3)_3CCOC(CH_3)_3$, will not react with the Grignard reagent, or react abnormally. In general, the *branching of the chain* near the functional group and the introduction of reactive groups (halogen, OH, NH_2, etc.) modify the reactions greatly. Increasing the length of the chain as a rule has little disturbing influence; hence the general methods of synthesis give good results where primary alkyl groups are attached to the reacting group.

QUESTIONS AND PROBLEMS

1. What is a coupled reaction?
2. Show how acetaldehyde can be obtained from carbohydrates, or coal, or petroleum.
3. Discuss the sources and uses of the vinyl polymers.

4. Given methyl and ethyl alcohols, ether, and any necessary inorganic reagents, show how you would prepare:

(*a*) $CH_3CH_2CH_2OH$,	(*b*) $(CH_3)_3COH$,
(*c*) $CH_3CH_2CH_2CH_2COCH_2CH_3$,	(*d*) $CH_3C(OH)(C_2H_5)_2$,
(*e*) $CH_3CH_2CHOHCH_2CH_3$,	(*f*) $CH_3CH_2CHClCHClCH_3$.

5. Write equations for the reactions involved in the preparation of chloroform from ethyl alcohol.

6. Assuming that hydroelectric power is available, outline a procedure for preparing at low cost the following compounds: acetone, acetic anhydride, butyl acetate.

7. What are the important industrial methods of preparing acetic anhydride?

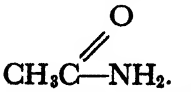
8. List the reactions of the Grignard reagent which have been mentioned up to this point and write examples of each reaction.

CHAPTER 10

Derivatives of Ammonia: Amides and Amines

A large portion of the preceding chapters has been devoted to compounds which are related to water. Thus, alcohols, ROH, may be regarded as alkyl derivatives of water; ethers, ROR, as dialkyl derivatives; acids, RCOOH, as acyl derivatives and acid anhydrides as diacyl derivatives $(RCO)_2O$. We shall now consider the corresponding nitrogen compounds which are related to ammonia. These are the amines, RNH_2, R_2NH, R_3N, and the amides, $RCONH_2$. In these substances, one or more hydrogen atoms of ammonia have been replaced by alkyl or acyl groups. We shall find the differences between water and ammonia reflected in these compounds; the derivatives of water are more or less acidic, those of ammonia more or less basic. An understanding of these simple derivatives of ammonia is an essential preliminary to a study of the proteins and the other nitrogen-containing substances involved in the life process.

AMIDES

Preparation of Amides. Of the acyl derivatives of ammonia only those containing one acyl group are of importance. They are known as the amides, $RCONH_2$. The best known is **acetamide,**  $CH_3C(=O)\text{—}NH_2$. The following equations represent the typical methods of preparing amides as applied to acetamide.

$$CH_3COCl + 2NH_3 \longrightarrow CH_3CONH_2 + NH_4Cl$$
$$(CH_3CO)_2O + 2NH_3 \longrightarrow CH_3CONH_2 + CH_3COONH_4$$
$$CH_3COOC_2H_5 + NH_3 \longrightarrow CH_3CONH_2 + C_2H_5OH$$

The first two reactions usually take place rapidly; the reaction of esters with ammonia is slow. The parallelism between the action of ammonia (ammonolysis) and water (hydrolysis) is striking. If we substitute water for ammonia in these reactions, an acid is formed.

Amides from Ammonium Salts. Another convenient method of preparing amides is to heat the ammonium salt of the corresponding acid.

$$CH_3COONH_4 \overset{100^\circ\text{-}200^\circ}{\rightleftarrows} CH_3CONH_2 + H_2O$$

This reaction is reversible; it proceeds at an appreciable rate only at about 100° or higher. If we can remove the water as rapidly as it is formed, the reaction will go to completion in spite of an unfavorable equilibrium. Since the amides are high-boiling and the ammonium salts essentially nonvolatile substances, this is easy to accomplish by using a suitable apparatus.

Hydrolysis of Amides. The amides are hydrolyzed by boiling a water solution with acid or alkali which catalyzes the reaction. If we add one equivalent of sodium hydroxide, the reaction goes to completion for the same reason that the saponification of esters with alkali is complete (p. 118). With 1 mole of acid the reaction also goes to an end, since the ammonia is removed as the ammonium salt.

The equations for the reactions are given below.

$$RCONH_2 + NaOH \xrightarrow{\text{Boil}} RCOONa + NH_3$$
$$RCONH_2 + H_2O + H_2SO_4 \xrightarrow{\text{Boil}} RCOOH + NH_4HSO_4$$

Reaction with Nitrous Acid. When treated with nitrous acid, amides yield nitrogen and the corresponding acid. This reaction, like the hydrolysis of amides, may be used for preparing acids from the corresponding amides. Since nitrous acid is known only in dilute water solutions which slowly decompose, it is prepared by adding hydrochloric acid to an aqueous solution of sodium nitrite.

$$RCONH_2 + HONO \xrightarrow{NaNO_2 + HCl} RCOOH + N_2 + H_2O$$

Physical and Chemical Properties. The simple amides are very soluble in water and are surprisingly high-melting and high-boiling substances; formamide, $HCONH_2$, melts at 2° and boils at 193°; acetamide, CH_3CONH_2, melts at 81° and boils at 222°.

The acidic and basic properties of amides are so weak that they are not manifested in water solution. This is in contrast to the parent compound, ammonia, which is a base. The substitution of an acyl group for hydrogen has greatly decreased the basic properties of the NH_2 group.

The Hofmann Reaction. The most important reaction of amides is known as the *Hofmann reaction:* the amide is converted into an alkyl derivative of ammonia, an amine, RNH_2. The mechanism of this extraordinary change is complicated. The first step consists in the replacement of a hydrogen atom by a halogen atom; the resulting compound is rapidly decomposed by alkali with the *elimination of a carbon atom as* carbon dioxide.

$$CH_3CONH_2 + NaOCl \longrightarrow CH_3CONHCl + NaOH$$

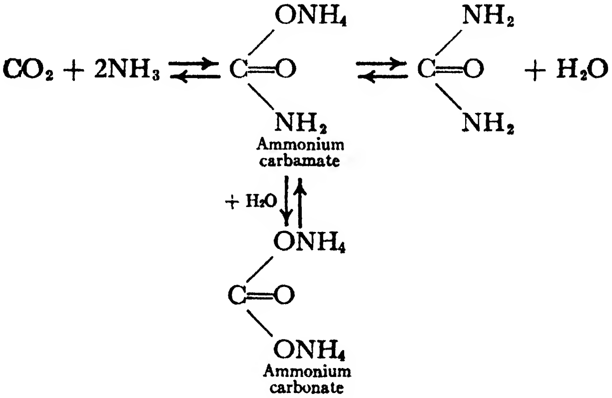
$$CH_3CONHCl + 3NaOH \longrightarrow CH_3NH_2 + NaCl + Na_2CO_3 + H_2O$$

The reaction is carried out by treating an aqueous solution of the amide with sodium hypochlorite, or sodium hypobromite, and sodium hydroxide. On distilling the mixture, the amine, which is volatile, distils, and is collected.

It is evident that the Hofmann reaction amounts to clipping one carbon atom from the end of a carbon chain. For this reason, it has been of importance in preparing simpler compounds from more complicated ones and in determining the structure of compounds with long carbon chains.

Urea. The most important amide is the diamide of carbonic acid, urea. It is the principal end product of the metabolism of nitrogen foods in the human body and is excreted in the urine.

Urea is now prepared in large quantities for use as a fertilizer and in the manufacture of resins and plastics (p. 317). The reaction employed is similar to one of the general methods of preparing amides; namely, heating an ammonium salt. Carbon dioxide and ammonia are heated under pressure. The exact control of the temperature and pressure is important because a series of reversible reactions is involved; a good yield of urea is only obtained under special conditions.



Reactions of Urea. The hydrolysis of urea in water solution is brought about in the presence of the enzyme **urease,** which has been isolated from the soy bean. This method forms the basis of a clinical method of determining urea. The amount of ammonia formed from a known weight of sample can be easily determined colorimetrically, or by titration with a standard acid.

$$CO(NH_2)_2 + H_2O \xrightarrow[\text{urease}]{\text{Enzyme}} CO_2 + 2NH_3$$

The reaction with sodium hypobromite (in a sense, the Hofmann reaction) has also been used for the determination of the amount of urea in urine. The volume of nitrogen evolved from a known sample can easily be measured in a suitable apparatus.

$$CO(NH_2)_2 + 3NaOBr + 2NaOH \longrightarrow Na_2CO_3 + N_2 + 3NaBr + 3H_2O$$

AMINES

Nomenclature. The amines are the alkyl derivatives of ammonia. They may be divided into the following classes:

1. A primary amine, RNH_2, e.g., CH_3NH_2 methylamine,
2. A secondary amine, R_2NH, e.g., $(CH_3)_2NH$ dimethylamine,
3. A tertiary amine, R_3N, e.g., $(CH_3)_3N$ trimethylamine.

The usual method of naming amines is illustrated by the above examples. In more complicated amines, the position of the group may be indicated and the name of the parent hydrocarbon given. Thus, $(CH_3)_2CHCHNH_2CH_3$ is 2-amino-3-methylbutane. It should be noted that the group NH_2 is called *ami***no** when present in an *amine* and *ami***do** when present in an *amide.*

General Properties of Amines. The simpler amines resemble ammonia. They are soluble in water and the solutions are basic. On boiling the solution the volatile amines are expelled. The boiling points of some of the simpler amines are given below.

BOILING POINTS OF SIMPLE AMINES

Name	*Formula*	*Boiling Point*	*Class*
Methylamine	CH_3NH_2	−7°	Primary amine
Dimethylamine	$(CH_3)_2NH$	+7°	Secondary amine
Trimethylamine	$(CH_3)_3N$	+4°	Tertiary amine
Ethylamine	$C_2H_5NH_2$	+17°	Primary amine
n-Propylamine	$CH_3CH_2CH_2NH_2$	+49°	Primary amine

Neutralization of Amines. All three classes of amines are bases like ammonia. The water solutions turn red litmus blue and may be neutralized with acids. The salts which are thus formed are obtained as white solids by evaporating the solution. Like inorganic salts they are nonvolatile solids, readily soluble in water and insoluble in organic solvents. Their water solutions are ionized. All these facts are best represented by the following ionic equations, using trimethylamine as the example.

$$(CH_3)_3N + H_2O \rightleftharpoons (CH_3)_3NH^+ + OH^-$$

$$(CH_3)_3NH^+ + OH^- + H^+ + Cl^- \longrightarrow (CH_3)_3NH^+ + Cl^- + H_2O$$

Similar equations may be written for the primary and secondary amines. The chlorides may also be formed by bringing together the base and acid in an anhydrous medium.

$$(CH_3)_3N + HCl \longrightarrow (CH_3)_3NHCl$$

The salts of the amines are alkyl derivatives of the ammonium salts and are usually named on this basis, thus: CH_3NH_3Cl, methylammonium chloride; $(CH_3)_2NH_2Br$, dimethylammonium bromide; $(CH_3)_3NHNO_3$, trimethylammonium nitrate. The formulas of the salts are also written to show more clearly the original amine and are named as hydrochlorides, thus:

$CH_3NH_2 \cdot HCl$ Methlyamine hydrochloride

This method corresponds to an obsolete method of writing ammonium salts, thus: $NH_3 \cdot HCl$, the hydrochloride of ammonia.

Preparation of Amines from Their Salts. On treating a solution of the salt of an amine with sodium hydroxide, the free amine is formed in the solution. If the solution is then boiled, the amine will be expelled, if volatile; if the solution is extracted with ether, the amine will pass into the ether layer.

$$(CH_3)_3NHCl + NaOH \longrightarrow (CH_3)_3NHOH + NaCl$$

$$(CH_3)_3NHOH \rightleftharpoons \underset{\text{Distil or extract}}{(CH_3)_3N} + H_2O$$

This behavior of the salts of the amines is exactly parallel to the reaction of ammonium salts. It shows that the amines like ammonia are *weak anhydro bases.* Thus, to obtain weak bases from their salts, we treat a solution of the salt with a strong base, and boil or extract; if the weak base is insoluble (as are the higher amines), it will precipitate. This general method should be compared with the preparation of weak acids from their salts by the action of a strong nonvolatile acid (p. 104).

Basic Dissociation Constants. The relative strength of weak bases may be best expressed in terms of a basic dissociation constant. This is similar to the acid dissociation constant which we have already mentioned (p. 106). All the weak organic bases belong to the class of substances which are called *anhydro bases*. A water solution of such a base contains the anhydro base itself (e.g., RNH_2), any undissociated hydrated base (RNH_3OH) and the dissociated base ($RNH_3^+ + OH^-$). In measuring the strength of an anhydro base we lump together both the unhydrated base, RNH_2, and the undissociated base, RNH_3OH, and call this total the *free base*. A measure of the strength of the base is thus the amount of dissociated base ($RNH_3^+ + OH^-$) compared to the total free base ($RNH_3OH + RNH_2$). Therefore, we write:

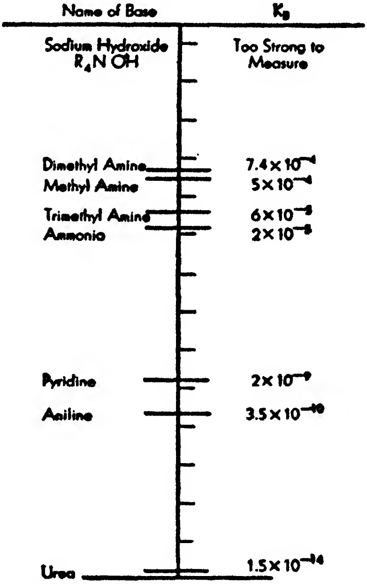


Fig. 8. The relative strengths of certain bases. The strongest bases are at the top of the scale; each scale unit corresponds to a ten-fold change in the basic dissociation constant.

$$\text{Basic dissociation constant } (K_B) = \text{Conc. OH}^- \times \left(\frac{\text{Conc. of ion } (RNH_3^+)}{\text{Conc. free base}}\right)$$

A solution containing equal molecular amounts of a weak anhydro base and its salt has a concentration of hydroxyl ion equal to the basic dissociation constant. The constant K_B for ammonia is 2×10^{-5} and the hydroxyl ion concentration of an ammonium hydroxide—ammonium chloride mixture is about 10^{-5}; since conc. $H^+ \times$ conc. $OH^- = 10^{-14}$, the conc. of hydrogen ion in this solution is about 10^{-9}.

The basic dissociation constants for some of the common amines are as follows:

Methylamine $K_B = 5 \times 10^{-4}$
Dimethylamine $K_B = 5.4 \times 10^{-4}$
Trimethylamine $K_B = 5.9 \times 10^{-5}$

It is evident that they are somewhat stronger bases than ammonia itself. The relative strengths of certain bases are shown in the diagram in Fig. 8 on p. 157.

Preparation of Primary Amines. Special methods are employed for preparing a number of the different amines; we shall mention two general methods of preparing primary amines. The first is the Hofmann reaction, which was discussed on p. 153. The second is the reduction of a nitrile.

$$RCN + 2H_2 \xrightarrow{\text{Catalyst}} RCH_2NH_2$$

Preparation of Amines from Ammonia. On heating ammonia with an alkyl halide, the two combine to form the salt of a primary amine. Unfortunately the reaction does not stop here, but forms secondary and tertiary amines and also substances known as *quaternary ammonium salts.* This unpromising mixture can be separated, and a number of amines have been prepared by this method. Since, however, so many products are formed, the process is not efficient for the preparation of any one amine.

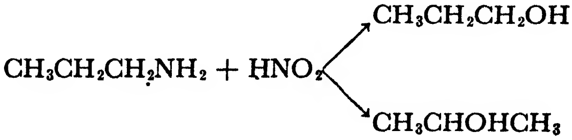
$$C_2H_5Br + NH_3 \longrightarrow C_2H_5NH_3Br$$
$$C_2H_5NH_3Br + NH_3 \rightleftarrows C_2H_5NH_2 + NH_4Br$$

$$C_2H_5NH_2 + C_2H_5Br \longrightarrow (C_2H_5)_2NH_2Br$$
$$(C_2H_5)_2NH_2Br + NH_3 \rightleftarrows (C_2H_5)_2NH + NH_4Br$$

$$(C_2H_5)_2NH + C_2H_5Br \longrightarrow (C_2H_5)_3NHBr$$
$$(C_2H_5)_3NHBr + NH_3 \rightleftarrows (C_2H_5)_3N + NH_4Br$$

$$(C_2H_5)_3N + C_2H_5Br \longrightarrow \underset{\substack{\text{Tetraethylammonium}\\ \text{bromide}\\ \text{(a quaternary ammonium}\\ \text{salt)}}}{(C_2H_5)_4NBr}$$

Reactions of Amines with Nitrous Acid. Primary, secondary, and tertiary amines can be distinguished by their behavior toward nitrous acid. Primary amines react rapidly with an aqueous solution of nitrous acid, liberating nitrogen and forming an alcohol. An exception to this rule is the behavior of methylamine in which the product is methyl nitrite CH_3ONO. With ethylamine the product is ethyl alcohol. The higher amines yield a mixture of alcohols due to a shift of the hydroxyl group. This is a rather unusual type of replacement reaction in which the entering group may not occupy the position of the displaced group.



$$CH_3CH_2CH_2NH_2 + HNO_2 \begin{cases} \nearrow CH_3CH_2CH_2OH \\ \searrow CH_3CHOHCH_3 \end{cases}$$

Secondary amines react slowly with nitrous acid forming **nitroso compounds** which often separate from the solution as oils.

$$(CH_3)_2NH + HONO \xrightarrow{\text{Warm}} \underset{\text{Nitrosodimethylamine}}{(CH_3)_2NNO} + H_2O$$

Tertiary amines form the corresponding salt (a tertiary amine nitrite) when treated with nitrous acid, but undergo no further change; the amine may be recovered from the nitrite in the usual manner by adding alkali.

Tests for Amines and Amides. Amides are distinguished from amines by their inability to form salts with acids in water solution, and by the formation of ammonia on alkaline hydrolysis. The amines cannot be hydrolyzed with either acids or bases. Both amides and *primary* amines liberate nitrogen when treated with nitrous acid but the products are different; the former yields an acid, the latter an alcohol.

There are a number of tests to enable one to distinguish between a primary, a secondary, and a tertiary amine. The difference in behavior with nitrous acid is often used; if nitrogen is evolved a primary amine is present (it having been first proved that the compound is not an amide). Another characteristic reaction of primary amines is the peculiarly offensive odor produced when they are warmed with chloroform and potassium hydroxide. This is due to the formation of an evil smelling substance known as an **isonitrile.**

$$RNH_2 + CHCl_3 + 3KOH \longrightarrow \underset{\text{Isonitrile}}{RNC} + 3KCl + 3H_2O$$

Secondary and tertiary amines may be distinguished the one from the other by (1) the nitrous acid reaction mentioned above (p. 158); and (2) the fact that secondary (and primary) amines, but not tertiary amines, can be acylated. The acylation products are alkylated amides. The reactions involved as applied to ammonia were given on p. 111. They are illustrated by the equations below for a primary amine, methylamine, and a secondary amine, dimethylamine.

$$CH_3COCl + 2CH_3NH_2 \longrightarrow \underset{\text{Methylacetamide}}{CH_3CONHCH_3} + CH_3NH_3Cl$$

$$CH_3COCl + 2(CH_3)_2NH \longrightarrow \underset{\text{Dimethylacetamide}}{CH_3CON(CH_3)_2} + (CH_3)_2NH_2Cl$$

QUATERNARY AMMONIUM COMPOUNDS

We have seen that (p. 158) when a tertiary amine is heated with an alkyl halide the two combine, forming a substance known as a *quaternary ammonium salt.*

$$R_3N + RX \longrightarrow R_4NX$$

For example, trimethylamine, $(CH_3)_3N$, when heated with methyl iodide yields tetramethylammonium iodide, a quaternary ammonium salt.

Physical and Chemical Properties. Quaternary ammonium salts resemble the salts of amines in their physical properties, being crystalline solids soluble in water. They differ very markedly, however, in their chemical behavior. The salts of the amines when treated with a strong base like sodium hydroxide are decomposed, forming the free amine. The quaternary ammonium salts do not react with sodium hydroxide in aqueous solution. The reason for this becomes evident when one examines the product of the reaction of silver hydroxide on a quaternary ammonium iodide. In this case a reaction does take place because silver iodide is insoluble in water.

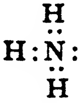
$$(CH_3)_4NI + AgOH \longrightarrow (CH_3)_4NOH + \underset{\text{Insoluble}}{AgI}$$

If the silver iodide is filtered, the resulting aqueous solution is found to be *strongly alkaline;* on evaporation at low temperature a crystalline solid is obtained which has the composition corresponding to $(CH_3)_4NOH \cdot 5H_2O$. This substance (which is very deliquescent) is a strong base comparable with potassium or sodium hydroxide. It will absorb carbon dioxide from the air, forming a carbonate. An examination of the properties of the aqueous solution of this strong base shows that it is a solution of the hydroxyl ion and the quaternary ammonium ion, $(CH_3)_4N^+$. When neutralized with an acid, the quaternary ammonium base forms the corresponding salt. In this way the iodide may be regenerated by neutralizing the solution with hydrogen iodide.

$$(CH_3)_4NOH + HI \longrightarrow (CH_3)_4NI + H_2O$$

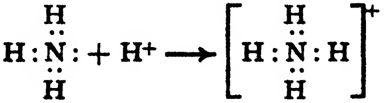
Quaternary ammonium salts containing one large alkyl group (e.g., dimethylethyloctadecylammonium bromide) are detergents (p. 132) and effective bactericides.

Electronic Formulas for Nitrogen Compounds. The nitrogen atom has five valence electrons and the maximum number that can be in the outer shell is eight. In ammonia three of these are used in pairing with the electrons of three separate hydrogen atoms. This leaves in ammonia an *unshared pair of electrons.*



$$\mathrm{H}:\overset{\textstyle \mathrm{H}}{\overset{\cdot\cdot}{\underset{\textstyle \mathrm{H}}{\underset{\cdot\cdot}{\mathrm{N}}}}}:$$

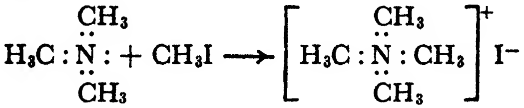
The basic properties of ammonia are due to this unshared pair which can attract and hold a hydrogen ion (often called a *proton*). The resulting product has a positive charge and is an ion because the total number of valence electrons is *one less* than the number belonging to each of the component atoms (8 as compared with 3 + 1 + 5). The essential reaction which is involved in the neutralization of ammonia by hydrochloric acid may be represented as follows.



$$\mathrm{H}:\overset{\textstyle \mathrm{H}}{\overset{\cdot\cdot}{\underset{\textstyle \mathrm{H}}{\underset{\cdot\cdot}{\mathrm{N}}}}}: + \mathrm{H}^+ \longrightarrow \left[\mathrm{H}:\overset{\textstyle \mathrm{H}}{\overset{\cdot\cdot}{\underset{\textstyle \mathrm{H}}{\underset{\cdot\cdot}{\mathrm{N}}}}}:\mathrm{H}\right]^+$$

In a similar way, in trimethylamine three of the five electrons of the nitrogen atom are involved in forming pairs with three electrons from three different methyl groups. Here again an unshared pair of electrons is left on the nitrogen atom and, like ammonia, trimethylamine is a base.

The unshared pair of electrons in trimethylamine can not only combine with a proton, but it can also combine with another methyl group. This occurs slowly when the compound is heated with methyl iodide and the resulting product is the quaternary salt, tetramethylammonium iodide. All the nitrogen valence electrons are used in forming electron pairs. In this process the iodine atom has gained one electron, making a total of eight, and thus acquired a negative charge (since it has one more electron than in the neutral atom). The electron which the iodine atom has gained has been lost from the nitrogen, thus giving a positive charge of one unit to the whole ion.



$$\begin{array}{c}\mathrm{CH_3}\\ \mathrm{H_3C:\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}:}\\ \mathrm{CH_3}\end{array} + \mathrm{CH_3I} \longrightarrow \left[\begin{array}{c}\mathrm{CH_3}\\ \mathrm{H_3C:\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}:CH_3}\\ \mathrm{CH_3}\end{array}\right]^{+} \mathrm{I^-}$$

Of the eight electrons surrounding the nitrogen atom in the positive ion, four may be regarded as being contributed by the four carbon atoms and four from the nitrogen. This latter number is one less than the number of electrons associated with this normal nitrogen atom, and it is the loss of this electron which gives the positive charge to the ion.

We are now ready to consider the distinction between the tetramethylammonium ion $(CH_3)_4N^+$ and the trimethylammonium ion $(CH_3)_3NH^+$. The latter is the substance which is formed by the addition of a proton to trimethylamine when the amine is neutralized with an acid. The gain and loss of a proton from a nitrogen atom is a process which is instantaneous and reversible. Therefore, when we treat the trimethylammonium ion with a strong base, that is, with a high concentration of hydroxyl ions, the hydroxyl ion takes away the proton, forming water.

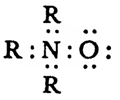
$$(CH_3)_3NH^+ + OH^- \longrightarrow (CH_3)_3N + H_2O$$

This cannot happen when the tetramethylammonium ion is treated with potassium hydroxide, because there is no proton on the nitrogen atom, and because the pair of electrons holding the methyl group to nitrogen does not break under these circumstances.

The Amine Oxides. When a tertiary amine is treated with hydrogen peroxide a very interesting substance known as an *amine oxide* is formed.

$$(CH_3)_3N + H_2O_2 \longrightarrow (CH_3)_3NO + H_2O$$

The amine oxides crystallize as hydrates, for example, $(CH_3)_3NO \cdot 2H_2O$ (mp 98°). If we regard the nitrogen atom as having a valence of five, we would be inclined to write the structure of an amine oxide as $(CH_3)_3N{=}O$. However, a variety of considerations have convinced physicists that nitrogen cannot have more than eight valence electrons in the outer shell. This excludes the formula which contains a double linkage; in place of this we must write the following formula.



$$\begin{array}{c} R \\ R:\underset{\cdot\cdot}{\ddot{N}}:\underset{\cdot\cdot}{\ddot{O}}: \\ R \end{array}$$

In this formula both the nitrogen and the oxygen atoms have octets. However, the covalent bond between nitrogen and oxygen has not been formed by the sharing of two electrons, one contributed by each of the two atoms joined by the bond. Instead both electrons have been furnished by a single atom, the nitrogen atom. To the extent that the nitrogen atom does share this pair of electrons with the oxygen atom, the nitrogen atom becomes relatively positive and the oxygen atom relatively negative. We call a covalent bond of this kind a coordinate covalence, and we represent it by a singly barbed arrow pointing toward the atom which accepts electrons, thus $(CH_3)_3N \rightharpoonup O$. The same linkage is to be found in sulfuric, nitric, and phosphoric acids and their organic derivatives. Thus the formula for phosphoric acid is $(HO)_3P \rightharpoonup O$, for sulfuric acid $(HO)_2\underset{\searrow \atop O}{S} \rightharpoonup O$, and for nitric acid $HO\underset{\searrow \atop O}{N}{=}O$.

Amines and Quaternary Bases of Biochemical Interest. Methylamine, dimethylamine, and trimethylamine are found in small quantities in nature. They are formed during bacterial decomposition of the proteins and other complex nitrogenous compounds. Trimethylamine occurs in herring brine and in the residues from the manufacture of beet sugar.

Two **diamines** (i.e., compounds with two amino groups) are formed in considerable quantities when **proteins** putrefy. They are **putrescine** (tetramethylenediamine),

$$NH_2CH_2CH_2CH_2CH_2NH_2 \text{ (bp 158°)},$$

and **cadaverine** (pentamethylenediamine),

$$NH_2CH_2(CH_2)_3CH_2NH_2 \text{ (bp 178°)}.$$

They both have a disagreeable odor. A tetramine, **spermine,** has been isolated from human sperm and its structure established as $NH_2(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$. It will be noted that it may be regarded as putrescine with the group $NH_2CH_2CH_2CH_2$ substituted on a nitrogen at each end of the chain.

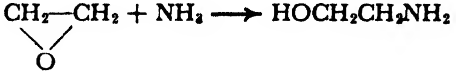
Choline. A quaternary ammonium base, β-hydroxyethyltrimethylammonium hydroxide, $HOCH_2CH_2N(CH_3)_3OH$ occurs widely distributed in nature, usually combined with an organic ester of phosphoric acid in the lecithins (p. 136). In the body choline is set free from the lecithin of the foodstuffs and its presence seems to be essential to the proper utilization of fats by the animal body.

Acetyl Choline, $CH_3COOCH_2CH_2N(CH_3)_3OH$, is a substance with a very powerful physiological action (100,000 times more powerful than choline itself). When injected into the blood stream it causes a fall of the blood pressure. It has a powerful contractile effect on muscle tissue even in minute quantities. In certain cases, the animal body appears to utilize this action of acetyl choline in transmitting a nerve impulse to a muscle. Acetyl choline is liberated at the nerve endings when the nerve is stimulated.

Cephalin (p. 137) on hydrolysis yields beta aminoethyl alcohol, known as *colamine;* $HOCH_2CH_2NH_2$. This amine bears the same relation to this phospholipid as choline does to lecithin, but it will be noted that we are here dealing with a primary amine not a quaternary ammonium salt. A more complex hydroxy amino compound is present in sphingomyelin (p. 137); it is known as *sphingosine;* the structure is

$$CH_3(CH_2)_{12}CH{=}CHCHOHCHOHCH_2NH_2$$

Those concerned with the industrial uses of organic compounds will be interested to note that β-aminoethyl alcohol, $HOCH_2CH_2NH_2$, also known as ethanolamine, is prepared in quantity by the interaction of ethylene oxide and ammonia.



Ethanolamine is used as a starting material for the manufacture of drugs and certain explosives.

QUESTIONS AND PROBLEMS

1. Define and illustrate the following terms: *unshared pair of electrons, ammonolysis, basic dissociation constant, quaternary ammonium salt.*

2. Write balanced equations for the preparation of propionamide from the acid chloride, the acid anhydride, and from ethyl propionate.

3. Write structural formulas for: isobutyramide, methyldiethylamine, ethylacetamide, dibutylamine, trimethylpropylammonium chloride.

4. Write equations for the reaction of nitrous acid and (*a*) trimethylamine, (*b*) butyramide, (*c*) propylamine, (*d*) diethylamine.

5. How would you prepare (*a*) ethylamine from its hydrochloride, and (*b*) octylamine from its hydrochloride?

6. Indicate the steps in the preparation of ethylamine from propionic acid.

7. Write electronic structures for triethylammonium bromide and tetraethylammonium bromide. Explain the difference in basicity between the two bases.

8. An unknown substance is either hexylamine, or ethylbutylamine or dimethylbutylamine. What chemical tests would you use to distinguish between these possibilities?

9. An amine has the molecular formula $C_4H_{11}N$. Write the possible structural formulas for the amine. On treatment with chloroform and alkali the amine forms an isonitrile, detectable by its odor. What struc-

tural formulas are eliminated by this reaction? What reactions would you use to distinguish between the remaining structures?

10. Write the electronic formula for triethylamine oxide.

11. What products would you expect to obtain from
(*a*) $CH_3CH_2CH_2COCl$ and CH_3NH_2, (*b*) $(CH_3)_2CHCOCl$ and $(CH_3)_2NH$?

12. The following pairs of compounds are allowed to interact: (*a*) methylethylpropylamine and methyl iodide, (*b*) dimethylpropylamine and ethyl iodide, (*c*) dimethylethylamine and propyl iodide. Are the three products identical or different? Explain. What is the significance of these results?

CHAPTER 11

Acids Containing Two or More Functional Groups

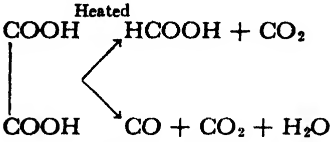
Fatty acids are of importance because of their relation to the fats. Two other classes of acids are of significance because individual members are found widely distributed in plants and animals; these are the dibasic acids and the hydroxy acids. Still another group of acids, the amino acids, are related to the proteins and with them are the subject of Chap. 14. The biochemist needs to be familiar with representatives of all these classes of substances which have one common feature, namely, that one or more carboxyl groups, COOH, are located somewhere in the molecule. All these types of acids belong to the general class of polyfunctional compounds whose study we commenced in Chap. 8.

Oxalic Acid. This is the simplest dibasic acid; it is the oxidation product of the corresponding dihydric alcohol ethylene glycol (p. 124). It occurs as the salt in many plants, in particular rhubarb and sorrel. Sodium oxalate is prepared industrially by heating sodium formate; hydrogen gas is the other product.

$$2HCOONa \xrightarrow{200^\circ} (COONa)_2 + H_2$$

Since sodium formate is prepared from sodium hydroxide and carbon monoxide (p. 104), the modern industrial synthesis of sodium oxalate is essentially *a synthesis from coal and sodium hydroxide.*

Oxalic acid crystallizes with two molecules of water, which it loses when heated to 100°. The anhydrous acid sublimes with partial decomposition above 150°. On rapid heating the decomposition is complete, the products being formic acid, carbon dioxide, carbon monoxide, and water.



$$\begin{matrix} COOH \\ | \\ COOH \end{matrix} \overset{\text{Heated}}{\begin{matrix} \nearrow HCOOH + CO_2 \\ \searrow CO + CO_2 + H_2O \end{matrix}}$$

In the presence of sulfuric acid the decomposition takes place rapidly when the mixture is slightly warmed; carbon monoxide, carbon dioxide, and water are the products.

Oxalic acid, like formic acid, is easily oxidized to carbon dioxide and water. In acid solution potassium permanganate is reduced to manganous salts by oxalates.

$$5(COOH)_2 + 2KMnO_4 + 3H_2SO_4 \longrightarrow K_2SO_4 + 2MnSO_4 + 10CO_2 + 8H_2O$$

This reaction is often used in quantitative analysis. Large quantities of oxalic acid and its salts are used in laundry work for removing iron stains and ink spots. Oxalic acid is oxidized by the ferric compounds, and they in turn are reduced to the more soluble ferrous salts.

Higher Dibasic Acids. Oxalic acid may be considered the first member of a series of acids of the general formula $(CH_2)_n(COOH)_2$. In oxalic acid, $n = 0$; the members in which $n = 1$ to 8 are listed below together with their melting points and solubility in water. In addition to the members of this series of dibasic acids, unsaturated dibasic acids are known in which one or more double linkages are present. Like the unsaturated monobasic acids found in the fats (Chap. 8) these acids can be readily transformed into the corresponding saturated acids by catalytic hydrogenation or reduction.

All these acids form *two types of salts*, neutral salts and acid salts; thus potassium oxalate, $(COOK)_2$ and acid potassium oxalate, HOOCCOOK. It will be noticed that, unlike most of the simple compounds hitherto studied, these substances are solids.

As would be expected from the predominance of the carboxyl groups, the lower members are soluble in water.

Name	*Formula*	*Melting Point*	*Solubility Grams per 100 Grams of Water at 20°*
Malonic	$HOOCCH_2COOH$	136°	74
Succinic	$HOOCCH_2CH_2COOH$	181°	6
Glutaric	$HOOCCH_2CH_2CH_2COOH$	98°	64
Adipic	$HOOC(CH_2)_4COOH$	153°	2
Pimelic	$HOOC(CH_2)_5COOH$	105°	5
Suberic	$HOOC(CH_2)_6COOH$	144°	0.2
Azelaic	$HOOC(CH_2)_7COOH$	106°	0.3
Sebacic	$HOOC(CH_2)_8COOH$	134°	0.1

Malonic Acid. The first two members of the dibasic acid series readily decompose on heating above the melting point. From malonic acid the products are acetic acid and carbon dioxide.

$$CH_2(COOH)_2 \xrightarrow{150^\circ} CH_3COOH + CO_2$$

As a rule the carboxyl group is a stable arrangement of atoms and does not undergo change even at 200°. The presence of certain kinds of atoms or groups on the carbon atom to which the carboxyl group is attached, however, alters the situation as illustrated by oxalic and malonic acids. Another relatively unstable acid is trichloroacetic acid, CCl_3COOH, which decomposes slowly at the temperature of boiling water.

$$CCl_3COOH \xrightarrow{100^\circ} CHCl_3 + CO_2$$

Succinic Acid. This is the only one of the higher dibasic acids which is a commonly occurring substance. It occurs in amber (a fossil gum) and was originally prepared by the distillation of this material. It has been isolated from a variety of plants, certain animal tissue, and the urine of animals. It plays an important part in the oxidation reactions in living cells.

Fumaric and Maleic Acids. The formula of the unsaturated acid corresponding to succinic acid is clearly

HOOCCH=CHCOOH. Two different acids, fumaric and maleic acids, corresponding to this structure are known; the explanation of this phenomenon is in terms of the relation in space of the two carboxyl groups; this will be considered in detail in the next chapter. Fumaric acid is the isomer which is commonly encountered. Together with succinic and certain other dibasic acids it is intimately involved in fundamental biochemical processes.

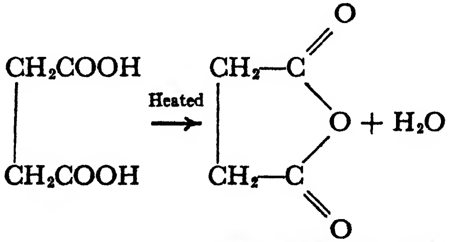
Fumaric acid is prepared industrially by the catalytic oxidation of benzene, C_6H_6 (p. 255), by air at 400° to 500°. On electrolytic reduction fumaric acid yields succinic acid, which is prepared for industrial use in this way.

$$\text{Benzene} \xrightarrow[\text{oxidation}]{\text{Catalytic}} \text{HOOCCH{=}CHCOOH} \xrightarrow[\text{reduction}]{\text{Electrolytic}} \text{HOOCCH}_2\text{CH}_2\text{COOH}$$

Fumaric acid melts at 287° and is very slightly soluble in water; maleic acid melts at 130° and is very soluble. On heating solutions of maleic acid containing a little mineral acid as a catalyst, fumaric acid is formed.

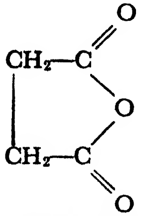
CYCLIC ANHYDRIDES

Succinic acid and glutaric acid differ from all the other members of the series $(CH_2)_n(COOH)_2$ by the fact that they readily form *cyclic anhydrides*. This may be illustrated by the preparation of succinic anhydride.

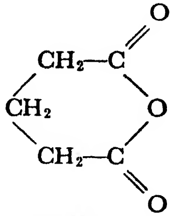


Succinic anhydride, mp 120°

The peculiar behavior of succinic and glutaric acids is connected with the fact that the ring in their anhydrides contains five and six atoms. In general we shall find that compounds containing five- and six-membered rings are usually more easily prepared than those with larger or smaller ring systems.

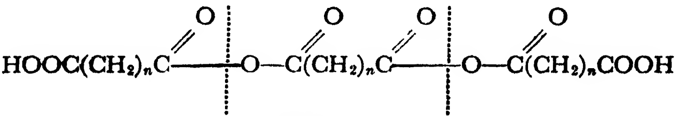


5-Membered ring; succinic anhydride



6-Membered ring; glutaric anhydride

Adipic and the higher acids do not lose water when they are heated by themselves; but, when they are heated with acetic anhydride or phosphorus oxychloride, they yield anhydrides of high molecular weight. These latter named anhydrides are the result of anhydride formation between carboxyl groups of **different** molecules and the structure of the anhydrides appears to be that of a long chain as the molecular weight is about 5000.

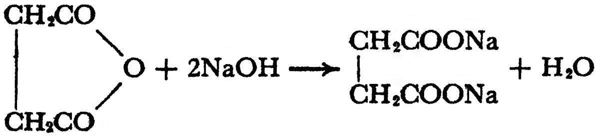


$$HOOC(CH_2)_n\overset{O}{\overset{\|}{C}}—O—\overset{O}{\overset{\|}{C}}(CH_2)_n\overset{O}{\overset{\|}{C}}—O—\overset{O}{\overset{\|}{C}}(CH_2)_nCOOH$$

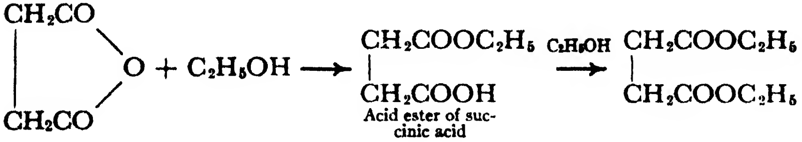
Repeating unit in polyanhydrides of higher dibasic acids

When heated in a very high vacuum the anhydrides of high molecular weight yield cyclic anhydrides which, on treatment with small amounts of acids as catalysts, revert to the anhydrides of high molecular weight. These cyclic anhydrides, both in their mode of formation and their ready conversion to high-molecular-weight anhydrides, are very different from succinic and glutaric anhydrides.

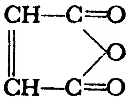
Reactions of Cyclic Anhydrides. In their reactions the cyclic anhydrides closely resemble the simple acid anhydrides. They are hydrolyzed by water with the formation of the corresponding acid; alkali is usually needed to catalyze this reaction and sometimes to complete it.



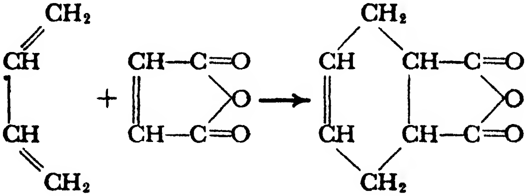
With alcohol an acid ester is formed which on further boiling with alcohol yields the neutral ester.


Acid ester of succinic acid

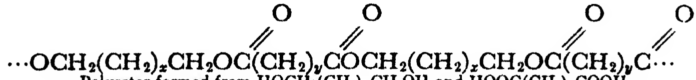
Maleic Anhydride. Fumaric acid when heated above 300° forms a cyclic anhydride; the same substance is formed much more readily by the dehydration of the isomeric maleic acid. On hydrolysis the anhydride yields maleic acid; it is therefore known as maleic anhydride. The structural formula is:



The reactions of maleic anhydride closely parallel those of succinic anhydride except for the fact that as an unsaturated compound it can enter into addition reactions. One of these addition reactions illustrates a method that has been widely used in the synthesis of ring compounds. Maleic anhydride readily combines with 1,3 dienes (p. 62); the reaction with butadiene is an example. The reaction is known as the diene synthesis.

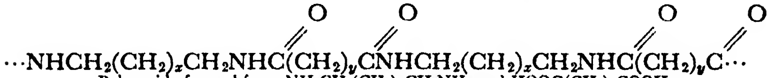


Esters and Amides of High Molecular Weight. The esterification of dibasic acids with glycols yields an interesting group of compounds analogous to the high-molecular-weight anhydrides considered on p. 171. In the esterification, unlike molecules (acid and alcohol) interact to form a long-chain molecule; depending on the catalyst, temperature, and time, substances with different average molecular weights are formed. A similar reaction takes place between diamines and dibasic acids; the products are amides of high molecular weight. These reactions have been studied with a variety of dibasic acids, glycols, and diamines. The structures of the products may be represented by the following general formulas:



$$\cdots OCH_2(CH_2)_xCH_2O\overset{O}{\overset{\|}{C}}(CH_2)_y\overset{O}{\overset{\|}{C}}OCH_2(CH_2)_xCH_2O\overset{O}{\overset{\|}{C}}(CH_2)_y\overset{O}{\overset{\|}{C}}\cdots$$

Polyester formed from $HOCH_2(CH_2)_xCH_2OH$ and $HOOC(CH_2)_yCOOH$



$$\cdots NHCH_2(CH_2)_xCH_2NH\overset{O}{\overset{\|}{C}}(CH_2)_y\overset{O}{\overset{\|}{C}}NHCH_2(CH_2)_xCH_2NH\overset{O}{\overset{\|}{C}}(CH_2)_y\overset{O}{\overset{\|}{C}}\cdots$$

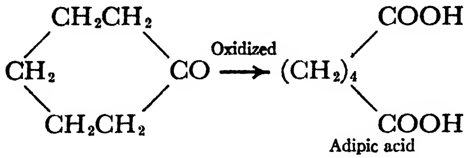
Polyamide formed from $NH_2CH_2(CH_2)_xCH_2NH_2$ and $HOOC(CH_2)_yCOOH$

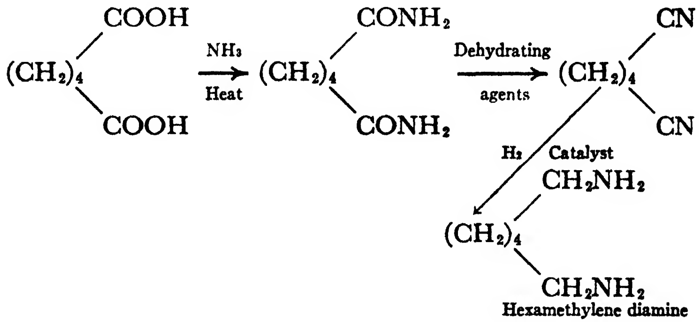
This type of reaction, where products of high molecular weight are formed by the repetitive splitting out of small molecules such as water or alcohol, is known as *condensation polymerization*. This is the second of two general methods of preparing polymers of high molecular weight; the other is *addition polymerization* as illustrated by ethylene (p. 57) and the synthetic rubbers.

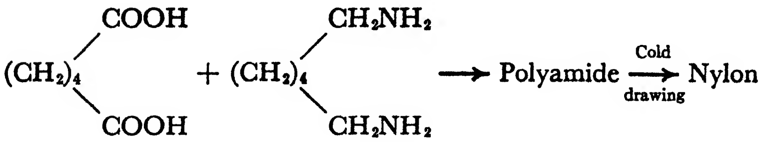
The interaction of polyfunctional molecules proceeds in a fashion similar to the interaction of monofunctional molecules. The only peculiarities arise when the two groups in the same molecule can react with each other because of their nearness in space, as in the formation of the cyclic anhydrides. If there are just two functional groups in each molecule, then long-chain compounds of high molecular weight are the normal products. These are related to natural and synthetic rubber in that they are of high molecular weight and the molecules are long chains. If more than two functional groups are present then, in addition to the linkages joining the molecules in a chain, *cross links* may be formed, as in vulcanized rubber. Thus a dibasic acid and glycerol (a *trihydroxy* compound) give esters of high molecular weight in which there are cross links joining the chains together; these cross links are formed by esterification of the secondary alcohol groups in two different chains by a molecule of the dibasic acid. A number of important resins extensively used in industry are of this type; they are considered later together with some other artificial resins (p. 314).

Nylon. A synthetic fiber, Nylon, is prepared industrially by the interaction of adipic acid and hexamethylene diamine. The resulting polyamide of high molecular weight (10,000 to 25,000) melts at about 260° and the molten material can be drawn into fine threads. These threads can be stretched to four times their length at room temperature, and, unlike elastic material, they do not contract when the tension is released. This process of "cold drawing" changes an essentially amorphous material into a fibrous one; the fiber has high tensile strength and luster and resembles silk in many ways.

The adipic acid required for this large industry is obtained by the oxidation of a cyclic ketone, cyclohexanone, which in turn is prepared from phenol (p. 271). The diamine is prepared from the acid by way of the amide and the nitrile.



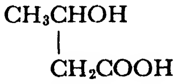
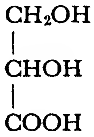
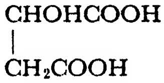
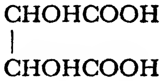
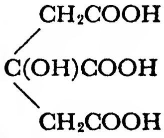




HYDROXY ACIDS

The important hydroxy acids which occur in nature are listed in the table on the opposite page.

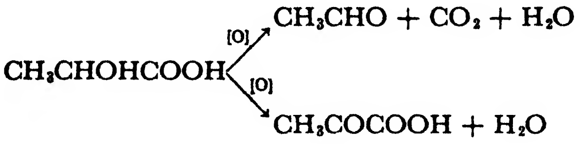
Hydroxy acids embody the properties of both an acid and an alcohol. As acids they form salts with bases, and esters with alcohols; for example, $CH_3CHOHCOONa$ is sodium lactate, and $CH_3CHOHCOOC_2H_5$ is ethyl lactate. As alcohols they form esters with other acids; thus the acetate of lactic acid is

Name	*Formula*	*Occurrence*
Glycolic acid	$CH_2OHCOOH$	Chief acid constituent of sugar cane; present in beet juice; unripe grapes
Lactic acid	$CH_3CHOHCOOH$	Sour milk, in muscle after activity, beet molasses, in blood and urine
β-Hydroxybutyric acid	 $\begin{array}{l} CH_3CHOH \\ \quad\;\; \vert \\ \quad\;\; CH_2COOH \end{array}$	Urine from those suffering with diabetes
Glyceric acid	 $\begin{array}{l} CH_2OH \\ \vert \\ CHOH \\ \vert \\ COOH \end{array}$	Intermediary in oxidation of glucose in living cells
Malic acid	 $\begin{array}{l} CHOHCOOH \\ \vert \\ CH_2COOH \end{array}$	Unripe fruits, gooseberries, rhubarb stalks, unripe grapes, cherries, tomatoes
Tartaric acid	 $\begin{array}{l} CHOHCOOH \\ \vert \\ CHOHCOOH \end{array}$	Argol (in wine casks) (monopotassium salt)
Citric acid		All citrus fruits

produced when lactic acid and acetic anhydride react. If the hydroxyl group is attached to a carbon atom carrying a hydrogen atom the hydroxy acid can be oxidized to aldehydic or ketonic acids just as alcohols are oxidized to aldehydes or ketones. These changes are of great significance to the biochemist (Chap. 15), particularly the change from the lactate ion to the pyruvate ion and vice versa.

$$\underset{\text{Lactate ion}}{CH_3CHOHCOO^-} \underset{\text{Reducing enzyme}}{\overset{\text{Oxidizing enzyme}}{\rightleftharpoons}} \underset{\text{Pyruvate ion}}{CH_3COCOO^-}$$

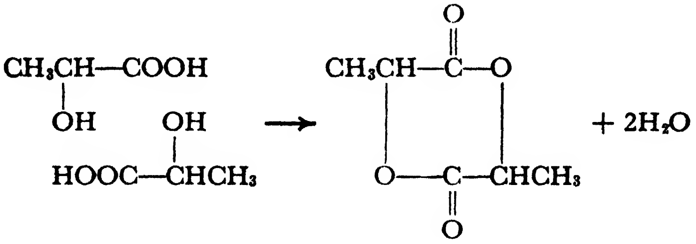
With the oxidizing agents used in the laboratory, the oxidation of hydroxy acids having the hydroxyl group on the carbon atom next to the carboxyl group may furnish either a ketonic acid or an aldehyde; the formation of the aldehyde involves the elimination of one carbon atom as carbon dioxide.



$$CH_3CHOHCOOH \xrightarrow{[O]} CH_3CHO + CO_2 + H_2O$$

$$CH_3CHOHCOOH \xrightarrow{[O]} CH_3COCOOH + H_2O$$

Alpha, Beta, and Gamma Hydroxy Acids. The hydroxy acids are often named with reference to the fatty acid or dibasic acid from which they may be considered to be derived; the position of the hydroxyl group is indicated by a Greek letter. Thus lactic acid is α-hydroxypropionic acid; glyceric acid, α,β-dihydroxypropionic acid. Depending on the position of the hydroxyl group, the acids lose water in different ways. Alpha hydroxy acids are not readily dehydrated. When they are dehydrated the product is a cyclic double ester.



Beta hydroxy acids, on the other hand, rapidly lose water when heated with dehydrating agents furnishing unsaturated acids; the reaction is parallel to the formation of ethylene from ethyl alcohol (p. 51).

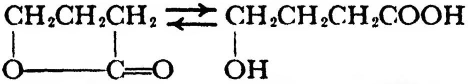
$$CH_3CHOHCH_2COOH \xrightarrow[\text{Acid catalyst}]{\text{Heated}} CH_3CH{=}CHCOOH$$

Alpha hydroxy acids may be prepared from the corresponding aldehydes or ketones by the addition of hydrocyanic acid (p. 90) and hydrolysis of the resulting cyanohydrin, which is the nitrile of the hydroxy acid.

$$\mathrm{RCHO + HCN \longrightarrow \underset{Cyanohydrin}{RCHOHCN} \xrightarrow{\text{Hydrolysis}} RCHOHCOOH}$$

$$\mathrm{R_2CO + HCN \longrightarrow R_2COHCN \xrightarrow{\text{Hydrolysis}} R_2COHCOOH}$$

Lactones. Gamma hydroxy acids lose water in a very interesting way, yielding cyclic esters formed from only *one* molecule of the acid. These compounds are called *lactones.* They are inner esters, and on hydrolysis yield the hydroxy acid. In the absence of base the reaction is a balanced one; in the presence of alkali the hydrolysis is complete by virtue of the neutralization of the acid.



$$\underset{\substack{\text{Lactone,}\\ \text{butyrolactone}}}{\begin{array}{l}\mathrm{CH_2CH_2CH_2}\\ \mathrm{|\qquad\quad\ |}\\ \mathrm{O{-\!\!-\!\!-}C{=}O}\end{array}} \rightleftharpoons \underset{\gamma\text{-Hydroxybutyric acid}}{\begin{array}{l}\mathrm{CH_2CH_2CH_2COOH}\\ \mathrm{|}\\ \mathrm{OH}\end{array}}$$

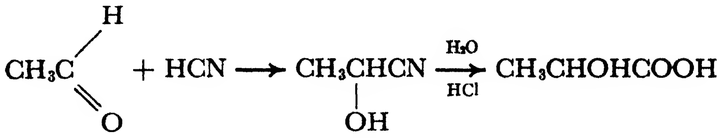
The point of equilibrium between a lactone and the hydroxy acid is often very favorable to the former, and some gamma hydroxy acids cannot be prepared. They are known only as salts or esters.

Lactic Acid. Lactic acid, $CH_3CHOHCOOH$, is formed when milk sours, according to the following reaction:

$$\underset{\text{Milk sugar}}{\mathrm{C_{12}H_{22}O_{11}}} + \mathrm{H_2O} \xrightarrow[\text{lactase}]{\text{Enzyme}} \mathrm{4CH_3CHOHCOOH}$$

For industrial purposes lactic acid is either isolated from sour milk or made by a bacterial fermentation of glucose. It is an oily liquid which is difficult to obtain pure. It is used in dyeing, and its ethyl ester is a commercial solvent.

Three isomeric lactic acids are known. One, dextro lactic acid, can be obtained from muscle; another, laevo lactic acid, can be obtained by the fermentation of lactose and certain other sugars; while the third, inactive lactic acid, results from the following synthesis.



All three lactic acids have been shown to have the same structure, that of α-hydroxypropionic acid. The explanation for their isomerism we shall discuss in the next chapter.

Lactic acid is a very important compound to the biochemist. The energy necessary for muscular action appears to be normally supplied by the decomposition of glycogen (p. 215) to lactic acid. Glycogen is a carbohydrate similar to starch; it is stored in the liver and carried by the blood stream to the muscle. A complicated series of reactions are involved in the change of glycogen to lactic acid (p. 250). Following the contraction of the muscle, the lactic acid disappears from the muscle by diffusion into the blood stream and by oxidation.

Citric Acid. One of the acids most widely distributed in nature is citric acid. It occurs particularly in citrus fruits as the name indicates. It crystallizes with a molecule of water which is lost on heating. The hydrated acid melts at about 100°; the anhydrous acid at 153°. The acid is very soluble in water. It forms a variety of salts, some of which are used in pharmaceutical preparations. The acid itself is widely used in the preparation of beverages. It is prepared either from citrus fruits which are not marketable or by the fermentation of glucose by a certain mold.

Tartaric Acid. Tartaric acid, $(CHOHCOOH)_2$, is obtained from the crude potassium acid tartrate, known as *argol*, which crystallizes in wine casks. This salt is probably present in the original wine and separates slowly. When purified by crystallization from water, it is known as *cream of tartar* and is widely used in the manufacture of baking powder.

The tartaric acid of commerce is a white, crystalline solid which melts at 168° to 170°; it is soluble in water and cannot be readily extracted from the solution. In its preparation from argol, the insoluble calcium tartrate is first formed by precipitation and is then decomposed with sulfuric acid. The free acid and its salts are used in dyeing, in medicine, and in the laboratory. Fehling's solution (p. 84) is prepared by adding sodium hydroxide and a tartrate to dilute copper sulfate solution. The deep blue solution contains a soluble complex cupric tartrate.

Isomerism of Lactic Acid and the Tartaric Acids. Tartaric acid has been shown by many reactions to be **dihydroxysuccinic acid.** It must be represented by the formula, HOOCCHOHCHOHCOOH. Yet there are three other compounds which also correspond in their reactions and transformations to the same structure. They are **laevo tartaric acid** (mp 168° to 170°); **racemic tartaric acid** (mp 205° to 206°); and **meso tartaric acid** (mp 140°). [Ordinary tartaric acid (mp 168° to 170°) is called *dextro tartaric acid.*] Similarly, lactic acid has been shown to be α-hydroxypropionic acid. But there are three lactic acids, all of which have this same structure.

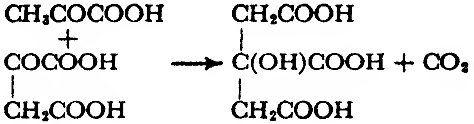
A number of such exceptional cases came to light during the rapid growth of organic chemistry in the last half of the nineteenth century. They remained a mystery until van't Hoff and Le Bel in 1874 independently arrived at a solution of the problem. These scientists extended the structural theory to three dimensions, and in this way provided an explanation of these cases of isomerism which were not accounted for by the Kekulé theory. This step in the development of the structural theory is described in the next chapter.

KETO ACIDS

In connection with our study of lactic acid (p. 175) we noted that this substance is readily oxidized in animal and plant cells to the corresponding keto acid, pyruvic acid, which under certain conditions is readily reduced to lactic acid; specific biochemical catalysts (enzymes) are responsible for these changes. Similar transformations occur in living cells with other hydroxy acids. The following table lists the hydroxy acids and the corresponding keto acids which are of special interest to the student of biology and medicine.

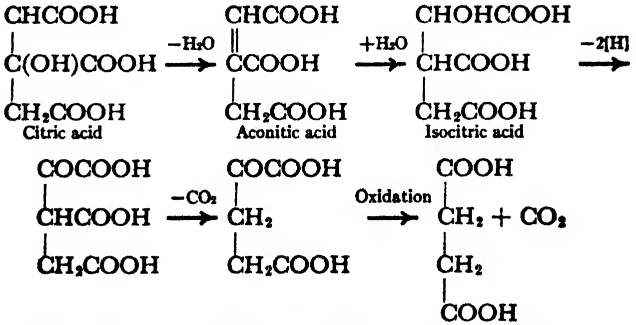
	Hydroxy Acid		*Corresponding Keto Acid*
Lactic	$CH_3CHOHCOOH$	Pyruvic	$CH_3COCOOH$
Malic	$\begin{array}{l}CHOHCOOH\\ \vert\\ CH_2COOH\end{array}$	Oxaloacetic	$\begin{array}{l}COCOOH\\ \vert\\ CH_2COOH\end{array}$
Isocitric	$\begin{array}{l}CHOHCOOH\\ \vert\\ CHCOOH\\ \vert\\ CH_2COOH\end{array}$	Oxalosuccinic	$\begin{array}{l}COCOOH\\ \vert\\ CHCOOH\\ \vert\\ CH_2COOH\end{array}$
β-Hydroxybutyric	$CH_3CHOHCH_2COOH$	Acetoacetic	CH_3COCH_2COOH

Isocitric acid and its oxidation product oxalosuccinic acid are of special interest as intermediates in the cycle by which pyruvic acid (from the metabolism of glucose, Chap. 15) is oxidized to carbon dioxide and water in plant and animal cells. This process, which takes place in a number of steps each brought about by a naturally occurring catalyst (an enzyme), probably involves the condensation of pyruvic acid and oxaloacetic acid to form citric acid and carbon dioxide.



$$\begin{array}{l}CH_3COCOOH\\ \quad +\\ COCOOH\\ \vert\\ CH_2COOH\end{array} \longrightarrow \begin{array}{l}CH_2COOH\\ \vert\\ C(OH)COOH\\ \vert\\ CH_2COOH\end{array} + CO_2$$

The citric acid is then converted to isocitric acid and, eventually, to succinic acid as follows:



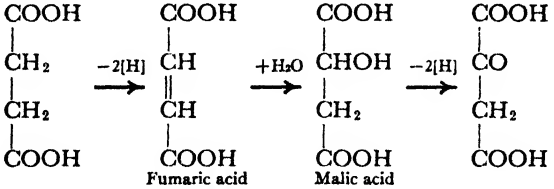
$$\begin{array}{l}CHCOOH\\ \vert\\ C(OH)COOH\\ \vert\\ CH_2COOH\end{array} \xrightarrow{-H_2O} \begin{array}{l}CHCOOH\\ \Vert\\ CCOOH\\ \vert\\ CH_2COOH\end{array} \xrightarrow{+H_2O} \begin{array}{l}CHOHCOOH\\ \vert\\ CHCOOH\\ \vert\\ CH_2COOH\end{array} \xrightarrow{-2[H]}$$

Citric acid Aconitic acid Isocitric acid

$$\begin{array}{l}COCOOH\\ \vert\\ CHCOOH\\ \vert\\ CH_2COOH\end{array} \xrightarrow{-CO_2} \begin{array}{l}COCOOH\\ \vert\\ CH_2\\ \vert\\ CH_2COOH\end{array} \xrightarrow{\text{Oxidation}} \begin{array}{l}COOH\\ \vert\\ CH_2\\ \vert\\ CH_2\\ \vert\\ COOH\end{array} + CO_2$$

Oxalosuccinic acid α-Ketoglutaric acid Succinic acid

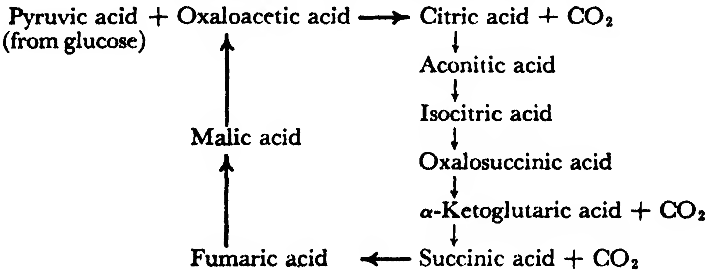
It will be noted that in this series of transformations three molecules of carbon dioxide have been evolved corresponding to the complete oxidation of the three carbon atoms of pyruvic acid. The succinic acid produced is now converted to oxaloacetic acid by dehydrogenation to fumaric acid and hydration of the latter followed by oxidation.



$$\begin{array}{c} COOH \\ | \\ CH_2 \\ | \\ CH_2 \\ | \\ COOH \end{array} \xrightarrow{-2[H]} \begin{array}{c} COOH \\ | \\ CH \\ \| \\ CH \\ | \\ COOH \end{array} \xrightarrow{+H_2O} \begin{array}{c} COOH \\ | \\ CHOH \\ | \\ CH_2 \\ | \\ COOH \end{array} \xrightarrow{-2[H]} \begin{array}{c} COOH \\ | \\ CO \\ | \\ CH_2 \\ | \\ COOH \end{array}$$

Fumaric acid Malic acid

The oxaloacetic acid is then ready to react with another molecule of pyruvic acid. Thus there is a cycle which may be summarized in the following way.



Acetoacetic Acid. In the common form of acidosis seen in diabetics, the body produces an abnormal amount of β-hydroxybutyric acid and acetoacetic acid. These are present in the body fluids and excreted in quantity in the urine; the acetoacetic acid slowly loses carbon dioxide forming acetone which is,

$$CH_3COCH_2COOH \longrightarrow CH_3COCH_3 + CO_2$$

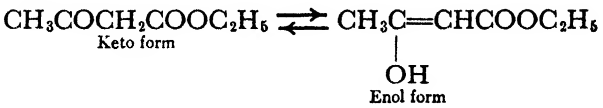
therefore, likewise present. All these substances are normal products of the oxidation of foodstuffs in the body, but are normally present in small amounts because they are further decomposed under usual circumstances; only under pathological conditions do they accumulate in the body and the urine.

It will be noted that acetoacetic acid is a beta ketonic acid. Substances of this structure readily lose carbon dioxide, sometimes even on standing in solution at room temperature.

Acetoacetic Ester. The ester of acetoacetic acid is prepared in the laboratory and industrially for use in certain types of synthetic reactions. It has the rather unusual property of forming a sodium derivative when treated in alcoholic or ethereal solution with sodium ethoxide or metallic sodium. This fact at first led chemists to write the structural formula as

$$CH_3C(OH){=}CHCOOC_2H_5$$

On the other hand the ester reacts with typical reagents for carbonyl groups as though the formula were $CH_3COCH_2COOC_2H_5$. The controversy over the structure of this ester lasted many years. We now know that the pure liquid is a mixture of two isomeric forms corresponding to the two structures just written; one substance is called the **keto form,** the other the **enol form.** In the liquid ester and in solutions of the ester the two forms are in a dynamic equilibrium.

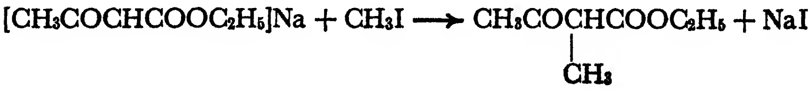


$$\underset{\text{Keto form}}{CH_3COCH_2COOC_2H_5} \rightleftharpoons \underset{\text{Enol form}}{CH_3\underset{\substack{|\\ OH}}{C}{=}CHCOOC_2H_5}$$

The change of one form into the other is spoken of as a **tautomeric change;** the shift of a hydrogen atom is involved. There are many instances of this type of change in complex organic compounds. Sometimes the two isomers can be isolated as with acetoacetic ester, sometimes the shift is too rapid to permit a separation of the two forms. Vinyl alcohol (p. 143) is unknown; all attempts to prepare it yield acetaldehyde.

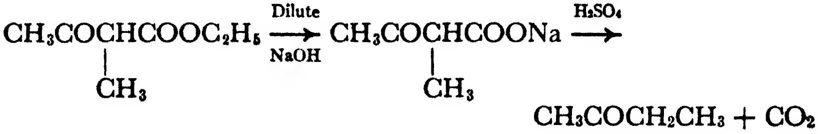
$$\underset{\text{Unknown}}{CH_2{=}CHOH} \xrightarrow{\text{Tautomeric shift}} CH_3CHO$$

Acetoacetic Ester Synthesis of Ketones. The sodium derivative of acetoacetic ester reacts with alkyl halides as though the sodium atom were attached to the central carbon atom. When



$$[CH_3COCHCOOC_2H_5]Na + CH_3I \longrightarrow CH_3CO\underset{\substack{|\\ CH_3}}{C}HCOOC_2H_5 + NaI$$

the product is saponified with *dilute* sodium hydroxide and the sodium salt acidified the resulting acid, being a β-ketonic acid, readily loses carbon dioxide.



$$\underset{\displaystyle CH_3}{CH_3COCHCOOC_2H_5} \xrightarrow[NaOH]{Dilute} \underset{\displaystyle CH_3}{CH_3COCHCOONa} \xrightarrow{H_2SO_4} CH_3COCH_2CH_3 + CO_2$$

QUESTIONS AND PROBLEMS

1. Write balanced equations to show the behavior of malonic, succinic, maleic, and acetoacetic acids on heating.

2. Outline the steps in the manufacture of Nylon from cyclohexanone.

3. Write names and structural formulas for the dibasic acids from oxalic through adipic acid.

4. Write equations for the dehydration of $CH_3CH_2CHOHCOOH$, $CH_3CHOHCH_2COOH$, and $CH_2OHCH_2CH_2COOH$.

5. Using acetoacetic ester as an example, define and illustrate tautomerism.

6. Write equations for the following reactions: (*a*) maleic anhydride and 1,3-butadiene, (*b*) sodium formate heated to 200°, (*c*) succinic anhydride and ethyl alcohol, (*d*) lactic acid and an oxidizing agent.

7. Compare addition polymerization and condensation polymerization, defining and giving examples of both types and indicating the conditions used for bringing about the polymerizations.

8. What are the steps in the enzymatic conversion of citric acid to succinic acid? What is the importance of this process?

9. Write equations for the synthesis of methyl propyl ketone from acetoacetic ester, sodium ethoxide, and ethyl iodide.

10. Write structural formulas for α-hydroxybutyric acid, malic acid, β-hydroxypropionic acid, ethyl lactate, and citric acid.

CHAPTER 12

Stereoisomerism

In connection with the study of several compounds in the preceding chapter we met a new type of isomerism: two or more substances were found to have the same structural formula. The differences between isomers of this kind result from the spatial arrangement of the atoms, and isomers such as these are called **stereoisomers.**

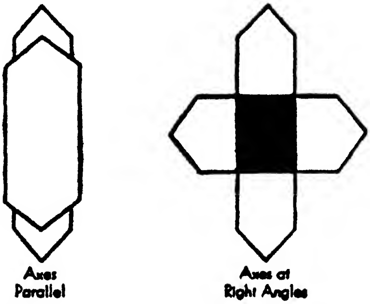


Fig. 9. Two tourmaline crystals crossed at right angles are opaque.

Before presenting the theory which enables us to predict the existence and number of stereoisomers we must discuss briefly the phenomenon known as *optical activity.* We have seen that two of the three isomeric alpha hydroxypropionic acids are called *dextro lactic acid* and *laevo lactic acid* respectively. The words *dextro* and *laevo* refer to the fact that solutions of these substances have the property of rotating the plane of polarized light—the one to the right (dextro), the other to the left (laevo). They therefore are said to be *optically active.*

Polarized Light. Light which has passed through a crystal of tourmaline or a Nicol prism (a specially constructed prism of Iceland spar) is said to be *polarized.* Such light will pass through a second tourmaline crystal or Nicol prism only if it is held parallel to the first. This can be demonstrated by placing two clear tourmaline crystals one against the other and interposing them between a light and the eye. They will be transparent if their crystal axes are parallel; when one crystal is turned so that its axis is at right angles to that of the other, the intersection of the two crystals appears opaque (Fig. 9). If one of these crystals is now firmly set in an apparatus such as that indicated in Fig. 10 and the other placed at some distance from it on a movable axis, we have what is known as a *polariscope*. When nothing is interposed between the two crystals, the maximum amount of light can come through the apparatus and strike the eye of the observer only when the second crystal is exactly parallel to the first. If we now insert an optically active substance between the two crystals, we find that we must turn the movable crystal to the right or left in order to get the greatest brightness. The direction and extent of this rotation depend on the nature of the substance and

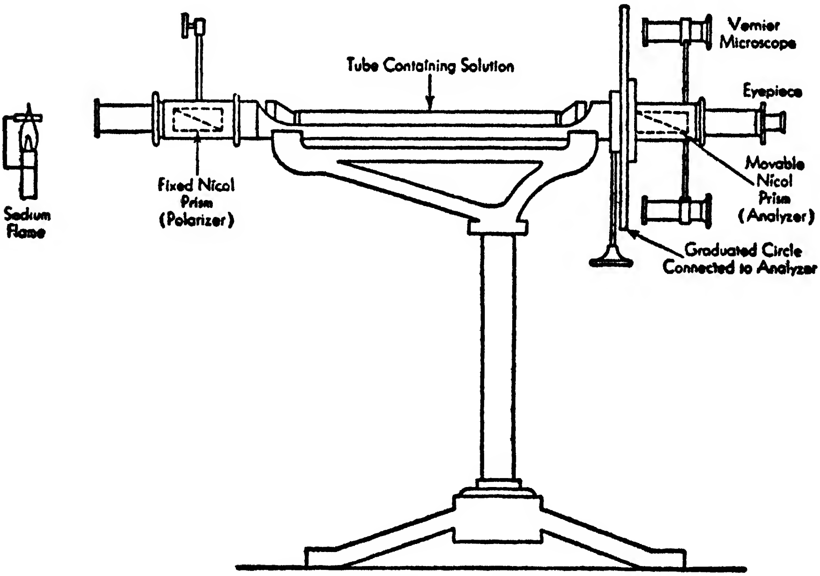


Fig. 10. Polariscope used in determining the optical activity of organic compounds. The solution of the compound is placed in the long glass tube which has parallel glass ends.

the amount of it through which the light passes. A number of organic liquids and solutions of solid compounds are optically active.

The physical explanation given for the phenomenon of optical activity is as follows. The light after passing through the first crystal is supposed to be vibrating in only one plane; therefore, the second crystal must be set in exactly the same plane in order to allow all the light to pass through it. Optically active substances have the power to rotate this plane of polarized light to the left or to the right.

The optical activity of many solids is caused by the nature of the arrangement of the molecules in the crystal; however, this phenomenon does not concern the organic chemist. *The optical activity of organic compounds is a property of the molecule* itself since it is manifested in the liquid state, in solution, and as a gas.

Pasteur's Separation of a Racemic Tartrate. The first important advance in the understanding of optical activity was made by Pasteur in 1848. At that time racemic tartaric acid, which is optically inactive, and the common dextro tartaric acid were both known. Pasteur was studying the crystal angles of the salts of the racemic acid. He noticed on examining certain very large crystals of the sodium ammonium salt that there seemed to be two different types of crystals which differed only slightly in the position of the crystal faces. These faces were arranged either in a left-handed fashion or in a right-handed fashion with regard to the crystal axis. Thus, one type of crystal could be considered the mirror image of the other, just as one's left hand is the mirror image of the right.

Pasteur laboriously separated these left-handed and right-handed crystals into two piles, dissolved them separately in water, and examined the two solutions in the polariscope. To his delight he found that one solution turned the plane of polarized light to the right, the other an equal amount to the left, this in spite of the fact that the original salt had been entirely inactive! This classic experiment proved that in one instance, at least, the *inactive compound could be separated into two active forms.* It was evidently only a mixture of the well-known dextro acid and a new laevo form. The isomers were found to differ only in their effect on polarized light.

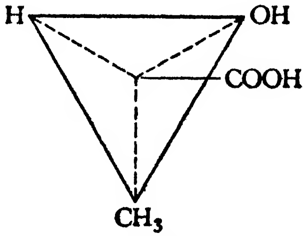
Going back from the sodium ammonium salts with which Pasteur worked to the acids from which the salts are derived, we can say that Pasteur's experiments showed that racemic tartaric acid is composed of dextro tartaric acid and laevo tartaric acid. And in fact by mixing equal quantities of laevo and dextro tartaric acids racemic tartaric acid can be obtained. These experiments therefore accounted for one of the isomeric tartaric acids. It was not possible to go further with this problem in Pasteur's time. The next step had to await the development of the structural theory, and it was not taken until some twenty-five years later by van't Hoff and Le Bel.

The Tetrahedral Carbon Atom. Le Bel and van't Hoff assumed that the valences of the carbon atoms were directed toward the corners of a more or less regular tetrahedron. To demonstrate this, they constructed solid models. These were not supposed to represent an actual picture of a carbon atom; they were only intended to show the spatial arrangement of the atoms in a molecule. The peculiar property of a tetrahedron is that *when four different things are attached to its corners, two arrangements are possible.* These differ as the *right hand differs from the left;* one arrangement is the mirror image of the other. If *two or more of the things attached to the four corners are the same, only one arrangement is possible.* This is a fact of geometry and in itself has nothing to do with chemistry; van't Hoff and Le Bel saw in it an explanation of optical activity and the isomerism which had been noted in the lactic and tartaric acids.

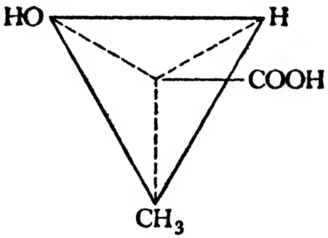
Optically Active Isomers Are Stereoisomers. If a tetrahedron with four different things attached can exist in two arrangements, so a carbon atom with four different atoms or groups arranged about it may exist in two forms. These two forms would be expected to differ in some right-handed or left-handed manner. This is exactly the case with optical isomers; the dextro and laevo forms are identical in all properties except their action on the plane of polarized light. According to this theory, therefore, optical isomers are stereoisomers and *differ only in the spatial arrangement of the atoms in the molecule.*

The fundamental postulate of the theory is that this isomerism is to be found only when the molecule can exist in two forms which are mirror images of each other. Such a molecule is said to be *asymmetric*. The most common cause of asymmetry in a molecule is the presence of an *asymmetric atom*, *an atom to which four different atoms or groups are attached.* It is possible, however, to secure asymmetric molecules which do not contain any asymmetric atoms; and, while we shall not consider such molecules in this text, it is important to realize that *optical activity is a property of an asymmetric molecule* regardless of the cause of the asymmetry in that molecule.

Compounds with One Asymmetric Carbon Atom. The Stereoisomers of Lactic Acid. The carbon atom underlined in the formula is asymmetric: $CH_3\underline{C}HOHCOOH$. Models of the two forms of lactic acid are shown below.



LAEVO LACTIC ACID



DEXTRO LACTIC ACID

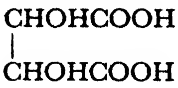
There is no way of telling which of the above models corresponds to the dextro acid and which to the laevo. It can only be said that if one is arbitrarily selected to correspond to the laevo form, the other must be the dextro. The racemic acid, of course, is a mixture of an equal number of molecules of the dextro and laevo forms.

If possible, the student should handle actual solid models and convince himself of the fundamental geometrical fact which is the basis of stereoisomerism. The theory predicts a dextro lactic acid, a laevo lactic acid, and a racemic mixture (inactive lactic acid). The experimental facts are in accord with this prediction. The acid which is prepared in the laboratory by synthetic methods is inactive; that formed by the fermentation of glucose may be dextro, laevo, or inactive according to the enzyme employed.

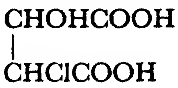
Propionic acid, CH_3CH_2COOH, contains no asymmetric carbon atom, and two different spatial arrangements are not possible. No stereoisomers are predicted, and none has ever been found. The theory of stereoisomerism has been drastically tested since it was first suggested. In every test, complete agreement has been found between the experimental facts and the predictions based on the theory.

Racemic Mixtures and Racemic Compounds. Two stereoisomers such as laevo and dextro lactic acid are sometimes spoken of as *enantiomorphs* or *enantiomers. They are identical in all physical and chemical properties except their action on polarized light.* The two isomers have the same rotating power, but turn the plane in opposite directions, one to the right and the other to the left. A mixture of two enantiomorphs may be merely a mechanical mixture of the two isomers, or it may be a loose molecular compound of the two. The first we speak of as a *racemic mixture,* the second, as a *racemic compound.* The racemic compound is met with when we are dealing with solids; it has physical properties different from those of the component isomers. In solution, it is usually largely dissociated and behaves much like a solution of a racemic mixture.

Compounds with Several Asymmetric Atoms. When a molecule contains more than one asymmetric carbon atom, these asymmetric atoms may be similar or dissimilar. Similar asymmetric carbon atoms are those in which the four unlike atoms or groups attached to one asymmetric carbon atom are identical with the four attached to the other asymmetric carbon atoms. The tartaric acids furnish examples. Dissimilar asymmetric carbon atoms are those in which the four unlike atoms or groups attached to one asymmetric carbon atom are not all identical with the four attached to the other asymmetric carbon atoms. The chlorohydroxysuccinic acids furnish examples.



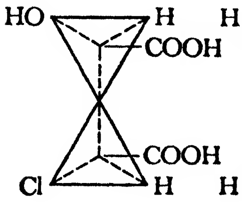
$$\begin{array}{l}\mathrm{CHOHCOOH}\\ |\\ \mathrm{CHOHCOOH}\end{array}$$



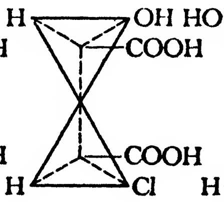
$$\begin{array}{l}\mathrm{CHOHCOOH}\\ |\\ \mathrm{CHClCOOH}\end{array}$$

Dissimilar asymmetric carbon atoms are by far the more common and the more important.

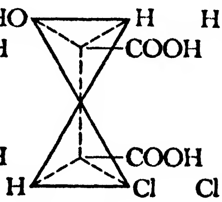
Dissimilar Asymmetric Atoms. The chlorohydroxysuccinic acids contain two dissimilar asymmetric carbon atoms. The configurations of all the stereoisomeric chlorohydroxysuccinic acids are shown in the diagrams which follow.



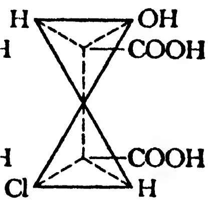
1



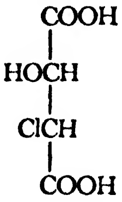
2



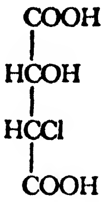
3



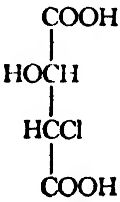
4



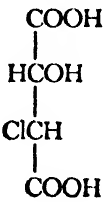
$$\begin{array}{c}\mathrm{COOH}\\ |\\ \mathrm{HOCH}\\ |\\ \mathrm{ClCH}\\ |\\ \mathrm{COOH}\end{array}$$



$$\begin{array}{c}\mathrm{COOH}\\ |\\ \mathrm{HCOH}\\ |\\ \mathrm{HCCl}\\ |\\ \mathrm{COOH}\end{array}$$



$$\begin{array}{c}\mathrm{COOH}\\ |\\ \mathrm{HOCH}\\ |\\ \mathrm{HCCl}\\ |\\ \mathrm{COOH}\end{array}$$



$$\begin{array}{c}\mathrm{COOH}\\ |\\ \mathrm{HCOH}\\ |\\ \mathrm{ClCH}\\ |\\ \mathrm{COOH}\end{array}$$

It is possible in the following way to derive these four configurations and to show that they are the only configurations. Using either the models or their planar projections described in the next section, set up any one configuration and its mirror image; say numbers 1 and 2 above. Then reverse, by interchanging two substituents, the configuration of *either one* of the asymmetric carbon atoms. Set up the mirror image of this arrangement. (Reversing the configuration of the lower asymmetric carbon atom in 1 this way gives us 3.) Now complete the possibilities by reversing the configuration of the *second* asymmetric carbon atom. The configurations thus obtained will be found to be identical with two of these already derived.

We have four possible stereoisomers all of which are optically active. These four stereoisomers are the components of two racemic mixtures (or racemic compounds) as indicated above. These two different racemic mixtures differ in physical properties. The two known chlorohydroxysuccinic acids are these two racemic mixtures; they melt at 145° and 154°. Both are inactive and both are separable. Stereoisomers which are not enantiomorphs are called *diastereoisomers*, often shortened to *diamers*. Thus, 1 and 3, or 2 and 4 in the illustration above are diastereoisomers. *Not being mirror images they differ in rotation and also in their physical properties.*

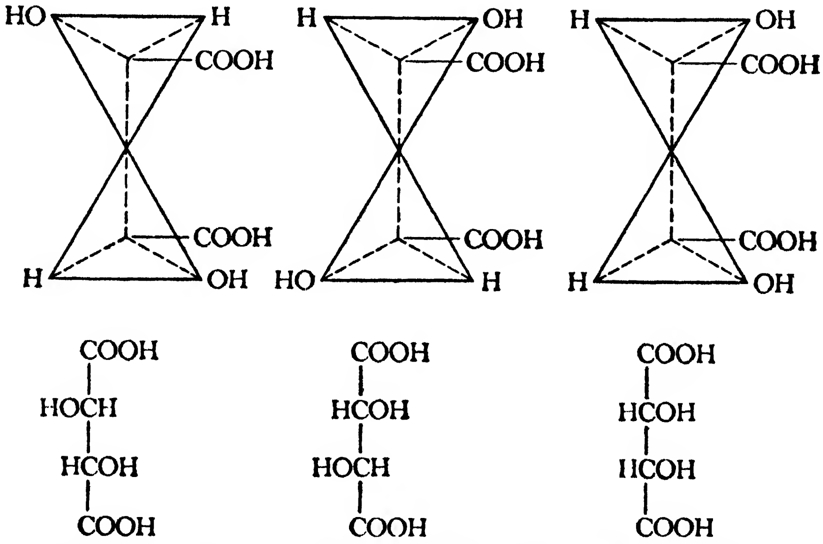
By studying models it can be shown that in a compound with n dissimilar asymmetric carbon atoms there are 2^n optically active isomers and $2^n/2$ racemic mixtures.

Plane Representation of Stereochemical Formulas. Drawings of three-dimensional models such as those shown above or the models themselves are essential for the understanding of the subject of stereoisomerism. After the principles have been mastered, however, such methods of representing stereoisomers are cumbersome. A compact and convenient method of representing the models consists in projecting them onto a plane. Projections of the dibasic acids by agreement always have the carboxyl groups at the top and the bottom of the plane diagram. This corresponds to a model in which the carboxyl groups are below the plane occupied by the other substituents. Plane diagrams of the chlorohydroxysuccinic acids are shown on p. 190, just below the drawings of the three-dimensional models.

Similar Asymmetric Atoms. The tartaric acids contain two similar asymmetric atoms. Since both asymmetric atoms have the same groups about them, they will affect the plane of polarized light to the same extent, but each may be either dextro rotatory or laevo rotatory.

We are thus led to predict the following possible combinations: (1) both atoms dextrorotatory; (2) both atoms laevorotatory; (3) one atom dextro, the other laevo. In the first two, the effect of each atom reinforces that of the other. In the third, they cancel each other, and, since the two atoms are *exactly opposite* in their effect on polarized light, the compound will be *optically* *inactive.* Such a compound is said to be *inactive by internal compensation.* It is not a racemic compound and obviously cannot be separated into active forms; every molecule is exactly like every other molecule and each is inactive. **Mesotartaric acid** is the isomer which is inactive by internal compensation.

The following diagrams show the spatial arrangement of the groups in dextro tartaric acid, laevo tartaric acid, and meso tartaric acid.



LAEVO TARTARIC ACID DEXTRO TARTARIC ACID MESO TARTARIC ACID

RACEMIC ACID

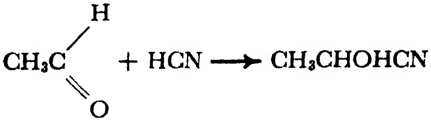
Racemic tartaric acid, as the name implies, is a racemic compound; in solution, it is a mixture of the dextro and laevo isomers. The solid is a molecular compound of one molecule each of the two forms.

The tartaric acids are remarkable in that two of the four isomers have had their original names generalized into the names of kinds of compounds. Thus the name *racemic* derives from racemic acid, and *meso* from mesotartaric acid.

Synthetic Products. We can generate an asymmetric carbon atom in two ways: by substitution, as in the preparation of α-bromopropionic acid from propionic acid;

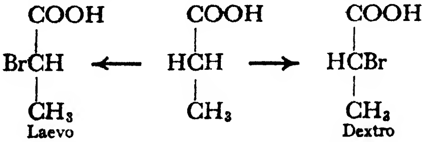
$$CH_3CH_2COOH + Br_2 \longrightarrow CH_3CHBrCOOH + HBr$$

or by addition, as in the preparation of acetaldehyde cyanohydrin from acetaldehyde.



$$CH_3C\overset{H}{\underset{O}{}} + HCN \longrightarrow CH_3CHOHCN$$

Whichever method we use, a racemic mixture (or racemic compound) results. An examination of the models shows that this result is to be expected. The two alpha hydrogen atoms in propionic acid are identical, and replacement of one of them is just as probable as is replacement of the other. If replacement of one furnishes the laevo acid, replacement of the other would furnish the dextro acid.



$$\begin{matrix} COOH \\ | \\ BrCH \\ | \\ CH_3 \end{matrix} \longleftarrow \begin{matrix} COOH \\ | \\ HCH \\ | \\ CH_3 \end{matrix} \longrightarrow \begin{matrix} COOH \\ | \\ HCBr \\ | \\ CH_3 \end{matrix}$$

On the average, an equal number of dextro and laevo molecules of bromopropionic acid will be formed. The smallest amount of the product which we can examine in our polariscope contains many million molecules; even if there were one or two more dextro than laevo molecules in this sample, we could not detect their presence by our most delicate apparatus.

The student should work through for himself the reasoning that applies to the generation of an asymmetric carbon atom by addition.

Nature Produces Optically Active Compounds. The chemical transformations which take place in living things almost always produce optically active materials. This is the most striking distinction between chemical reactions in the laboratory and in plants or animals. Practically all natural products which contain an asymmetric carbon atom occur in an optically active form. The enzymes which are the natural catalysts can differentiate between a dextro and a laevo form; in their presence the odds are no longer even as to the formation of the one enantiomorph or the other. The second method of separating racemic mixtures given below illustrates this point.

Although all the physical and chemical properties of a pair of enantiomorphs are identical, their biochemical behavior is different. This is even true of drugs which manifest their chemical action by some change in a large and complex organism. In most cases where both a dextro and laevo form of a drug have been prepared, the two have been found to differ markedly in their physiological action.

Separation of Racemic Mixtures. Resolution. As we have just seen, when we synthesize compounds containing asymmetric atoms, we always obtain inactive products, racemic mixtures or compounds. As we have also seen, the two components of a racemate have identical physical properties except for their action on polarized light, and cannot be separated by crystallization or distillation. In order to be able to obtain optically active products, it is, therefore, essential to have some method of separating racemic mixtures. Such a method is generally referred to as *resolution.*

The methods of separating racemic mixtures are as follows:

1. If the compound forms crystals with two different arrangements of the faces, as do the salts of tartaric acid, one may separate the crystals by hand. This laborious method, for obvious reasons, is rarely employed.

2. If the compound is fermented by bacteria or molds, usually one of the stereoisomers will be destroyed faster than the other. In this way, by the proper choice of bacteria it is often possible to prepare both forms from the inactive compound. At best, however, one enantiomorph is destroyed in each separation.

3. The most general method is to combine the compound with some optically active substance. There are certain complex amines found in nature which are optically active; they are known as *alkaloids* (Chap. 23). These compounds form salts with acids. If the acid is a racemic mixture, there will be two sets of salts, corresponding to the two stereoisomers.

$$\left.\begin{matrix}\text{Dextro acid}\\ \text{Laevo acid}\end{matrix}\right\} + 2\text{ moles dextro base} \longrightarrow \begin{matrix}\text{(I) dextro acid—dextro base}\\ \text{(II) laevo acid—dextro base}\end{matrix}$$

The salts I and II are not enantiomorphs. They stand in a similar relationship to each other as do the isomeric chlorohydroxysuccinic acids 1 and 3, or 2 and 4 on p. 190. That is, the salts I and II are **diastereoisomers**; they have different physical properties and can be separated by crystallization.

After they have been separated, the two salts can be treated *separately* with a mineral acid and the pure dextro and laevo forms of the acid can be obtained.

I. Dextro acid − dextro base + HCl ⟶ dextro acid + *d*-base hydrochloride

II. Laevo acid − dextro base + HCl ⟶ laevo acid + *d*-base hydrochloride

In a similar manner optically active acids may be used to resolve racemic mixtures which, like amines, contain a basic group.

Racemization. Some optically active compounds lose their activity on heating or treating with certain reagents. This process, which may interfere with the transformation of one optically active substance into another active compound, is known as *racemization.* Many compounds are either racemized with great difficulty or not at all. When racemization occurs readily, it is usually possible to show that some special mechanism is involved in the transformation of the + to the − isomer and vice versa.

GEOMETRICAL ISOMERISM

In connection with our study of fumaric acid (p. 169) mention was made of the isomer with the same structural formula, *maleic acid.* These isomers represent a type of stereoisomerism different from that resulting from an asymmetric molecule. Neither of the isomers is optically active; they differ markedly in their physical properties and in certain chemical reactions. The explanation of this type of stereoisomerism has been found in the fact that the double linkage is a rigid union of the carbon atoms involved. The restriction of rotation around this bond results in two different stereochemical configurations.

A double linkage must be represented by the union of two tetrahedra along one edge. This is shown in the accompanying diagrams.

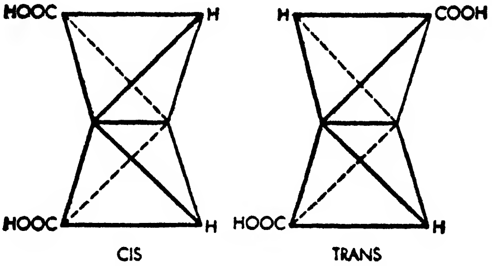
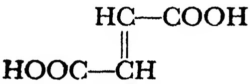
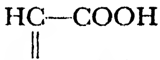


Fig. 11. Diagram of models of maleic and fumaric acids.



$$\begin{array}{rl} & \mathrm{HC{-}COOH} \\ & \;\| \\ \mathrm{HOOC{-}} & \mathrm{CH} \end{array}$$

Fumaric acid (trans)

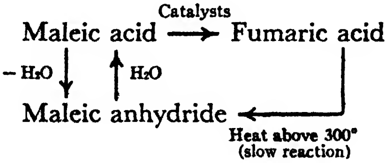


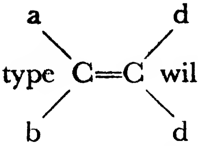
$$\begin{array}{l} \mathrm{HC{-}COOH} \\ \;\| \\ \mathrm{HC{-}COOH} \end{array}$$

Maleic acid (cis)

The names *cis* and *trans* are applied to the isomers to denote whether the similar groups are over each other or in the opposite configuration. Such isomers are called *geometrical isomers.*

The fact that maleic acid readily forms an anhydride (p. 172) is taken as evidence that it corresponds to the *cis* form. The construction of models shows that two carboxyl groups adjacent to each other in space could readily lose water to form a cyclic anhydride. On the other hand, the two carboxyl groups which are in the *trans* position could not. Maleic acid is readily converted into fumaric acid by the catalytic action of warm acid, halogen, or sunlight. The relationship of the two isomers is shown below.



In general, it is evident that geometrical isomers may be expected only if both unsaturated carbon atoms carry two different atoms or groups. Thus, compounds of the general type  will not have geometrical isomers since the two groups on one carbon atom are the same, and two different spatial arrangements are not possible.

QUESTIONS AND PROBLEMS

1. Indicate the total number of stereoisomers and the number of active forms to be expected for each of the following compounds: $CH_3CHBrCHBrCOOH$, $CH_3CHClCHClCH_3$, $CH_3CHClCHBrCH_3$, $CH_2OH(CHOH)_4COOH$, $CH_2OHCHOHCHOHCH_2OH$, and $CH_3CHBrCH_3$.

2. Outline the steps in the resolution of $CH_3CH(C_2H_5)NH_2$.

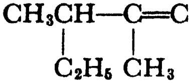
3. Explain why the addition of bromine to propylene furnishes only inactive material.

4. Define and illustrate the following terms: *asymmetric carbon atom, racemic mixture, similar asymmetric atoms, diamers, enantiomorphs.*

5. In what ways do enantiomorphs resemble each other, and how do they differ?

6. In what ways is the following statement incorrect? "Stereoisomers are isomers which differ from each other only in their action on polarized light."

7. Draw planar diagrams representing all the active forms of $HOOCCHBrCHBrCOOH$ and of $CH_3CHBrCHBrCOOH$. Why does one of these compounds exist in more isomeric forms than the other?

8. In the addition of hydrogen to the inactive hydrocarbon 

$CH_3\underset{C_2H_5}{\underset{|}{CH}}{-}\underset{CH_3}{\underset{|}{C}}{=}CHCH_3$, how many isomers would you expect? Would they be active or inactive?

9. Indicate the number of isomeric forms in which each of the following compounds would be expected to occur: $CH_3CH{=}CHCH_3$, $HOCH_2CH{=}CHCOOH$, $CH_3CH{=}CHCl$, $HOCH_2CH{=}CHCH_2OH$, $CH_3CH{=}CHCOOH$. Would any of the substances show optical activity?

10. If you were to add bromine to 2-pentene and were to work up the reaction mixtures by ordinary methods such as fractional crystallization or distillation, how many products would you expect to isolate?

11. Given samples of each of the four forms of tartaric acid, how would you identify each one?

CHAPTER 13

The Carbohydrates

Sugar, starch, and cellulose are common examples of the class of substances known as *carbohydrates* (p. 2). The name originated from the fact that the empirical formulas of these compounds and many other carbohydrates can also be written as $C_y(H_2O)_x$; e.g., glucose, $C_6H_{12}O_6$, ($C_6(H_2O)_6$), and cane sugar, $C_{12}H_{22}O_{11}$, ($C_{12}(H_2O)_{11}$). Such formulas have no structural significance, of course.

The carbohydrates are divided into three classes: the **monosaccharides,** the **disaccharides,** and the **polysaccharides.** The monosaccharides are **polyhydroxy aldehydes** or **polyhydroxy ketones.** The disaccharides and polysaccharides, on hydrolysis, yield monosaccharides. A knowledge of the monosaccharides, therefore, is essential to an understanding of the more complex carbohydrates.

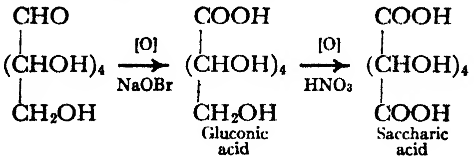
MONOSACCHARIDES

Glucose, $C_6H_{12}O_6$, also known as *dextrose* or *grape sugar*, is the commonest monosaccharide and occurs widely distributed in nature. Its commercial manufacture from starch will be discussed later (p. 216). The structure and the reactions of glucose are complex and are best presented in the stepwise, historical order in which they were worked out by several generations of organic chemists.

The following facts are of importance in determining the constitution of glucose: (1) glucose is easily oxidized to an acid of the formula $C_6H_{12}O_7$; (2) it forms a pentaacetate, $C_6H_7O(OCOCH_3)_5$, when treated with acetic anhydride; (3) on reduction with hydrogen iodide and phosphorus (above 100°), a mixture of *n*-hexyl iodide and secondary hexyl iodide is formed. From this third fact we can conclude that the six carbon atoms in glucose are arranged in a straight chain, and from the second, that there are five hydroxyl groups in the molecule. The oxidation reaction indicates that the substance is an aldehyde. In connection with this last conclusion it will be recalled that an aldehyde RCHO is easily oxidized to an acid RCOOH; primary alcohols are also oxidized to acids, but there is a loss of two hydrogen atoms. The acid from glucose has the same number of both carbon and hydrogen atoms as the sugar itself and, therefore, an aldehyde group and not an alcohol group is involved in the oxidation. One of the five hydroxyl groups is that of a primary alcohol since a *dibasic* acid with six carbon atoms and four hydroxyl groups can be prepared by drastic oxidation.

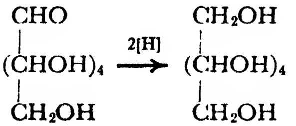
Since it has been found that the occurrence of two or more hydroxyl groups on the *same* carbon atom is very unusual, we may distribute the 5 hydroxyl groups on five of the six carbon atoms of the straight chain. This leaves the terminal carbon atom for the aldehydic group.

This formula accounts satisfactorily for most of the reactions of glucose. Thus, the oxidation of glucose to a monobasic acid, *gluconic acid*, and to a dibasic acid, *saccharic acid*, may be represented as follows.



$$\begin{array}{c} \mathrm{CHO} \\ | \\ (\mathrm{CHOH})_4 \\ | \\ \mathrm{CH_2OH} \\ \\ \end{array} \xrightarrow[\text{NaOBr}]{[O]} \begin{array}{c} \mathrm{COOH} \\ | \\ (\mathrm{CHOH})_4 \\ | \\ \mathrm{CH_2OH} \\ \text{Gluconic} \\ \text{acid} \end{array} \xrightarrow[\mathrm{HNO_3}]{[O]} \begin{array}{c} \mathrm{COOH} \\ | \\ (\mathrm{CHOH})_4 \\ | \\ \mathrm{COOH} \\ \text{Saccharic} \\ \text{acid} \end{array}$$

Similarly, the reduction of glucose to the hexahydroxy compound, *sorbitol* or *sorbite*, may be represented:



$$\begin{array}{c} \mathrm{CHO} \\ | \\ (\mathrm{CHOH})_4 \\ | \\ \mathrm{CH_2OH} \end{array} \xrightarrow{2[H]} \begin{array}{c} \mathrm{CH_2OH} \\ | \\ (\mathrm{CHOH})_4 \\ | \\ \mathrm{CH_2OH} \end{array}$$

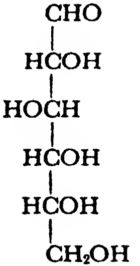
The Aldohexoses. The formula for glucose shows the existence of four asymmetric carbon atoms (indicated by underlining).

$$\overset{6}{\mathrm{CH_2OH}}\overset{5}{\underline{\mathrm{C}}\mathrm{HOH}}\overset{4}{\underline{\mathrm{C}}\mathrm{HOH}}\overset{3}{\underline{\mathrm{C}}\mathrm{HOH}}\overset{2}{\underline{\mathrm{C}}\mathrm{HOH}}\overset{1}{\mathrm{CHO}}$$

The number of possible stereoisomers of a substance with this formula is 2^4 or 16. Glucose is only one of these sixteen isomers; it is scientifically known as *D-glucose*, its enantiomorph as *L-glucose*. All the isomers are known; some occur in nature and others have been prepared in the laboratory. This group of sixteen stereoisomers is known as the *group of aldohexoses.*

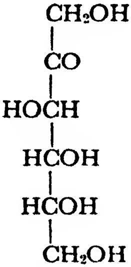
Sugars which have an aldehydic group are called *aldoses;* those which contain a ketonic group *ketoses.* The number of carbon atoms in the sugar can also be indicated in the name. Thus, the **hexoses** are all sugars with six carbon atoms; the **pentoses** with five. The name *aldohexose* indicates a six-carbon sugar with an aldehydic group. Similarly the name *aldopentose* indicates a five-carbon sugar with an aldehydic group and the name *ketohexose* a ketonic sugar with six carbon atoms.

The methods of determining the spatial relationships of the asymmetric carbon atoms in the sugars are too complicated and specialized to be given in this book. The configurational formulas of the two most important monosaccharides, D(+)glucose and D(−)fructose are given below. In the names for these and other sugars the D or L refers to the configuration of the carbon atom next to the CH_2OH group, while the (+) or (−) refers to the sign of the optical rotation. The reference compound for these configurations is D(+)glyceraldehyde, which is arbitrarily assigned the configuration shown below.



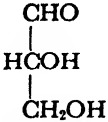
$$\begin{array}{c} CHO \\ | \\ HCOH \\ | \\ HOCH \\ | \\ HCOH \\ | \\ HCOH \\ | \\ CH_2OH \end{array}$$

D(+)Glucose
(dextrose)



$$\begin{array}{c} CH_2OH \\ | \\ CO \\ | \\ HOCH \\ | \\ HCOH \\ | \\ HCOH \\ | \\ CH_2OH \end{array}$$

D(−)Fructose
(laevulose)



$$\begin{array}{c} CHO \\ | \\ HCOH \\ | \\ CH_2OH \end{array}$$

D(+)Glyceraldehyde

Other Aldohexoses of Importance. Besides the very important sugar, D(+)glucose (dextrose), two other of the sixteen possible isomers should be mentioned. These are **D(+)mannose** and **D(+)galactose.** The former may be prepared by the hydrolysis of ivory-nut fragments. The latter, **D(+)galactose,** is contained in the cell walls of plants in polymerized anhydro forms known as *galactans*. It is formed by hydrolysis of galactans and other vegetable materials known as *pectins*. Together with D(+)glucose, it is formed by the hydrolysis of milk sugar (lactose).

Laevulose, a Ketohexose. The ketohexoses are a class of sugars represented by the following general formula (asymmetric atoms underlined).

$$\overset{6}{CH_2OH}\overset{5}{\underline{C}}HOH\overset{4}{\underline{C}}HOH\overset{3}{\underline{C}}HOH\overset{2}{CO}\overset{1}{CH_2OH}$$

There are 2^3 or 8 isomeric ketohexoses. Of these only one is of general interest. This is **D(−)fructose,** commonly called *laevulose* or *fruit sugar*. The configurational formula was given above.

D(−)Fructose occurs in many fruits and, together with dextrose, is a product of the hydrolysis of cane sugar. It is best prepared by the hydrolysis of a polysaccharide, **inulin,** which occurs in dahlia tubers and the Jerusalem artichoke.

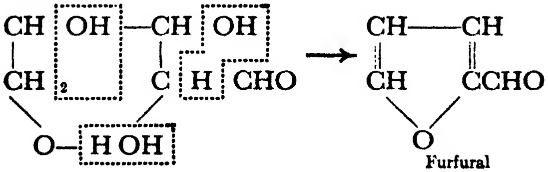
The Aldopentoses. Of the eight isomeric aldopentoses only three are of general interest. Two are formed by the hydrolysis of polysaccharides of high molecular weight known as *pentosans.* These are L(+)**arabinose** and D(+)**xylose.** The pentosans together with similar compounds which yield mannose or galactose on hydrolysis are known as *hemicelluloses.* They occur widely distributed in plants particularly associated with cellulose in cell walls. Cherry gum consists largely of a pentosan which yields L(+)arabinose on hydrolysis. The hydrolysis of straw or bran furnishes D(+)xylose. The third pentose of importance is D(+)**ribose** which occurs in nucleic acids (p. 373) and in a number of other compounds of interest to the biochemist.

Desoxyribose is present in one type of nucleic acid; it differs from D-ribose by having a CH_2 group instead of a CHOH adjacent to the aldehydic group.

$CH_2OHCHOHCHOHCHOHCHO$ Ribose

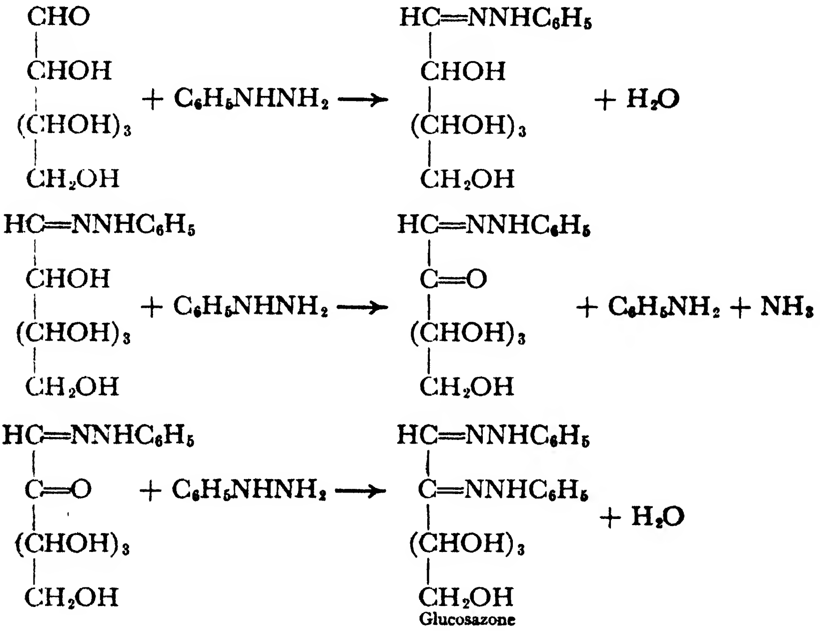
$CH_2OHCHOHCHOHCH_2CHO$ Desoxyribose

The aldopentoses resemble the aldohexoses closely in most of their reactions. The action of hot hydrochloric or sulfuric acid serves to differentiate the two classes; only the pentoses form a volatile aldehyde known as *furfural.* This substance contains a five-membered ring containing oxygen. Its presence can be established by a number of color reactions. Its formation can be visualized by writing the dehydration of an aldopentose in the following way.



REACTIONS OF THE MONOSACCHARIDES

Both the aldoses and the ketoses are oxidized by warm Fehling's solution and warm ammoniacal silver nitrate. The ketoses differ from the aldoses in that the latter, on cautious oxidation with bromine water, yield an acid with the same number of carbon atoms; the ketoses yield acids with fewer atoms. Neither aldoses nor ketoses give the characteristic aldehyde test with Schiff's reagent (p. 96). Both react with phenylhydrazine (p. 95), $C_6H_5NHNH_2$, to form yellow crystalline **osazones** which are less soluble than the sugars. This reaction was discovered by Emil Fischer and is of great value in identifying and purifying the monosaccharides.



$$\begin{array}{c} CHO \\ | \\ CHOH \\ | \\ (CHOH)_3 \\ | \\ CH_2OH \end{array} + C_6H_5NHNH_2 \longrightarrow \begin{array}{c} HC{=}NNHC_6H_5 \\ | \\ CHOH \\ | \\ (CHOH)_3 \\ | \\ CH_2OH \end{array} + H_2O$$

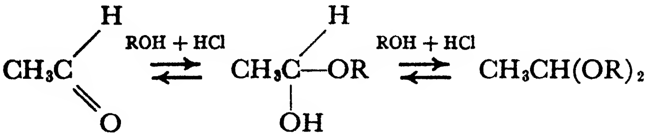
$$\begin{array}{c} HC{=}NNHC_6H_5 \\ | \\ CHOH \\ | \\ (CHOH)_3 \\ | \\ CH_2OH \end{array} + C_6H_5NHNH_2 \longrightarrow \begin{array}{c} HC{=}NNHC_6H_5 \\ | \\ C{=}O \\ | \\ (CHOH)_3 \\ | \\ CH_2OH \end{array} + C_6H_5NH_2 + NH_3$$

$$\begin{array}{c} HC{=}NNHC_6H_5 \\ | \\ C{=}O \\ | \\ (CHOH)_3 \\ | \\ CH_2OH \end{array} + C_6H_5NHNH_2 \longrightarrow \begin{array}{c} HC{=}NNHC_6H_5 \\ | \\ C{=}NNHC_6H_5 \\ | \\ (CHOH)_3 \\ | \\ CH_2OH \end{array} + H_2O$$

Glucosazone

A similar reaction takes place with ketoses, except that the terminal CH_2OH group next to the CO group is involved in the oxidation. It is possible to isolate the phenylhydrazones before the reaction proceeds further.

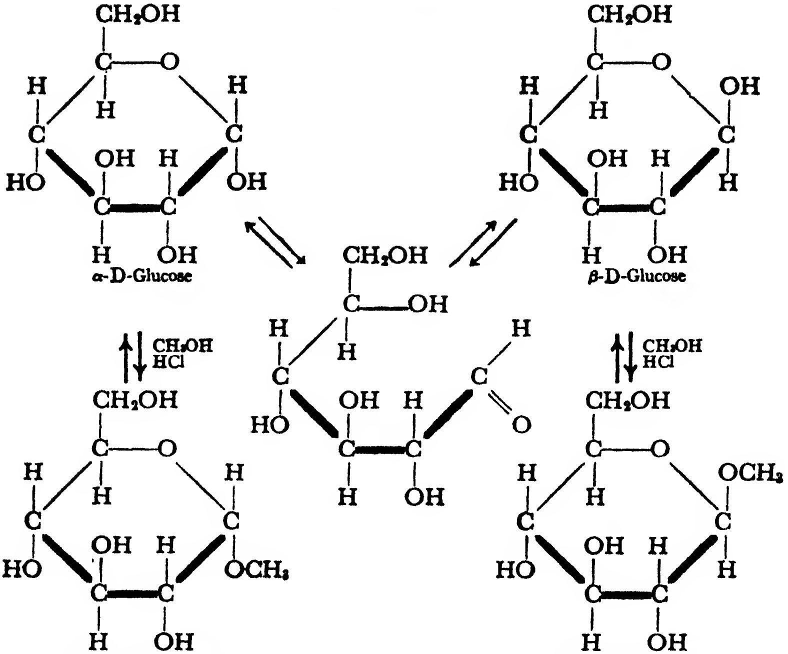
Glucosides. We are now ready to consider the reactions of glucose that are not satisfactorily accounted for by the aldohexose formula and to see what modifications of that formula they make necessary. When glucose and an alcohol are treated with a small amount of acid, products known as *glucosides* are obtained. The glucosides differ in composition from glucose by the replacement of one hydrogen atom by the group R of the alcohol ROH. If we look back over the chemistry of the aldehydes, we see that they react with alcohols to form acetals (p. 95). In this reaction two molecules of the alcohol are involved, but there is reason to believe that a product involving only one molecule of alcohol, a hemiacetal, is an intermediate.



If now we examine the aldohexose formula for glucose we see not only that it contains both the functional groups of an alcohol and an aldehyde (hydroxyl and carbonyl), but also that these groups are in position to react with each other and form a six-membered ring. A reaction between a hydroxyl group and the carbonyl group in glucose would lead to a hemiacetal; reaction between this product and alcohol would lead to an acetal, a glucoside.

The reactions of the glucosides are consistent with their formulation as acetals. They do not reduce Fehling's solution, and they are readily hydrolyzed in acid solution.

All aldoses and ketoses, when treated with an alcohol in the presence of a catalyst, form compounds similar to the glucosides; these are given the general name *glycosides*. In most cases two isomeric forms can be obtained known as the *alpha* and *beta*. These differ in their physical properties, particularly in their rotatory power. These isomers are predicted from the theory of stereoisomerism. There are *five* asymmetric carbon atoms in methyl glucoside. The interaction with the alcohol makes the terminal atom asymmetric; corresponding to this asymmetric atom, there are two stereoisomers. In one, the terminal atom is laevorotatory; in the other, it is dextrorotatory. Although a vast number of the naturally occurring glycosides are glucose derivatives, glycosides of other hexoses and of pentoses are found in plant and animal products.



α-D-Glucose

β-D-Glucose

α Methyl D-glucoside

β Methyl D-glucoside

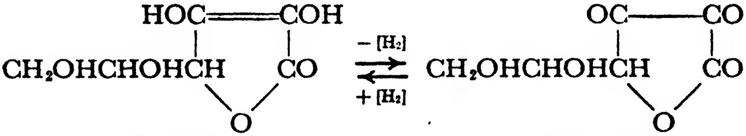
The Cyclic Structure of Glucose. We have just seen that the existence of two isomeric methyl glucosides is a necessary consequence of the cyclic structure. This fact provides the clue to the explanation of two isomeric forms of glucose itself. These are known as *α-glucose* and *β-glucose*. The former crystallizes from water as a hydrate, the latter is anhydrous. A freshly prepared aqueous solution of the alpha form has a specific rotation of +109.6°; a similar solution of the beta form has a specific rotation of +20.5°. On standing, the specific rotation of both solutions slowly changes until a final value of +52.3° is reached. This corresponds to an equilibrium mixture of the two forms. This change is known as *mutarotation*.

The two isomeric forms of glucose are clearly parallel to the two isomeric methyl glucosides discussed above. α-Glucose and β-glucose correspond respectively to a laevo- and a dextrorotation of the *terminal* atom. Their existence shows that we must write cyclic structures for the two isomeric forms of glucose itself. The ease with which the two isomers pass into each other is in marked contrast to the stability of the two isomeric methyl glucosides. In glucose the migration of a hydrogen atom can take place as in keto-enol tautomerism. It is probable that both cyclic forms are in equilibrium in solution with a small amount of an open-chain form corresponding to the aldohexose formula for glucose.

α-Glucose (cyclic) $\rightleftharpoons$ Open-chain aldehyde $\rightleftharpoons$ β-Glucose (cyclic)

If we consider the cyclic formula as a general formula for the aldohexoses, it is evident that 2^5 or 32 isomers are predicted in place of the 2^4 or 16 on the basis of the open-chain formula. A careful study has shown the existence of two forms of many aldohexoses corresponding to α- and β-glucose. Thus, the number of isomeric aldohexoses now known is greater than can be accounted for on the open-chain formula; in time we may expect that all the thirty-two isomers corresponding to the cyclic formula will be prepared.

Ascorbic Acid, Vitamin C. A substance of considerable importance which is now manufactured by a series of reactions which starts with glucose is ascorbic acid. This vitamin is present in a great variety of vegetables and in particular in citrus fruits. It is a strong reducing agent, reducing both ammoniacal silver nitrate and Fehling's solution in the cold. This behavior is due to the presence of an **ene-diol** system in the molecule.



Ascorbic acid (Vitamin C)

Dehydroascorbic acid

Ascorbic acid is a sufficiently strong acid to react with sodium carbonate solutions; the acidity is due to one of the hydrogens of the ene-diol system. Since it is also a lactone, it may be opened by treatment with alkali. The absence of ascorbic acid from an otherwise normal diet ultimately leads to scurvy.

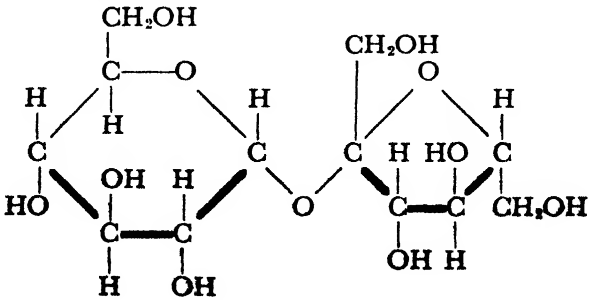
DISACCHARIDES

Sucrose or cane sugar, $C_{12}H_{22}O_{11}$, is the most familiar sugar. It is readily hydrolyzed in the presence of a little acid or by the action of the enzyme **invertase**; the products of hydrolysis are one molecule of glucose and one of fructose.

$$C_{12}H_{22}O_{11} + H_2O \xrightarrow[\text{acid}]{\text{Enzyme or}} \underset{\text{D}(-)\text{Fructose}}{C_6H_{12}O_6} + \underset{\text{D}(+)\text{Glucose}}{C_6H_{12}O_6}$$

This reaction is called *inversion* because the mixture of products rotates the plane of polarized light in the opposite direction from pure sucrose, which is dextrorotatory. Since fructose is laevorotatory and glucose dextrorotatory, one might imagine that an equimolar mixture of the two would be inactive. This is not so, however, for the rotation of fructose is greater than that of glucose; a mixture of the two in equal amounts therefore rotates the plane of polarized light to the left. The name *invert sugar* is applied to a mixture of glucose and fructose.

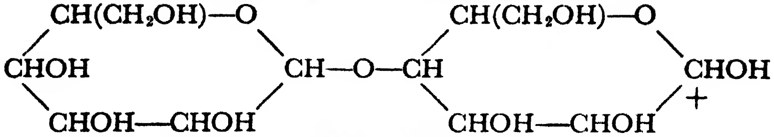
The hydrolysis of sucrose establishes the fact that its molecule is built up of one molecule of glucose and one of fructose joined together with the loss of water. The ease with which the hydrolysis takes place suggests that the nature of the linkage is similar to that in the glucosides. Sucrose does not reduce Fehling's solution. This fact indicates that neither the aldehydic nor ketonic groups of the constituent monosaccharides are free in the disaccharide. The following formula represents the sucrose molecule.



Maltose and Lactose. Two other disaccharides are of general interest: they are maltose and lactose. They both crystallize with a molecule of water of crystallization and have the molecular formula $C_{12}H_{22}O_{11} \cdot H_2O$. **Maltose** is the product of the enzymatic hydrolysis of starch. This hydrolysis is the first step in the digestion of starchy foods; the saliva contains an enzyme, **ptyalin,** which rapidly converts starch into maltose. Maltose is the sugar produced by the action of diastase (from malt) on starch, and its biochemical transformation to alcohol was mentioned in the first chapter of this book (p. 19). On hydrolysis maltose yields two molecules of glucose. This hydrolysis to glucose is the first step in the formation of alcohol from maltose. The reaction is brought about by an enzyme present in the yeast. The glucose thus produced is then fermented to alcohol by another group of enzymes in the yeast cell (zymase).

Lactose is the sugar which occurs in milk. It is present to the extent of about 4 per cent. On hydrolysis it yields a molecule of glucose and one of **galactose.** Lactose is fermented to lactic acid by the lactic acid ferment which is responsible for the souring of milk (p. 177); it is not fermented by ordinary yeast.

Both maltose and lactose are **reducing sugars** like the monosaccharides; that is, they are oxidized by warm Fehling's solution. In this respect they differ from sucrose which has no action on Fehling's solution. The reason for this difference is seen by comparing the formula for sucrose with that for maltose or lactose which is given below. Maltose and lactose both have one of the original aldehydic groups of glucose still free in the molecule (shown by a cross in the cyclic form written below). The free terminal group in maltose or lactose (a potential aldehyde group) confers on these disaccharides all the properties of aldoses. Sucrose, on the other hand, has no such group. It is both a glucoside and a fructoside in which the monosaccharide residues are joined together through the potential aldehydic group of glucose and the potential ketonic group of fructose.



Maltose or lactose
(In maltose the sugar residue on the left is glucose; in lactose it is the isomeric galactose.)

Enzymatic Hydrolysis of Glucosides. The disaccharides may be regarded as glucosides. This is evident from the formula for maltose written above; one molecule of glucose (written on the right) is in place of the methyl alcohol which has condensed with glucose in the methyl glucosides. It will be recalled that there are two isomeric glucosides possible in each case which we designate as *alpha* or *beta*. It has been found that there are enzymes which *specifically* hydrolyze the one form of glucoside or the other. These enzymes act almost independently of the nature of the hydroxyl compound condensed with the glucose residue. One of these enzymes is known as *maltase*, because it hydrolyzes this sugar to two molecules of glucose. It occurs widely distributed in nature; for example, in yeast and in the pancreas. It acts on all the glucosides of the one series which are known as the *alpha glucosides*. The other enzyme is known as *emulsin* and hydrolyzes only *beta glucosides*. Both enzymes are very specific and will not act on the glucoside of the other configuration. Once this fact had been established, it was possible to use these enzymes in determining the configuration of a glucoside.

POLYSACCHARIDES

Starch, glycogen (animal starch), and **cellulose** are all substances of high molecular weight which on hydrolysis yield glucose. They may all be represented by the empirical formula $(C_6H_{10}O_5)_x$ or $(C_{12}H_{20}O_{10})_n$. The polysaccharides are either insoluble in water and organic solvents, or form colloidal dispersions which often are jellies. They do not show the aldehydic reactions of monosaccharides; the presence of three hydroxyl groups connected with each group of six carbon atoms is readily demonstrated by acetylation with acetic anhydride.

While the molecules of the three important polysaccharides mentioned above are composed of only glucose molecules joined together, the class includes other types of compounds. For example, inulin is a polysaccharide which on hydrolysis yields the ketohexose, fructose.

CELLULOSE

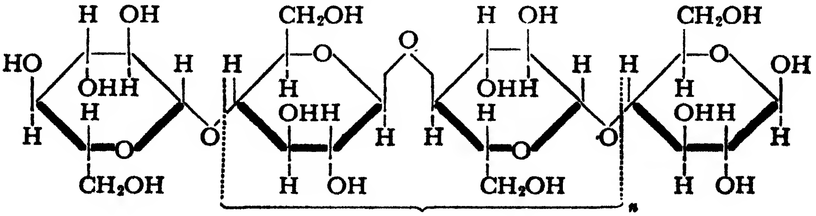
Common Forms of Cellulose. The structural material of the plant world is largely cellulose. It is the substance present in vegetable fibers and fabrics. Pure filter paper and "cotton wool" are examples of nearly pure cellulose. In wood the cellulose fibers are embedded in an amorphous material of high molecular weight known as *lignin.* In the manufacture of cellulose from wood, the operations are designed to remove this lignin and hemicellulose (p. 203). The cellulose fibers can be separated from these materials by treatment with such reagents as sodium hydroxide or calcium bisulfite which decompose or dissolve the lignin.

The manufacture of paper from wood consists essentially in separating the cellulose and then matting the fibers together. The cheaper papers are prepared from mechanical pulp which is merely soft wood disintegrated in a stream of water. Lignin and other impurities are present, and their presence can be shown by a yellow coloration with aniline hydrochloride solution.

Properties. Cellulose is insoluble in water and all organic solvents. It dissolves in Schweitzer's reagent (an ammoniacal solution of copper hydroxide), as the result of a chemical reaction. On acidification the cellulose is precipitated.

Cellulose is much more resistant to hydrolysis than starch or glycogen and is attacked only slowly by boiling with dilute acids. Cellulose dissolves in concentrated sulfuric acid; on diluting the solution and boiling it, glucose is formed as the final product.

Chemical Constitution of Cellulose. On careful hydrolysis of cellulose, a disaccharide, cellobiose, is formed. This disaccharide on further hydrolysis yields two molecules of glucose. It has been shown that cellobiose has the same structural formula as maltose (p. 209) except that it is a beta glucoside while maltose is an alpha glucoside. The cellulose molecule is composed of a long chain of cellobiose molecules joined together as shown below.



The value of *n* in the above formula is estimated as greater than 3000 for native cellulose; for cotton purified by extracting the fats and treatment with dilute alkali the value is 1000 to 3000; for cellulose in wood pulp it may be as low as a few hundred; and in some cellulose derivatives the number of molecules in the chain may even be as small as 50.

Intermolecular forces between the long-chain cellulose molecules are sufficient to hold the molecules in a fairly definite pattern; thus cellulose fibers show an x-ray pattern characteristic of the crystalline state, have high tensile strength, and are insoluble in water and organic solvents.

Cellulose Nitrates. The hydroxyl groups in the polysaccharides form esters as would be expected. The esters of nitric acid can be formed by the direct action of a mixture of nitric and sulfuric acids on the polysaccharide. The cellulose nitrates which are prepared in this way are substances of very great importance. They are often erroneously called *nitrocellulose*. If the reaction is carried out in such a manner that all the free hydroxyl groups are esterified, the material is known as highly *nitrated cotton* or *gun cotton*. It is used as a high explosive in torpedoes. It has the empirical formula $[C_6H_7O_2(ONO_2)_3]_x$ or $[C_{12}H_{14}O_4(ONO_2)_6]_n$. It should be noted that since the molecular weight of cellulose is unknown we may express the analysis either in terms of a unit of six or twelve carbon atoms.

$$[C_{12}H_{20}O_{10}]_n + n6HNO_3 \longrightarrow [C_{12}H_{14}O_4(ONO_2)_6]_n + n6H_2O$$

The lower nitrates of cotton are called *pyroxylin*. They are important because they are soluble in mixtures of various organic solvents. The partial nitration of cotton is accomplished by careful control of the temperature, the concentration of acid, and the length of time of the action. The nitrated cotton resembles the original cotton in its general appearance. In the process of manufacture it is washed free from acid and finally dried by whirling in a centrifuge. After this treatment it still contains considerable water and in this form is not explosive. The water is usually replaced by soaking in denatured alcohol and the material is again centrifuged. It is shipped without danger when it is moist with alcohol.

Smokeless Powder. When a mixture of gun cotton and the lower nitrates is treated with alcohol and ether, or certain other mixtures of organic solvents, it swells into a jellylike mass. This can be rolled into strips or cords of material which when dry have the consistency of dry gelatine. In the manufacture of smokeless powder, nitrated cotton is "gelatinized" in this way and molded into various shapes and sizes. When ignited in the open in small quantities, smokeless powder burns without exploding. When ignited in the absence of air, smokeless powder decomposes, utilizing the oxygen which is chemically bound in the solid. The decomposition may be represented by the following equation:

$$[C_{12}H_{14}O_4(ONO_2)_6]_n \longrightarrow n5CO + n7CO_2 + n4H_2 + n3H_2O + n3N_2.$$

Under the confinement obtaining in a gun or rifle, the decomposition is rapid and much heat and gas are evolved. The expanding gases propel the shell from the gun. Since there is no solid residue left by the decomposition of smokeless powder, there is no smoke.

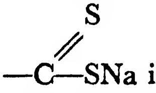
Celluloid and Lacquer Paints. Celluloid is manufactured by gelatinizing pyroxylin with alcohol and heating it with camphor. The product may be molded into a variety of shapes by heating to about 100°. At room temperature it is hard and somewhat brittle. As would be expected from its close relationship to smokeless powder, it is very flammable.

Pyroxylin dissolves in a mixture of ether and alcohol, and the solution is known as *collodion.* This material may be regarded as the forerunner of the lacquer paints which are widely used in the automobile industry. The development of these lacquers has been made possible by the cheap production of the higher alcohols (p. 21) and by the discovery of a method of modifying pyroxylin.

Pyroxylin is modified (i.e., made soluble in mixtures of organic solvents to furnish solutions of low viscosity) by heating it for a considerable time in slightly alkaline solution. Modified pyroxylin in a suitable solvent mixture, together with pigments and other additives, constitutes the modern lacquer paints. Large amounts of such organic solvents as butyl acetate are used in their preparation.

Artificial Silks. The essential difference between the appearance of silk and cotton goods is due to the mechanical structure of the fibers. Silk fibers are long, continuous, smooth tubes, whereas cotton fibers are relatively short and irregular. Silk is a protein (Chap. 14), but this is of little significance. The production of artificial silk from cotton is a matter of changing the mechanical structure of the carbohydrate fiber. This may be done by a variety of methods which are based on the same principle. A solution of cellulose or some cellulose derivative is forced through a very fine hole in such a manner that a continuous thread of solid material is formed. These almost invisible threads are then twisted together and the larger thread woven into cloth which closely resembles silk in its luster. **Rayon** is a name which has been given to artificial silk prepared by certain processes.

The manufacture of rayon is a major industry today. During 1948 more than 550,000 tons of rayon were produced in the United States. One-third was made by the acetate process and the balance, save for minor amounts, was made by the viscose process.

In the **viscose process** the cellulose is treated with carbon disulfide and alkali which gives a **cellulose xanthate** in which the group  $-\overset{\overset{S}{/\!/}}{C}-SNa$ is joined to one or more hydroxyl groups. This cellulose xanthate with a small amount of water forms a thick solution known as *viscose.* This may be converted into threads of cellulose by squirting through a fine orifice into dilute acid which removes the xanthate group. **Cellophane** is the name given to thin, transparent sheets of regenerated cellulose prepared by forcing viscose through a narrow slot into the regenerating solution; it is rendered moistureproof by coating with a transparent lacquer.

Cellulose Acetate. The cellulose esters of the organic acids cannot be prepared by direct esterification. It is necessary to use the acid anhydride. By the action of acetic anhydride on cotton in the presence of a little acid, cellulose acetate can be prepared. It has the formula $[C_{12}H_{14}O_4(OCOCH_3)_6]_n$. It is soluble in several organic solvents, particularly the halogen derivatives of the aliphatic hydrocarbons. On partial hydrolysis the material becomes soluble in a wider variety of solvents. Material thus prepared is soluble in acetone, and can be obtained as a strong flexible film or thread by evaporating the solvent. Unlike the cellulose nitrates, cellulose acetate burns with difficulty. For this reason moving-picture films prepared from it may be used without the precautions against fire which are necessary with the ordinary films manufactured from cellulose nitrate. Large quantities of acetic anhydride are manufactured for the use of this industry (pp. 112, 140, 142).

STARCH AND GLYCOGEN

Starch occurs as white granules in nearly all plants. Starch granules from different plants differ greatly in size and shape. The food value of cereals and many other vegetable foods is due primarily to the starch which is present in them. For example, *rice* is about 75 per cent starch, *corn* 50 per cent, and *potatoes* 20 per cent.

Starch is practically insoluble in cold water, but when a suspension of starch in water is heated, the granules swell and form a viscous solution which on cooling sets to a jelly. On dilution a colloidal solution of starch can be obtained which is liquid at room temperature. Such a solution shows none of the characteristic reactions of a monosaccharide. If it is boiled with dilute hydrochloric acid, the starch is completely hydrolyzed to glucose. If the enzyme diastase is allowed to act on a suspension or solution of starch, a solution of maltose results. Starch gives a characteristic blue color with iodine; the test is very delicate. Glycogen gives a brown to violet color. No color is formed when the mono- and di-saccharides are treated in the same manner.

Structure of Starch and Glycogen. Naturally occurring substances of high molecular weight are composed of molecules of somewhat different size, though the spread may not be so large as it is with many synthetic polymers. Nevertheless, when we consider the size of the molecules we speak in terms of a range or average molecular weight. The spread of molecular weight of the molecules in starch is very marked. By treatment of starch with hot water it is possible to separate two fractions, apparently without degradation of the original molecules. One fraction (amylose) has a molecular weight of 10,000 to 60,000; the other fraction (amylopectin), which constitutes the major portion of the material, is composed of much larger molecules which have molecular weights from 60,000 to 1,000,000.

Starch differs from cellulose in two respects. Cellulose consists of long chains of glucose residues joined together by beta glucoside links; in starch the glucoside links correspond to alpha glucosides. Furthermore, in amylopectin there appear to be branched chains of glucose units attached to a straight-chain interior unit through the —CH_2OH groups of the chain and the usual alpha glucoside link. Evidence of this structure has been obtained by studying the effect of certain enzymes which degrade the molecule by hydrolysis in steps. The structure of glycogen appears to be similar to that of amylopectin.

One consequence of the lack of compactness of the starch molecules as compared with those of cellulose is seen in the different behavior of the two materials toward water. The straight chains in cellulose are favorable to a close packing of the molecules in crystal-like fibers where the intermolecular forces are relatively large. Solvent molecules therefore have no effect on cellulose; this is true even of hydroxyl-containing solvents such as water and the alcohols and is true in spite of the fact that cellulose is a polyhydroxy compound. The more bulky starch molecules do not form so coherent and rigid a pattern; therefore, starch swells when placed in water and readily forms a colloidal dispersion. Glycogen, in structure and behavior with solvents, resembles starch.

The mechanical properties and solubilities of substances of high molecular weight are the resultant of a number of different effects. The old rule that like dissolves like has even more validity with large molecules than with small. Rubber (p. 74) swells in hydrocarbon solvents, not with water; some of the polyhydroxy compounds (starches) swell with water and form colloidal solutions, but none interacts with hydrocarbons. The physical properties are determined by forces between the molecules, but the shape of the molecule and the ability to pack into coherent patterns are of great importance. While all substances of high molecular weight have very high boiling points and are without exception either crystalline, fibrous, or amorphous solids, solubility cannot be so readily generalized. A striking example of this is the behavior of polyvinyl alcohol (p. 143). Although starch, cellulose, and polyvinyl alcohol all contain one hydroxyl group for each two carbon atoms, only polyvinyl alcohol is completely soluble in water. This is attributed to the fact that the intermolecular forces and the shape of the molecule do not give a crystal-like pattern at room temperature.

Manufacture of Starch, Glucose, and Dextrine. Starch is usually prepared commerically from corn or potatoes by a mechanical process of grinding and washing. A suspension of impure starch in water is thus obtained; by allowing it to settle slowly, the impurities are deposited first and may be removed. A microscopic examination of starch will reveal the source of the material, as the granules are characteristic of the plant from which they come. Starch is used in laundry work, in cooking, in the manufacture of pastes, and in the preparation of dextrines and glucose.

The hydrolysis of starch to glucose is carried out on a very large manufacturing scale. A few per cent of hydrochloric acid is used as the catalyst, and, after the completion of the hydrolysis, this is carefully neutralized. The evaporation of the glucose solution thus prepared yields thick, syrupy solutions, which are widely sold as sweetening materials for domestic use and in the manufacture of candy.

When dry starch is heated to 200° to 250°, a material known as *dextrine* is produced. It is soluble in cold water yielding a syrupy solution which has strong adhesive properties. Dextrine is used in manufacturing the mucilage used on postage stamps. From its behavior, dextrine appears to be a polysaccharide of smaller molecular weight than starch. On hydrolysis it yields glucose. Dextrines are also formed as intermediate compounds in the enzymatic hydrolysis of starch to maltose.

QUESTIONS AND PROBLEMS

1. Write stereochemical formulas for sucrose, maltose, and lactose. Explain with the aid of the formulas why one of these three is a reducing sugar.

2. What are the differences between lacquer paints and paints based on the vegetable oils?

3. Outline the evidence which indicates that glucose is a simple open-chain pentahydroxy aldehyde.

4. What is the meaning of the prefixes *d*- and *l*- and (+) and (−)? Illustrate with examples from carbohydrate chemistry.

5. If a naturally occurring substance is shown to be a glucoside since it furnishes glucose and an alcohol on hydrolysis, how would you determine whether it was an alpha or beta glucoside?

6. What is mutarotation? Show how occurrence of mutarotation

and the existence of two isomeric glucosides made it necessary to modify the open-chain structure of glucose.

7. Describe the preparation and use of dextrine and the cellulose nitrates.

8. What is the structural unit in cellulose? What is the evidence for your statement?

9. Compare the structures of starch and cellulose.

10. Write structural formulas for an osazone, for Vitamin C, and for sorbitol.

11. Describe the manufacture of rayon.

12. Write equations for the reaction between phenylhydrazone and (*a*) glucose and (*b*) fructose.

CHAPTER 14

The Amino Acids and Proteins

Occurrence of Proteins. Fats, carbohydrates, and proteins are the three great classes of compounds which are of prime importance to the biologist and biochemist. We have already considered the first two of these classes and shall devote this chapter to the proteins alone. Proteins occur widely distributed in both plants and animals and are an essential constituent of foodstuffs. Both vegetable proteins and animal proteins occur as solids and in solution. The animal proteins are in part in solution in the body fluids, e.g., in the blood, but in larger part they are the insoluble materials of which the animal tissues are composed. Thus, skin, hair, muscle tissue, and the horny material of nails, horns, and hoofs are essentially proteins. The proteins serve as structural materials for animals much as the polysaccharides (e.g., cellulose) do for plants. Proteins, like fats and carbohydrates, may be used as a source of energy when they are consumed by animals. In plants, proteins are found in all the living parts but usually in relatively small quantities except in the seeds.

Relation of Proteins to Amino Acids. In their physical properties proteins differ widely from one another. The water-soluble material, white of egg, the partially soluble gelatine, and the insoluble hide of animals are all proteins. In one fundamental respect all proteins are similar — by boiling with dilute acid they are all hydrolyzed to a mixture of **alpha amino acids.** Twenty-four different amino acids have been isolated from the hydrolysis of a variety of proteins. These substances are the building blocks out of which the complex protein molecules are constructed. Therefore, before proceeding further we must consider briefly the amino acids themselves.

AMINO ACIDS

The amino acids are classified according to the relative positions of the amino group and carboxyl group. The nomenclature follows the same principle used with the hydroxyl derivatives of acids (p. 176). Thus **α-aminobutyric acid** is $CH_3CH_2CHNH_2COOH$ and **β-aminobutyric acid** is

$$CH_3CHNH_2CH_2COOH.$$

Fortunately, the amino acids which are formed by the hydrolysis of proteins are all of one class. They are alpha amino acids and we shall confine our attention to them.

Alpha Amino Acids from Proteins. The amino acids which have been isolated from the mixtures obtained by hydrolysis of a great variety of proteins are listed below for reference. The student is advised to familiarize himself with the special names and formulas of one or two representatives of each of the three groups into which the acids are divided. The special names are used in this field to the almost complete exclusion of a rational nomenclature.

AMINO ACIDS OBTAINED BY THE HYDROLYSIS OF PROTEINS

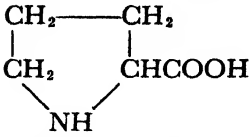
A. Acids with equal number of basic and acid groups (one each except No. 17):

1. Glycine (Glycocoll):	$CH_2(NH_2)COOH$
2. Alanine:	$CH_3CH(NH_2)COOH$
3. Valine:	$(CH_3)_2CHCH(NH_2)COOH$
4. Leucine:	$(CH_3)_2CHCH_2CH(NH_2)COOH$
5. Norleucine:	$CH_3CH_2CH_2CH_2CH(NH_2)COOH$
6. Isoleucine:	$C_2H_5CH(CH_3)CH(NH_2)COOH$
7. Phenylalanine:	$C_6H_5CH_2CH(NH_2)COOH$
8. Tyrosine:	p-$HOC_6H_4CH_2CH(NH_2)COOH$

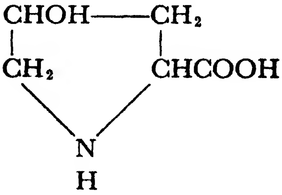
9\. Threonine: $CH_3CHOHCH(NH_2)COOH$

10\. Serine: $CH_2OHCH(NH_2)COOH$

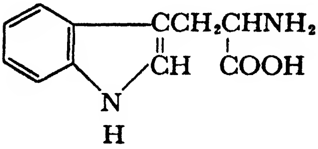
11\. Proline:



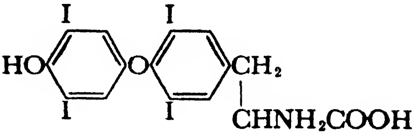
12\. Hydroxyproline:



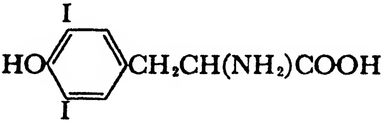
13\. Tryptophane:



14\. Thyroxine:

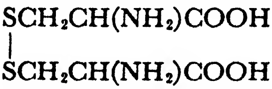


15\. Iodogorgoic acid:



16\. Methionine: $CH_3SCH_2CH_2CH(NH_2)COOH$

17\. Cystine:



$$\begin{array}{l}SCH_2CH(NH_2)COOH\\ |\\ SCH_2CH(NH_2)COOH\end{array}$$

18\. Cysteine: $HSCH_2CH(NH_2)COOH$

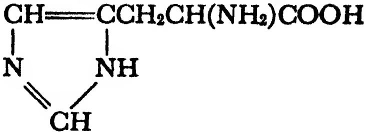
B. Basic Amino Acids (several basic groups and one acid group):

1\. Lysine: $CH_2NH_2CH_2CH_2CH_2CH(NH_2)COOH$

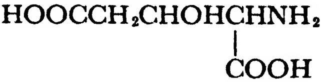
2\. Arginine:

$$NH{=\!=}\overset{\overset{\displaystyle NH_2}{|}}{C}NHCH_2CH_2CH_2CH(NH_2)COOH$$

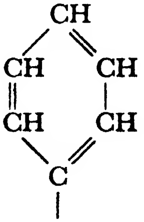
3. Histidine:



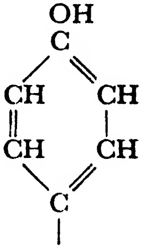
C. Acid Amino Acids (several acid groups and one basic group):

1. Aspartic acid:	$HOOCCH_2CH(NH_2)COOH$
2. Glutamic acid:	$HOOCCH_2CH_2CH(NH_2)COOH$
3. β-Hydroxyglutamic acid:	 $HOOCCH_2CHOHCH(COOH)NH_2$

Heterocyclic and Aromatic Groups. The student will note that in several of the amino acids, he encounters for the first time special cyclic groups. In particular he will find in phenylalanine (A7), the phenyl group, $C_6H_5—$, encountered earlier in Buna S synthetic rubber, and in tyrosine (A8) the closely related hydroxyphenyl group, $HOC_6H_4—$. The structures of these two cyclic groups are:



$C_6H_5—$ Phenyl



$HOC_6H_4—$ Hydroxyphenyl

We shall consider in Chaps. 16 to 20 the special chemistry of this type of unsaturated ring which is called an *aromatic ring*. The same ring occurs in thyroxine (A14) and iodogorgoic acid (A15). Still more complex unsaturated rings containing nitrogen are present in tryptophane (A13) and histidine (B3).

Classification. The alpha amino acids have been classified above according to the relative number of acid and basic groups in the molecule. The importance of this relationship from the point of view of the behavior of the substances will soon become apparent. Although tryptophane has a cyclic $>$NH group in addition to the alpha amino group, it is placed in group A because the second nitrogen atom has no basic properties. On the other hand, the $>$NH groups in the saturated rings in proline (A11) and hydroxyproline (A12) and in the heterocyclic ring in histidine (B3) are basic. The hydroxyl group in tyrosine is weakly acidic; if this group is counted as an acid group, tyrosine would be put in class C.

With the exception of glycine (α-aminoacetic acid) all the alpha amino acids contain one or more asymmetric carbon atoms. Therefore, as would be expected, those amino acids which are prepared from proteins are optically active.

Synthesis of Alpha Amino Acids. The appropriate fatty acid is halogenated in the alpha position by the action of chlorine on the acid itself or of bromine on the acid bromide.

$$CH_3COOH + Cl_2 \longrightarrow CH_2ClCOOH + HCl$$
$$CH_3COBr + Br_2 \longrightarrow CH_2BrCOBr + HBr$$

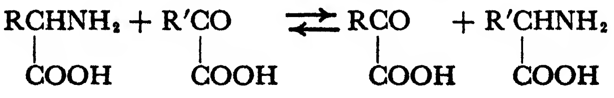
On treatment with ammonia, alpha chloro or bromo acids readily yield alpha amino acids.

$$CH_2ClCOOH + 2NH_3 \longrightarrow CH_2NH_2COOH + NH_4Cl$$

Another method of preparation of alpha amino acids involves the reduction of alpha ketonic acids in the presence of ammonia.

$$RCOCOOH + NH_3 + 2[H] \longrightarrow RCH(NH_2)COOH + H_2O$$

Transamination. The methods by which plant and animal cells synthesize amino acids and proteins are still largely unknown. It seems probable, however, that some of the amino acids are formed from the corresponding alpha keto acids. Specific catalysts (enzymes) have been found in nature which bring about the interchange of amino and keto groups in the alpha position according to the following general reaction.



$$\underset{\displaystyle COOH}{\underset{|}{RCHNH_2}} + \underset{\displaystyle COOH}{\underset{|}{R'CO}} \rightleftarrows \underset{\displaystyle COOH}{\underset{|}{RCO}} + \underset{\displaystyle COOH}{\underset{|}{R'CHNH_2}}$$

An inspection of the formulas will show that the amino acid alanine corresponds to pyruvic acid, glutamic acid to keto glutaric acid, and aspartic acid to oxaloacetic acid; all three of these keto acids are important intermediates in glucose metabolism.

Amino Acids as Inner Salts. The amino acids have both basic and acidic properties; when treated with mineral acids or strong bases they form crystalline salts in which the organic residue is the cation or the anion. The neutral molecule itself is in a sense a salt for the hydrogen atom of what would be the carboxyl group is joined to the basic nitrogen atom. Thus the correct formula for an amino acid is $R\underset{\underset{\displaystyle COO^-}{|}}{C}HNH_3^+$. This inner formula corresponds to the physical and chemical properties of the amino acids.

$$R\underset{\underset{\displaystyle COOH}{|}}{C}HNH_3Cl \underset{HCl}{\overset{NaOH}{\rightleftarrows}} R\underset{\underset{\displaystyle COO^-}{|}}{C}HNH_3^+ \underset{HCl}{\overset{NaOH}{\rightleftarrows}} R\underset{\underset{\displaystyle COONa}{|}}{C}HNH_2$$

The total net electrical charge on the organic molecule will clearly depend on the acidity of the solution. In acid solution the amino acid will be present as a positive ion, $RCHNH_3^+COOH$, in alkaline solution as a negative ion, $RCHNH_2COO^-$, and at a certain acidity the *net* charge will be zero since the molecule has the structure $RCHNH_3^+COO^-$. In acid solutions, the amino acids migrate to the cathode (−) when the solutions are electrolyzed; in alkaline solutions, the molecules move to the anode (+). At a definite hydrogen ion concentration, when the net charge is zero, the compound moves neither to the cathode nor to the anode. This point is known as the *isoelectric point.* Its value depends on the relative strengths and number of acid and basic groups in the amino acid molecule.

Dipolar Ions. It is not surprising to find that organic molecules which are inner salts are in a class by themselves. We may speak of such molecules as dipolar ions. The amino acids and proteins are by far the most important examples. The amino acids, though of low molecular weight, are nonvolatile solids. This means that the forces holding the molecules to each other are very large; indeed, they are comparable with the forces holding the ions together in salts. Many amino acids are not only nonvolatile solids, but they even decompose before melting — additional evidence of the strong forces holding the crystal lattice together. They are extremely insoluble in all nonpolar solvents (such as hydrocarbons) and are relatively far more soluble in water or salt solutions. Many of them will form quite concentrated solutions in water. This is so because they greatly increase the dielectric constant of the solution, which in turn means that the dipolar ions are more soluble.

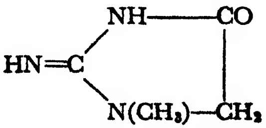
Reactions of Amino Acids. As would be expected, the alpha amino acids show the characteristic reaction of both organic acids and primary aliphatic amines. They are readily esterified in the usual manner and the esters may be purified by distillation. This fact may be taken advantage of in the separation of the acids of group A. The reaction with nitrous acid liberates nitrogen and forms a hydroxy acid (p. 158). This is the basis of a convenient quantitative method used in studying amino acids and proteins.

$$RCHNH_2COOH + HNO_2 \longrightarrow RCHOHCOOH + N_2 + H_2O$$

Creatine. $NH_2C(=NH)N(CH_3)CH_2COOH$. In addition to the amino acids which have been obtained from the hydrolysis of proteins (listed above), a few others also occur in nature. The most important of these is creatine, which may be regarded as derived from glycine since it contains the chain $N—CH_2COOH$.

Creatine is present in muscle tissue partially free and partially combined (amide linkage) with the phosphoric acid group. Creatine phosphoric acid together with adenosine triphosphate (p. 375) are involved in the changes which take place during contraction and relaxation of muscle.

Small amounts of creatine are normally excreted in the urine in the form of a cyclic compound creatinine formed by the loss of water between the amino and carboxyl groups in creatine.

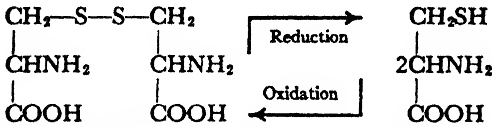


Ornithine. Another alpha amino acid, not itself a product of protein hydrolysis, but closely related to one of the twenty-four acids, is α,δ-diaminovaleric acid, $NH_2CH_2CH_2CH_2CH(NH_2)COOH$, known as *ornithine.* It is produced in the liver by the hydrolysis of arginine by the enzyme **arginase.** It has been shown that ornithine goes through a cyclic process by which the liver synthesizes urea from ammonia and carbon dioxide. Each step is brought about by an enzyme but only the last step can be brought about outside the intact cell by an enzyme preparation.

$$NH_3 + CO_2 + \underset{\text{Ornithine}}{NH_2(CH_2)_3CH(NH_2)COOH} \longrightarrow \underset{\text{Citrulline}}{NH_2CONH(CH_2)_3CH(NH_2)COOH} \xrightarrow{+NH_3}$$

$$\underset{\text{Arginine}}{NH_2C(=NH)NH(CH_2)_3CH(NH_2)COOH} \xrightarrow{+H_2O} \text{Urea} + \text{Ornithine}$$

Cysteine and Cystine. Cystine is a disulfide which on reduction readily forms two molecules of cysteine, which contains the mercaptan group (—SH). On oxidation cysteine forms cystine.



$$\begin{array}{lll} CH_2\text{—}S\text{—}S\text{—} & CH_2 & \\ | & | & \\ CHNH_2 & CHNH_2 & \\ | & | & \\ COOH & COOH & \end{array} \underset{\text{Oxidation}}{\overset{\text{Reduction}}{\rightleftarrows}} \begin{array}{l} CH_2SH \\ | \\ 2CHNH_2 \\ | \\ COOH \end{array}$$

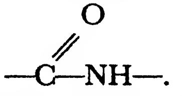
Cystine Cysteine

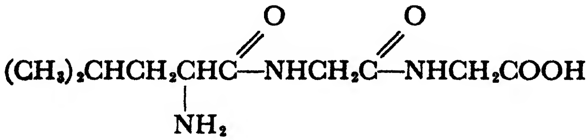
Glycine Derivatives. The simplest amino acid glycine is found combined with a variety of substances as acyl derivatives. Thus **hippuric acid** or benzoylglycine, $C_6H_5CONHCH_2COOH$, is excreted in the urine of animals which are fed benzoic acid C_6H_5COOH (p. 304). The **bile salts** found in the liver and stored in the gall bladder are a mixture of sodium glycocholate and sodium taurocholate; both contain the complex acid cholic acid, $C_{23}H_{36}(OH)_3COOH$ (p. 346), joined as an acyl group to the amino group of an amino acid. In glycocholic acid, the amino acid is glycine, in taurocholic acid it is **taurine,** $NH_2CH_2CH_2SO_3H$. Taurine contains a sulfonic acid group $—SO_3H$, it should be noted; it is not a member of the class of amino acids of which proteins are composed, but one of the relatively few derivatives of sulfuric acid found in nature. The bile salts are an aid to digestion, having the property of keeping the lipids in aqueous solution or emulsion.

PEPTONES AND POLYPEPTIDES

Proteins are completely hydrolyzed to amino acids by boiling for several hours with 10 per cent sulfuric acid or 30 per cent hydrochloric acid. The decomposition is also brought about by **enzymes.** These are involved in the digestion of proteins. **Pepsin** is present in the stomach and acts in a somewhat acid solution; **trypsin,** which occurs in the pancreatic juice, and **erepsin,** in the intestines, are involved also in the complete disintegration of the complex molecule. Each animal undoubtedly resynthesizes from the individual amino acids the particular proteins which constitute its tissue.

By studying the action of the proteolytic enzymes which can be isolated from living tissue, it has been possible to obtain mixtures of substances which are intermediate between proteins and amino acids. These are known as *proteoses* and *peptones.* They are water-soluble materials; unlike most proteins they do not coagulate on heating. Their molecules must be a great deal smaller than those of the proteins but they are still complex substances.

The synthetic work of Emil Fischer showed that the proteoses and peptones are built up of many molecules of amino acids joined by the amide linkage,  $-\overset{O}{\overset{/\!/}{C}}-NH-$. Fischer synthesized substances which he called *peptides.* The simplest is **glycylglycine,** $CH_2NH_2CONHCH_2COOH$; this is a **dipeptide.** A more complicated example is **leucyl-glycyl-glycine,** a **tripeptide.**



$$(CH_3)_2CHCH_2\underset{\displaystyle NH_2}{\underset{|}{CH}}\overset{O}{\overset{/\!/}{C}}-NHCH_2\overset{O}{\overset{/\!/}{C}}-NHCH_2COOH$$

The most complicated peptide that he prepared was composed of eighteen molecules of amino acids (fifteen of glycine and three of leucine). This substance had a molecular weight of 1213 and in its general behavior was very similar to the natural peptones and proteoses. This polypeptide was even hydrolyzed by the enzymes, trypsin and erepsin. When it is recalled that the action of enzymes is very specific, it is clear that this fact is important evidence for the similarity between the synthetic material and the partial decomposition products of proteins.

A consideration of the structure of a peptide makes it evident why these substances can be hydrolyzed. The reaction is exactly like the hydrolysis of an amide (p. 152) and like this process is catalyzed by hydrogen or hydroxyl ions.

The Synthesis of Polypeptides. Fischer employed a number of closely related methods in his synthesis of complex polypeptides. Two examples only will be given. The acid chloride of an alpha halogen acid can be readily prepared from the alpha halogen acid. If this substance is treated with an amino acid, the following reaction takes place.

$$ClCH_2COCl + H_2NCH_2COOH \longrightarrow ClCH_2CONHCH_2COOH$$

On treating the product with ammonia, a dipeptide is formed.

$$ClCH_2CONHCH_2COOH + 2NH_3 \longrightarrow CH_2NH_2CONHCH_2COOH + NH_4Cl$$

The acid chlorides of the amino acids themselves are very difficult to prepare. These acid chlorides will react with an amino acid, producing a dipeptide, or with a dipeptide, forming a tripeptide. An example of the latter reaction would be the preparation of glycyl-glycyl-glycine.

$$CH_2NH_2COCl + H_2NCH_2CONHCH_2COOH \longrightarrow CH_2NH_2CONHCH_2CONHCH_2COOH$$

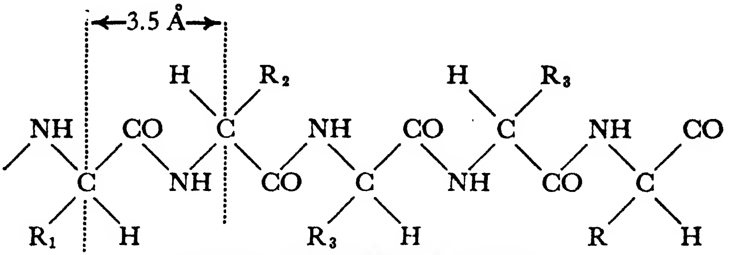
It is evident that by repeating either of these two methods a molecule may be constructed containing many of the simple amino acid residues. However, the preparation of acid chlorides of amino acids containing other reactive groups, such as hydroxyl, is not possible. As a result the methods just described are not applicable to the synthesis of polypeptides composed of acids of groups B and C (pp. 221–222) or even the more complicated acids of group A. Since Fischer's work, numerous special procedures, which are too involved for inclusion in this book, have been devised for synthesizing peptides from the more complicated amino acids.

PROTEINS

In considering the structure of the proteins, it is convenient to recognize at the outset two large subdivisions of this great class of naturally occurring compounds. In one group we may place those fibrous insoluble proteins such as constitute the major part of wool, hair, silk, and the connective tissues of animals. In the other we may place all the other plant and animal proteins which are soluble without decomposition in either water, water-alcohol mixtures, dilute aqueous salt solutions, or dilute aqueous alkali or acid. The substances in both classes are clearly of very high molecular weight and on hydrolysis are completely broken down to a mixture of amino acids. The differentiation of proteins into these two groups corresponds not only to very different physical and chemical properties (e.g., solubility), but also to a somewhat different composition and to a different shape of the molecule.

Hair and silk are nearly pure proteins; the former is known as *keratin*, the latter as *fibroin*. They dissolve only in strong acids and bases and are at least partially decomposed under these conditions. They are insoluble in all the ordinary solvents. By using essentially the same technique as is employed in determining the structure of crystals by x-ray diffraction, it has been shown that fibroin and keratin molecules contain a recurring pattern of atomic centers which are the recurring links of a peptide chain.

Certain protein fibers show two different x-ray patterns according to whether they are stretched or unstretched. The distances between recurring centers is much greater in the stretched form. This indicates that in the normal fiber the chain is somewhat coiled by virtue of attraction, perhaps, between alternating CO and NH groups. This would bring the side chains represented by R_1R_2 (below) nearer together. It is the recurring pattern of these branches which produces the characteristic x-ray diffraction. The distance between CHR groups in the extended chain is 3.5 Å according to the x-ray measurement.



Fragment of keratin molecule in stretched fiber

ment. If this structure is correct proteins must be regarded as condensation polymers (p. 173) of the amino acids. Starch, cellulose, and glycogen may likewise be regarded as condensation polymers of a simple sugar. The proteins are unique, however, as being also copolymers (p. 76) with a large number of different building units. This means that according to the arrangement of the building blocks there may be a host of individual proteins of the same general composition and class. The individuality of living organisms is undoubtedly closely related to this fact.

Classification of Proteins. Leaving aside the inert proteins we have just been considering, we may classify the others by their solubility relations. This is a rough, empirical, but useful classification, and we shall see that it is not unrelated to the preponderance of one type of amino acid or another in the molecule.

1. Albumins: Soluble in water and dilute salt solutions. **Egg albumin** (white of egg) is an example.
2. Globulins: Insoluble in water but soluble in dilute solutions of neutral salts. The vegetable protein, **edestin** (from hemp seed), and the animal protein, **serum globulin** (in the blood serum), are two examples of this class.
3. Glutelins: Insoluble in water or dilute neutral salt solutions. Soluble in alkaline or acid solution. **Glutenin,** which occurs in wheat, is a representative.
4. Prolamines: Insoluble in water or dilute salt solutions. Soluble in 80 per cent alcohol. All the representatives of this

class are vegetable proteins. **Zein** occurs in corn, **gliadin** in wheat.

5. Histones and Protamines: Basic proteins, soluble in water and acids. The two classes are usually separated on the basis of the insolubility of histones in ammonia. Protamines occur in ripe fish sperm.

In some classifications, fibroin, keratin, and the other fibrous proteins are classified as a sixth group, **albuminoids.** The name which suggests some relation to the albumins is, however, unfortunate.

Acid and Basic Properties. A large number of the proteins are amphoteric substances, that is they combine with acids or bases forming water-soluble salts. This process is strictly reversible unless very strong acid or alkali is employed; this may alter (denature) the protein. The globulins and glutelins which are insoluble in water dissolve in dilute acid or basic solution because they form water-soluble salts.

Like the amino acids, each amphoteric protein will migrate during electrolysis of the solution to either the anode or cathode, depending on the acidity of the medium. The **isoelectric point** at which no migration takes place is an important characteristic of each protein.

In general, proteins are least soluble *near* their isoelectric point. Therefore, in "salting out" proteins or precipitating water-insoluble proteins, care is taken to bring the acidity of the solution to the proper value. For egg albumin this is a hydrogen ion concentration of 15×10^{-6}; for hemoglobin, 2×10^{-7}. It will be recalled that pure water has a hydrogen ion concentration of 1×10^{-7}.

The Significance of Acid and Basic Amino Acids. If the protein molecules were composed only of the amino acids listed in class A of our tabulation (p. 220), they would be neutral substances without acid or basic properties. An approach to this condition is found in keratin and fibroin. If a large proportion of the constituent amino acids were of class C, the side chains would carry carboxyl groups. Unless these groups were present as amides (as in wool), the protein should be able to form salts with bases. The presence of a large proportion of basic amino acids (group B) in a protein should enable it to form salts with acids. If, however, representatives of both class B and C were present in goodly number, the large molecule should be amphoteric. This is the case with egg albumin, for example, which contains about 10 per cent of basic amino acids and about 15 per cent of acidic amino acids (class C). An examination of the amino acids formed by hydrolysis has shown that *the acid and base binding capacity of different proteins is determined by the nature of the amino acids of which their molecules are composed.*

A few examples will make this clear. Zein, which is so little basic that it will not dissolve in acids, contains an extremely small amount of basic amino acids. The protamines, which are basic, yield on hydrolysis large amounts of amino acids with basic groups (class B).

Purification of Proteins. The method of purifying proteins is based on their solubility. All proteins are insoluble in a concentrated salt solution such as saturated ammonium sulfate. Water-soluble proteins, therefore, may be "salted out" by the addition of solid ammonium sulfate. The precipitate redissolves on treatment with pure water. A number of proteins have been obtained in the crystalline condition by careful regulation of the hydrogen ion and salt concentration of saturated solutions. The recrystallization of such proteins is the best method of purification. The crystals are kept moist throughout the procedure as drying alters most soluble proteins to some extent.

During World War II the many important soluble proteins in blood plasma were separated with great success by precipitation at 0° to − 10° with organic solvents such as ethyl alcohol. By varying the salt concentration of the aqueous solution, the acidity, the temperature, the alcohol concentration, and the total protein concentration in a systematic fashion the separation of sensitive proteins has been done on a large scale. The alcohol can be removed in a vacuum at low temperature, whereas, if salt is used as a precipitant, it can only be removed by a tedious dialysis.

Irreversible Precipitation of Proteins. The reversible precipitations just mentioned are very different from the *irreversible precipitation* of proteins which is brought about by a number of reagents such as **trichloroacetic acid, tannic acid, picric acid, concentrated nitric acid,** and **phosphotungstic acid.** The mercury, lead, and copper salts of proteins precipitate when soluble salts of these metals are added to protein solutions. This is also essentially an irreversible process as the original protein cannot be obtained from these precipitates. The precipitation of proteins by such reagents is useful in testing for proteins or removing them from a solution, but cannot be used in purification as the process in some way alters the material.

Most water-soluble proteins are irreversibly precipitated when their solutions are heated. The "cooking" of white of egg is a common example of the **heat coagulation** of a protein.

Molecular Weights of Proteins. Even the water-soluble proteins are substances of very high molecular weight. The usual direct methods of determining molecular weight, for example, by the observation of the freezing point of solutions of known concentration cannot be employed. With substances of large molecular weight the depression is too slight to be measured accurately, and the presence of even small quantities of inorganic impurities would vitiate the result. Some determinations of the osmotic pressure of protein solutions have given fairly satisfactory information about the molecular weights, but the most reliable method depends on the use of the ultracentrifuge. In this procedure a solution of the substance of high molecular weight is spun at very high speeds. The centrifugal force thus generated moves the dissolved molecules away from the center. While the container is still being rotated at the desired speed the concentration gradient from the center to the outside edge is determined by a photographic method. Knowing the speed, the dimensions of the ultracentrifuge, and the change in concentration of the protein solution throughout the revolving container, it is possible to calculate the molecular weight. Some of the results obtained are given below.

MOLECULAR WEIGHTS OF SOME PROTEINS

Lactalbumin	17,500	
Gliadin	27,000	
Zein	50,000	
Insulin	46,000	
Egg albumin	43,000	(By osmotic pressure, 45,000)
Hemoglobin	68,000	(Same value by osmotic pressure)
Serum albumin	68,000	(By osmotic pressure, 70,000)
Serum globulin	167,000	(By osmotic pressure, 156,000)
Phycocyan	272,000	
Edestin	309,000	
Hemocyanin	8,900,000	

In solution the proteins are probably present in more or less spherical globular form. When they are distributed as a thin film, however, on the surface of a liquid, the soluble proteins appear to approach the condition of the fibrous proteins; the molecules then consist of parallel, extended, polypeptide chains.

Denaturation. Perhaps the most characteristic property of the soluble proteins is the ease with which they undergo a change known as *denaturation*. A denaturated protein is less soluble than the normal (or native) protein and it will not crystallize. Drying, treatment with rather concentrated acid or alkali, and the addition of alcohol to an aqueous solution at room temperature, denature many proteins; a concentrated solution of urea is also an effective agent for bringing about denaturation. The rate of denaturation increases rapidly with increase in temperature. Therefore many solutions of proteins can be kept for long periods of time at 0° but are rapidly denatured at 50° to 60°. The ease with which many proteins are thus altered makes the manipulation of this class of substances peculiarly difficult. The techniques employed with proteins are, therefore, quite different from those used with most organic compounds.

The coagulation of protein solutions on heating and the precipitation with many reagents, such as metallic salts and tannic acid, are examples of extreme denaturation. Certain proteins, if denatured by relatively mild reagents, can be slowly restored to the native state by dissolving in alkali and then adjusting the hydrogen ion concentration to a proper value. Measurements of the molecular weight by the osmotic pressure method indicate that in a number of instances there is no change in the molecular weight on denaturation. With a few proteins of very high molecular weight, denaturation appears to involve a dissociation of the molecule into as many as six parts.

Conjugated Proteins. A totally different method of classifying proteins from the one we have been using is sometimes employed. Proteins are divided into simple proteins, which yield only amino acids on hydrolysis; and others, called *conjugated proteins*, in which some other component is linked to the protein. The nonprotein portion is called a **prosthetic group.** If the group confers color on the protein, as in hemoglobin and the colored proteins present in algae (**phycocyan**), the protein may be known as a *chromoprotein.* If the prosthetic group is a carbohydrate the substance is a **glucoprotein.** Glucoproteins are found in mucous secretion. **Casein** (from milk) is often classed as a **phosphoprotein** as the prosthetic group contains phosphoric acid. The **nucleoproteins** contain a nucleic acid (p. 373) residue linked to the protein molecule. When the prosthetic group is colored it is easily recognized. In some proteins, e.g., hemoglobin, the prosthetic group is attached by a linkage that may be attacked by certain reagents without hydrolyzing the protein. If the prosthetic group is joined by an amide linkage, it may not be possible to separate it from the rest of the molecule without drastic decomposition of the protein. There may be a number of prosthetic groups (i.e., residues other than amino acids) which have not yet been isolated and identified from well-known proteins.

Virus Proteins. The filterable viruses are a group of nucleoproteins of great importance. In spite of their very high molecular weight (15,000,000 to 20,000,000), some of the filterable viruses have been isolated in crystalline condition by the usual procedures of protein chemistry. They are responsible for the transmission of various diseases of plants and animals. The first one to be isolated in crystalline condition was the virus which causes the tobacco mosaic disease. When denatured or slightly modified by the action of reagents, the protein loses the power of inducing the disease. A study of the physical properties of the virus proteins indicates that the molecules are rod-shaped.

The name *filterable virus* was originally given to these disease-producing agents because they would pass through filters which would hold back even the smallest bacteria. Unlike bacteria and almost all infectious organisms, filterable viruses do not multiply apart from the living cells of the plant or animal they infect. Virus particles range in size from 100 Å to 3000 Å. The smaller viruses are of the same order of size as the largest nonvirus proteins known. For example, hemocyanin, the blue protein which contains copper and transports oxygen in the horseshoe crab, has a molecular weight of nearly 9,000,000; this corresponds to a spherical molecule of about 250 Å diameter. The largest virus molecules studied, however, correspond to organisms which have been long recognized as living and which can multiply outside a living cell (diameter greater than 1500 Å). Thus from the point of view of size and the ability to infect a large organism (the host), there is no sharp distinction between viruses and the smallest living organisms which transmit disease. Whether there is a sharp distinction in regard to complexity of structure and the methods of reproduction or growth is still undetermined.

QUESTIONS AND PROBLEMS

1. What are the three general classes into which the naturally occurring amino acids may be conveniently divided?

2. Write structural formulas for two representatives of each of the three classes of amino acids.

3. In what respects are the members of the three classes similar? In what respects different? (Consider physical properties and chemical reactions.)

4. Would you expect alanine to be more or less soluble in water solutions containing (*a*) glycine, (*b*) a tetrapeptide, (*c*) albumin? Why?

5. By what chemical reactions could you distinguish between a dilute aqueous solution of (*a*) egg albumin, (*b*) a partially hydrolyzed

albumin, and (*c*) a mixture of the amino acids resulting from complete hydrolysis?

6. Outline two methods for preparing alpha amino acids.

7. How may polypeptides be synthesized?

8. Name three common substances of widely different properties which are proteins. What characteristics have they in common? What economic importance has each of these substances and on what properties does the economic importance of each depend?

9. If a water-insoluble protein yielded chiefly dibasic monoamino acids on hydrolysis and little or no ammonia, what would you predict in regard to its solubility in dilute acids and alkalies?

10. Define the terms: *prosthetic group*, *filterable virus*, *denaturation*, *isoelectric point*, *prolamine*, *protamine*, *conjugated protein*.

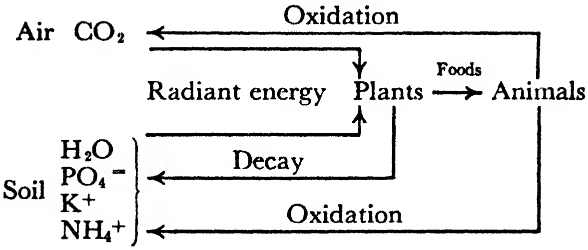
11. Gelatine is a partially hydrolyzed fibrous protein prepared commercially from hides. How would you distinguish it from a gelatinous carbohydrate, agar-agar? How would you determine the amount of gelatine in a mixture of the two?

12. Compare and contrast the phenomena of: (*a*) cooking an egg, (*b*) destroying bacteria by sterilization, (*c*) inactivation of an enzyme by heating.

CHAPTER 15

Biochemical Processes

The plant and animal products which we use in everyday life as food, for clothing, and for structural materials must be regarded as basically the product of photosynthesis. Similarly, as was pointed out in the introduction, coal and petroleum and materials produced from them represent the storage of the radiant energy of the sun by photosynthesis. The oxidation of foodstuffs represents the liberation of energy and the reconversion of the carbon atoms to carbon dioxide. This is the carbon cycle mentioned in the introduction. A similar cycle is involved in the formation and decomposition of nitrogen-containing compounds, particularly the proteins. Ammonia, inorganic nitrates, and such simple organic nitrogen compounds as urea (p. 153) are absorbed by plants and provide the necessary nitrogen atoms for the building of proteins. In the subsequent decomposition of the proteins, ammonia and urea are formed and returned to the soil. Elementary nitrogen cannot be absorbed by plants or animals, but certain bacteria have the property of converting the element into nitrogen compounds that can be utilized. These bacteria are present on the roots of leguminous plants such as peas and clover; by growing these plants the soil may be enriched in the nitrogenous material requisite for plant growth. Phosphorus and potassium are two other elements which must be present in considerable amounts in the soil in an assimilable form. Small quantities of many other elements such as sulfur, iron, and copper appear to play an important part in the growth of plants; they are usually present in sufficient amounts in the soil. The carbon, nitrogen, potassium, phosphorus cycles may be schematically represented as follows:



Photosynthesis. In spite of a great deal of experimentation and speculation about the mechanism of photosynthesis we are still far from having a clear picture of this essential biological process. Some of the earlier simple hypotheses, such as the assumption that formaldehyde is the first product, have been definitely disproved. The overall process may be partially summarized by the equation:

$$CO_2 + \underset{\text{(From water)}}{2[H]} + \text{Energy (as light)} \longrightarrow \underset{\substack{\text{(As complex}\\\text{compounds)}}}{\{CH_2O\}} + \tfrac{1}{2}O_2 \text{ (as gas)}$$

Photosynthesis is certainly a complex process and involves at least four and perhaps many more steps in each of which an increment of radiant energy enters into the reaction. The green coloring material of all photosynthetic plants is essentially the same and is known as *chlorophyll* (p. 361). This material absorbs the radiant energy of sunlight; whether or not it also enters directly into a series of oxidation or reduction reactions is uncertain. The overall reaction of photosynthesis is the hydrogenation (reduction) of carbon dioxide by water, the energy being supplied from outside. Until recently no evidence as to the intermediates was available; the first products to be identified were carbohydrates. Using radioactive carbon isotopes, however, it has been possible to show that in some plants the tagged carbon dioxide is absorbed in the absence of light with the formation of a carboxyl group. In the light this group disappears, probably through reduction. If the carboxyl group is thus involved its carbon atom must eventually turn up in the sugars, fats, and proteins in the state of reduction corresponding to an aldehyde, an alcohol, or a hydrocarbon.

About one-half of the energy in sunlight is of the wavelengths which can be absorbed by chlorophyll and which, therefore, is available for utilization in photosynthesis. Recent experiments have shown that under the most favorable conditions the efficiency of utilization of this light is about 65 per cent. Since the growing season is usually about one-third of the year, one can estimate that the maximum utilization of the radiant energy of sunlight theoretically possible in nature is $\frac{1}{2} \times \frac{1}{3} \times 65$ per cent or about 11 per cent. It is interesting to compare this figure with the conversion of sunlight into stored energy under very favorable conditions of a corn crop; assuming 100 bushels of shelled corn per acre and allowing for the organic material in the cobs, leaves, etc., one can estimate that 20×10^6 kcal of radiant energy are thus stored. The total radiant energy falling on this acre as sunlight throughout the year is 7300×10^6 kcal; the efficiency is therefore about 20/7300 or 0.0027 or 0.27 per cent.

Until a few years ago it was believed that the only way in which living organisms could obtain energy for a synthetic process was by absorbing light. We now know that this is not so. In plant and animal cells the fixation of carbon dioxide by hydrogenation (reduction) can take place without the absorption of light; the necessary energy may be supplied by oxidation reactions which are coupled with the reduction. Certain bacteria, for example, oxidize hydrogen sulfide to sulfur and sulfur to sulfuric acid; the energy thus liberated enables the bacterial cells to reduce carbon dioxide. It has been suggested that this type of **chemosynthesis** was involved in the early evolution of living cells and that photosynthesis represents a later development. Today, however, the role of these microorganisms is insignificant. Much more important is the fact that *many living cells of plants and animals reduce carbon dioxide to carbohydrates even while carbohydrates or their degradation products are being oxidized to carbon dioxide.*

This remarkable fact has been established by using carbon dioxide in which the carbon atom was either a heavy or light isotope of the normal carbon of atomic weight 12. The isotopic carbon was found in the carbohydrate even when the living cells were evolving carbon dioxide. This shows that the assimilation of carbon dioxide is a very general phenomenon probably characteristic of many, if not all, living cells.

We can no longer regard the synthesis of organic compounds from carbon dioxide as a reaction confined to green plants and a few bacteria. Nevertheless it is clear that only when the energy for the synthesis comes from some source other than the oxidation of organic compounds is there a real net gain in stored-up energy. Therefore, the significance of the *green plants as the primary source of organic compounds* is not altered by the new findings. The bacteria which oxidize inorganic substances are of very minor importance. We may still say that the green plants store up the energy of sunlight to the extent of some 100 to 150 kcal per mole of carbon dioxide, and the subsequent oxidation reactions in the plant or animal cells release this energy.

Metabolism. The chemical reactions which occur in living cells are often referred to as metabolic changes or *metabolism*. Sometimes the words *anabolism* and *catabolism* are used to designate the building up and the breaking down of complex molecules respectively. When the building-up process starts with carbon dioxide and uses light energy, we speak of *photosynthesis;* when the energy is supplied by other reactions the process is often referred to as *chemosynthesis*. This latter term may also be used when other substances than carbon dioxide are the primary factors.

A great variety of metabolic changes are going on all the time in living cells. For the most part we observe only the *net* change with respect to those substances which disappear and those which appear outside the cells. The two gases, oxygen and carbon dioxide, are obviously of prime importance and by measuring the absorption and evolution of these gases by an organism or by a group of cells one can learn a good deal about the net changes which are taking place. For example, if photosynthesis is taking place rapidly, carbon dioxide disappears and oxygen appears rapidly. Conversely, if oxidation is taking place rapidly and is not offset by a chemosynthetic process involving carbon dioxide, oxygen is absorbed and carbon dioxide is evolved. The rate of evolution and absorption of these gases is a measure of the rate of chemical activity within the cells and is sometimes referred to as the *metabolic rate.* The rate at which energy is liberated or absorbed in photosynthesis is closely related to the metabolic rate.

In a simple organism, a great variety of catabolic and anabolic reactions must occur within a single cell; this is true of the green algae, for example, which grow on inorganic aqueous media and carbon dioxide by a photosynthetic process. It is also true of yeasts and molds and bacteria which obtain their energy by oxidizing the organic materials (usually carbohydrates and proteins) on which they live by means of atmospheric oxygen (aerobic conditions) to carbon dioxide. In the absence of oxygen (anaerobic conditions) these colorless organisms obtain energy by converting their nutrient materials into products other than carbon dioxide; for example, lactic acid or ethyl alcohol may be formed. These anaerobic catabolic processes are often referred to as *fermentation.*

The Metabolic Pool. Very interesting evidence about the nature of the chemical transformations which go on in living tissue has been obtained by studying the higher animals. Not long ago it was thought that the body of a full-grown animal was nearly static, the organic compounds of which it was composed changed only slowly. If this were true, then the primary function of the foodstuffs would be to supply energy to keep the temperature of the body constant (in warm-blooded animals) and for mechanical energy (muscular work). The analogy with a combustion engine was sometimes stated. This point of view has been shown to be erroneous by feeding experiments in which organic compounds containing isotopic carbon, nitrogen, and hydrogen atoms were used. The "tagging" of certain of the atoms enabled the biochemist to trace their fate in the animal body. The "tagged" atoms were found widely distributed throughout the body, and the distribution took place very rapidly.

Many experiments have led to the conclusion that, even in a higher organism with clearly differentiated functions for different organs, the body seems to be perpetually in a state of flux. The appearance of stability is in a sense an illusion for it is only a *net* change which we ordinarily measure when we study foods, excreta, and tissue. It would appear that there is a sort of "metabolic pool" of relatively simple molecules in an organism from which the different types of cells keep reconstructing their components.

A candle flame is perhaps the nearest analogy we have in nonliving phenomena to a living organism. The flame appears to have a constant form or structure, but we know that it merely represents a balance between the fuel gases coming in and the products of combustion going out. The energy of the combustion heats the particles of carbon (product of the cracking of the fuel) to a glowing temperature. The candle itself is a mixture of complex compounds. To study the detailed reactions of the candle flame would seem nearly a hopeless undertaking, though to study the overall net effect is not hard at all. The biochemist is faced with a not dissimilar situation if the candle flame be the analog not of a higher organism but a single cell. He has been aided by the fact that cells differ a great deal in the predominant chemical reactions which take place within them; he has also been assisted by his ability to extract the catalysts involved in many processes. As a result we know a great deal about certain biochemical transformations, particularly the degradation of carbohydrates and their chemosynthesis. We know much less about their photosynthesis and almost nothing about the synthesis of proteins, though we have learned something about protein catabolism. Before considering a few special processes, some general considerations may not be out of place.

General Characteristics of Biochemical Processes. Water is necessary for life. All biochemical processes take place either in dilute aqueous solution or at or near the interface of such solutions with fatty or fibrous layers. The preservation of plant and animal material by desiccation depends on the fact that in the absence of water the enzymes which are initially present and would cause decomposition cannot act. For the same reason, bacteria, molds, and fungi cannot grow on dried material. With few exceptions, the aqueous fluids in plants and animals and the aqueous media on which organisms grow are nearly neutral. In the higher organisms the presence of salts of weak acids (particularly the phosphates) keeps the solutions at the proper acidity. In addition the presence of other salts keeps the osmotic pressure of the body fluids at the proper value.

As was pointed out in the introduction, biochemical reactions take place at an appreciable rate only in the presence of specific catalysts which are called *enzymes*. These enzymes are proteins and a number of them have been isolated in a pure crystalline condition. Like most reactions, these catalyzed biochemical transformations are accelerated by rise in temperature; some to a larger degree than the normal twofold increase per 10° rise. At temperatures of 0° and below a vast majority of them take place very slowly. On this fact depends the common practice of preserving foods by refrigeration.

Since the enzymes are proteins they can be denatured (p. 234) by heat or certain reagents. When they are denatured they are no longer active. In most common organisms, the enzymes are rendered inactive by heating for a short time above the boiling point of water. This is the basis for pasteurizing milk and sterilizing by heat; the denaturation of the proteins by heat destroys the enzymes and hence "kills" the bacteria in which they play literally the vital role. The preservation of plant and animal tissues in alcohol or with formaldehyde (present in embalming fluid) depends likewise on the denaturation of the enzymes. Preservation of material by small amounts of specific preservatives or antiseptics such as phenol (carbolic acid), salicylic acid, and similar substances is probably another story. Here we are dealing with special interactions between microorganisms and organic compounds. How specific this interaction may be is shown by the fact that some compounds which are nontoxic to higher organisms are very toxic to the microorganisms which cause disease (Chap. 23).

Essential Nutrients and Metabolites. The food of the higher animals contains proteins, fats, and carbohydrates. It has been found that certain amino acids must be present in the food supply; these essential amino acids apparently cannot be synthesized by the cells in the animal body. Small amounts of complex substances of widely differing structure, formerly known as accessory factors now called vitamins (p. 334), must likewise be present in the diet of animals if they are to be healthy.

The growth of unicellular organisms, particularly bacteria, has been studied in terms of the nutrient material in the medium in which they grow. There is an enormous range of what may be required as essential nutrients for a given organism. The biochemical processes in each cell demand a certain number of essential metabolites; if the cell cannot build these substances itself, they must be supplied from outside. Pathogenic bacteria are characterized by their inability to synthesize many essential metabolites and a study of the nature and function of these essential metabolites has thrown light on the action of drugs (p. 392).

Enzymes. Extracts of living cells contain those naturally occurring catalysts known as enzymes. By evaporating the extracts from certain plant and animal cells under diminished pressure at room temperature, amorphous powders can be obtained which have high catalytic activity. But such powders are still very impure and contain large quantities of inert organic and inorganic material.

A great step forward was made in the study of enzymes when it was found that certain crystalline proteins could be isolated which had high enzymatic activity. They retained this activity as the purification by crystallization proceeded. More than a dozen enzymes have now been prepared in the crystalline condition. They include urease (p. 154), several protein-splitting enzymes such as pepsin, and several enzymes required in the oxidation of carbohydrates. Like all proteins these substances are easily altered or denatured. When this occurs the enzymatic activity disappears. In a few instances this loss of activity can be restored by the same procedure used in reversing the denaturation of proteins. More often the change is irreversible. Enzymes usually lose their activity not only when heated, but also when treated with such powerful reagents as strong acids or strong alkalies or oxidizing agents. All these facts, taken together with what is known of the enzymes which have been crystallized, demonstrate that enzymes are proteins.

Enzymes are specific in their action. It will be recalled, for example, that emulsin will bring about the hydrolysis of beta glucosides but not of alpha, while maltase acts in just the reverse manner (p. 210). The catalytic activity of each enzyme is usually at a maximum at some temperature not greatly above room temperature and at a certain acidity. This maximum is the result of the operation of two conflicting tendencies: raising the temperature increases the rate of the reaction, but it also increases the rate of denaturation of the enzyme. The concentration of the material which is undergoing the chemical change (the substrate) is also often important. In certain processes, the accumulation of the products of the reaction slows down the enzymatic reaction. Coenzymes (or coferments) are relatively thermostable substances which are essential for the enzymatic action. Thus, calcium (in the ionic form) is a coenzyme for the clotting of milk by the enzyme rennin (conversion of the soluble protein caseinogen to the insoluble casein). We do not know why the calcium ions are necessary. Sometimes the thermostable molecule characteristic of the particular enzyme is so firmly attached to the protein that we consider it a *prosthetic* group (p. 235). In other enzymes the union is reversible and in solution the thermostable group is largely uncombined; the thermostable molecule is then called a *coenzyme.*

It has been often stated that the enzyme and substrate are related as a key to a lock. One can imagine that certain specific linkages must be present in both enzyme and substrate in order to allow the two substances to interact. Whether the interaction involves the formation of a chemical compound or is in the nature of adsorption is still an open question. Why the substrate undergoes chemical change after combination with or adsorption on the enzyme is far from clear. But there is nothing more mysterious about the nature of enzymatic action than about the action of catalysts in general. In a few instances, of which certain oxidizing enzymes are the best examples, the function of the prosthetic group or the coenzyme can be understood: the protein may be thought of as a carrier, but one essential for the action of the enzyme. The enzyme which decomposes hydrogen peroxide (catalase) and several oxidizing enzymes have prosthetic groups or coenzymes whose molecular structure has been determined.

Classification of Enzymes. Enzymes are often classified according to the chemical transformation they bring about. On this basis we may separate the enzymes which bring about hydrolysis from those which are involved in oxidation and reduction. Of the former we recognize the following special types.

SOME CLASSES OF HYDROLYZING ENZYMES

1. Esterases, which hydrolyze esters.
   a. Lipases which hydrolyze fats.
   b. Phosphatases which hydrolyze esters of phosphoric acid.
   c. Other esterases.
2. Proteinases which hydrolyze proteins.
3. Peptidases which hydrolyze peptides.
4. Urease which hydrolyzes urea.
5. Deaminases which remove amino groups by hydrolysis.
6. Carbohydrases.
   a. Amylases which hydrolyze starch and glycogen.
   b. Glycosidases which hydrolyze glycosides.

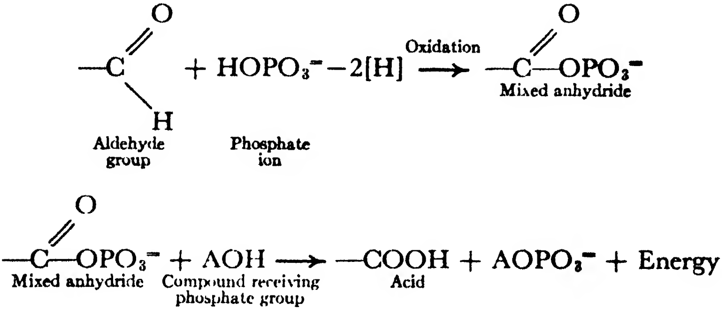
Closely related to the hydrolyzing enzymes are those enzymes (phosphorylases) which cause the transfer of a phosphate group from one compound to another in the course of carbohydrate metabolism, and those which bring about the cleavage of a complex carbohydrate by the introduction of a phosphate group. *Hexokinase* is the one example of the latter group. The enzyme which greatly accelerates the liberation of carbon dioxide gas from an aqueous solution of carbon dioxide is known as *carbonic anhydrase*. *Carboxylase* catalyzes the liberation of carbon dioxide from pyruvic acid. All three of these enzymes have been obtained in pure crystalline condition.

The oxidizing and reducing enzymes may be subdivided into those which contain a metallic atom and those in which the prosthetic group or coenzyme can add or lose two hydrogen atoms. Of the former, *peroxidase* which accelerates the decomposition of peroxides, *catalase* which acts in a similar fashion on hydrogen peroxide, and *cytochrome* all contain iron. Cytochrome which is distantly related to hemoglobin (p. 361) is involved in one of the steps in the oxidation of carbohydrates. Certain other oxidizing enzymes contain a copper atom. *Lactic dehydrogenase* and *flavoprotein* (an enzyme involved in respiration) are examples of oxidizing enzymes containing a strictly organic prosthetic group.

Among the enzymes which have been obtained in pure crystalline condition are urease, pepsin (a peptidase), trypsin (a proteinase), catalase, lactic dehydrogenase, flavoprotein, hexokinase, carboxylase, and carbonic anhydrase.

Equilibria and Rates in Biochemical Reactions. Catalysts, it will be recalled, change the rate of a reaction but do not alter the position of an equilibrium. Since in a living cell a continuous and rapid metabolic process is going on, we are concerned primarily with rates of *competing* chemical reactions. Furthermore, biochemical reactions as a rule liberate or absorb relatively small amounts of energy; a balanced or nearly balanced equilibrium is often at hand. It seems that living cells operate with reversible reactions where possible and can utilize or absorb energy in only small increments. Thus in the oxidation of carbohydrates a complex series of changes takes place so that at no one step is anything like the full amount of energy liberated which would result if all at once one carbon atom of a carbohydrate were oxidized by air to carbon dioxide.

Coupled Reactions. Coupled reactions are of the greatest importance in biochemistry. A very simple example of a coupled reaction was met early in this book in considering one of the industrial methods of preparing acetic anhydride (p. 140). In this process, the oxidation of acetaldehyde by oxygen, a strongly exothermic reaction was coupled with the dehydration of acetic acid to acetic anhydride, an endothermic reaction. As a consequence the overall reaction, acetaldehyde + oxygen → acetic anhydride + water, was slightly exothermic and proceeded to completion. In a somewhat similar fashion a number of endothermic reactions in living cells appear to be coupled with exothermic reactions. For example, one of the steps in the metabolism of sugars in the animal body involves the oxidation of an aldehyde group which provides energy and the fixation of a phosphate group on the newly formed carboxyl group which absorbs energy. Later, in the transformations, this phosphate group is transferred to other compounds with release of energy. The portion of the molecule involved in these changes is indicated in the following scheme.



The biochemist speaks of the bond between the carboxyl group and the phosphate in the mixed anhydride indicated above as an *energy-rich bond*. Hydrolysis of this anhydride, like the hydrolysis of acetic anhydride, proceeds with the evolution of considerable heat. Compounds with energy-rich bonds play an extremely important role in the chemistry of living cells. Their transformations are coupled with other reactions, and the energy released by the oxidation of carbohydrates is thus used by the organisms for bringing about many chemical reactions. Specific enzymes have been developed in nature which bring about many of the usual types of chemical reactions by specific paths so that the mechanism of the reaction will involve a substance with an energy-rich bond. It must be remembered that one cannot bring about a strongly endothermic reaction by placing the reactants in contact with other substances which will react and give off heat. The one reaction will make the other go only if both are coupled together in some way. This is provided in nature by special enzymes.

Carbohydrate Metabolism. Proteins, carbohydrates, and fats are the important classes of compounds found in plants and animals. The processes by which these compounds are built up and degraded have been the subject of intensive study by biochemists in recent years. We are still largely in the dark about the manufacture of proteins, but a mass of information has been obtained about the transformations of carbohydrates. For example, the energy required by an animal for muscular action is now known to be provided by the rapid decomposition of glycogen (p. 210), the reserve carbohydrate of the animal body. This is known as **muscle glycolysis.** The product is lactic acid and certain complex compounds containing an energy-rich phosphate bond. The latter then react with the protein of the muscle fiber and in so doing produce contraction of the muscles together with the liberation of heat. This rapid series of actions takes place without any oxidation. The slower recovery process, however, involves an oxidation of some of the lactic acid to carbon dioxide and water and the resynthesis of glycogen from the rest of the lactic acid. The complicated steps involve many coupled reactions. The steps by which the lactic acid is eventually oxidized to carbon dioxide probably involve first oxidation to pyruvic acid and then the cycle of reactions shown on pp. 180–181.

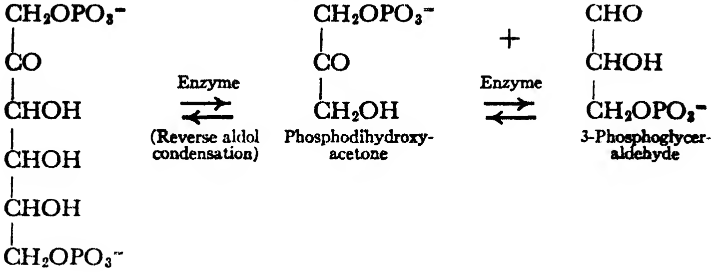
Metabolism of Glucose. The metabolism of glucose has been the subject of much intensive study. Not all the steps are known with certainty, and an exact description of all that is known would be too involved to be given here. However, a simplified outline of some of the steps is worth while.

In the metabolism of glucose important roles are played by a number of enzymes and by a complex phosphorylating agent, *adenosine triphosphate*, whose structure is considered later (p. 375). Here we shall refer to it as ATP, and to the corresponding diphosphate as ADP.

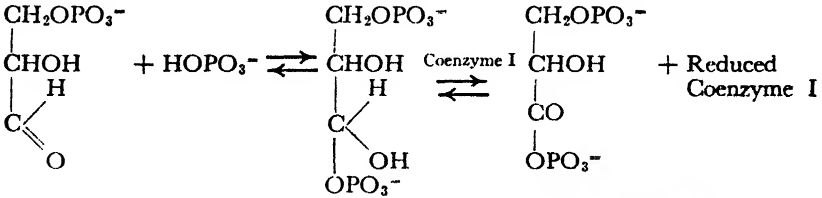
In the first step glucose is phosphorylated by ATP to glucose 6-phosphate which is enzymatically isomerized to fructose 6-phosphate. The latter product is phosphorylated by ATP to fructose 1,6-diphosphate which is cleaved reversibly to two three-carbon fragments. One of these, phosphodihydroxyacetone, is enzymatically isomerized to the other, 3-phosphoglyceraldehyde.

$$\begin{tikzcd} \text{Glucose} + \text{ATP} \arrow[r, shift left, "\text{Enzyme}"] & \text{Glucose 6-phosphate} + \text{ADP} \arrow[l, shift left] \arrow[d, shift left, "\text{Enzyme}"] \\ & \text{Fructose 6-phosphate} \arrow[u, shift left] \end{tikzcd}$$

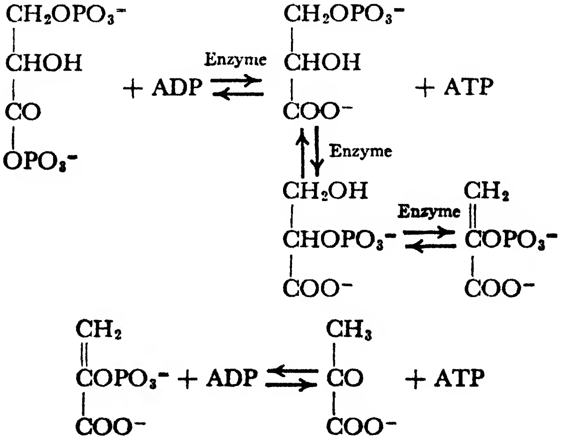
Fructose 6-phosphate + ATP $\xrightleftharpoons{\text{Enzyme}}$ Fructose 1,6-diphosphate + ADP



The net result so far is the conversion of one molecule of glucose to two molecules of 3-phosphoglyceraldehyde. No oxidation has taken place. Next the aldehyde combines with phosphate ion to form a product which gives up two hydrogen atoms to Coenzyme I (p. 375) and furnishes 1,3-diphosphoglycerate.


1,3-Diphosphoglycerate

1,3-Diphosphoglycerate next undergoes a series of enzymatic changes including isomerization and dehydration as a result of which it is converted to pyruvate ion and ATP is formed from ADP.



As a result of all these changes one molecule of glucose has furnished two pyruvate ions. Four atoms of hydrogen have been transferred to Coenzyme I, the two molecules of ATP used have been regenerated, and two additional molecules of ATP have been formed from the phosphate ions picked up by the 3-phosphoglyceric aldehyde. (In checking this summary statement the student should remember that, since one molecule of glucose furnishes two molecules of 3-phosphoglyceraldehyde, the equations beginning with 3-phosphoglyceraldehyde must be doubled to secure the correct material balance.)

In the steps which follow, the bulk of the oxidation takes place. Pyruvate ion is oxidized, probably through the formation and breakdown of four-carbon hydroxy and ketonic acids as outlined on p. 180 and certainly with the intervention of Coenzyme I to pick up hydrogen. The reduced Coenzyme I transfers its hydrogen eventually to oxygen in a number of steps. In the absence of oxygen, the pyruvic acid is reduced to ethyl alcohol as indicated in the next section.

Alcoholic Fermentation. The fermentation of sugar to alcohol by yeast is not only a very ancient art but a biochemical reaction which in recent years has been exhaustively studied. Indeed, one of the earliest observations about enzyme action was the demonstration that aqueous extracts of crushed yeast could also bring about the conversion of glucose to alcohol. This showed that the biochemical catalyst could in some instances, at least, be separated from the living cells without damage.

As a result of many experiments it has been established quite conclusively that *in the absence of oxygen* the yeast cells transform glucose to ethyl alcohol as follows: Glucose through the series of reactions involving phosphate is broken down to pyruvic acid. The yeast cell contains an enzyme (not found in animal tissue) which catalyzes the decarboxylation of pyruvic acid to acetaldehyde. This aldehyde in turn is the acceptor of the hydrogen atoms removed by Coenzyme I in the course of the formation of pyruvic acid.

$$\underset{\text{Glucose}}{C_6H_{12}O_6} \xrightarrow[\substack{\text{involving phosphate and} \\ \text{specific enzymes as outlined} \\ \text{in the preceding section}}]{\text{Through several steps}} \underset{\text{Pyruvic acid}}{CH_3COCOOH} + \text{Reduced Coenzyme I}$$

$$CH_3COCOOH \xrightarrow{\text{Enzyme}} CH_3CHO + CO_2$$

$$CH_3CHO + \text{Reduced Coenzyme I} \xrightarrow{\text{Enzyme}} CH_3CH_2OH + \text{Coenzyme I (returns to cycle)}$$

Muscle glycolysis and alcoholic fermentation have much in common. Both are **anaerobic reactions,** that is, they take place in the absence of oxygen. In muscle, the glucose molecules of glycogen are converted into lactic acid by way of pyruvic acid which is reduced to lactic acid by hydrogenated Coenzyme I. In alcoholic fermentation, the pyruvic acid first loses carbon dioxide yielding acetaldehyde which is then reduced to ethyl alcohol. Thus alcoholic fermentation differs from muscle glycolysis only in that acetaldehyde is reduced to alcohol, rather than pyruvic acid to lactic acid. Coenzyme I is the prosthetic group which carries hydrogen in a number of these reactions; a specific enzyme (protein) is required for each reaction.

QUESTIONS AND PROBLEMS

1. Give several examples of enzyme reactions previously considered in this book.
2. What is the evidence that enzymes are proteins?
3. What are some of the characteristics of enzyme reactions?
4. Explain the statement that "fermentation is life without oxygen."
5. Why is pyruvic acid often regarded as the key substance in the breakdown of carbohydrates?
6. What is the evidence that the materials of which the animal body is constituted are "perpetually in a state of flux"?
7. How have compounds containing an isotope of carbon been useful in elucidating the mechanism of biochemical processes?
8. Criticize the statement, "Carbon dioxide is assimilated in nature only by the absorption of radiant energy in green plants."
9. What is meant by the phrase, "coupled reaction"?
10. How is some of the potential energy in glycogen made available for muscular work?
11. Under what conditions is glycogen synthesized in the animal body from lactic acid?
12. Define and illustrate the following terms: *metabolic rate*, *chemosynthesis*, *metabolic pool*, *anaerobic conditions*, *phosphorylation*, *glycolysis*, *catabolism*, *an energy-rich link*, *substrate*, *coenzyme.*
13. Name four enzymes which have been isolated in the crystalline condition. What is the chemical reaction catalyzed by each?

CHAPTER 16

Benzene and the Alkylbenzenes

Cyclic Compounds. In the preceding chapters we have considered for the most part compounds in which the carbon atoms were arranged in an open chain. Only a few compounds, such as the cyclic anhydrides and lactones, contained a ring of atoms. The open-chain compounds are known as *aliphatic compounds* (fatty compounds). This name arose from the fact that the fatty acids (derived from the fats) are representatives of this class of substances.

In addition to these open-chain or aliphatic compounds a great variety of substances are known in which some of the atoms are combined in a ring. These **cyclic compounds** are divided into two classes, depending on whether or not the ring is composed entirely of atoms of the same kind. The **homocyclic compounds** contain only carbon atoms in the ring, while the **heterocyclic compounds** have atoms of other elements in the ring. The homocyclic compounds are for convenience further divided into two groups, namely, the **alicyclic compounds,** which resemble closely the aliphatic compounds, and the **aromatic compounds,** a group of substances containing a ring with a peculiar type of unsaturation. We shall consider some of these aromatic compounds in the next few chapters, since in both the scientific and industrial development of organic chemistry this class of substances has played a very important role.

The Development of Aromatic Chemistry. Certain hydrocarbons found in coal tar, notably benzene, C_6H_6, contain an aromatic ring. The chemistry of these hydrocarbons and the substances which can be prepared from them is called *aromatic chemistry*. The chemist's interest in aromatic chemistry has been connected with the industrial development of this subject during the last seventy-five years. The fact that certain substances can be readily and cheaply obtained from coal tar early led to their extensive study with a view to obtaining from them products of commercial importance. The efforts of the early investigators were richly rewarded as a great variety of dyes, drugs, flavors and perfumes, photographic developers, and explosives were discovered. All these could be prepared from coal tar by relatively simple procedures. In order to appreciate and understand some of the triumphs of the organic chemist in this truly remarkable development we must acquaint ourselves with the general properties and behavior of that peculiar group of aromatic compounds which are found in coal tar.

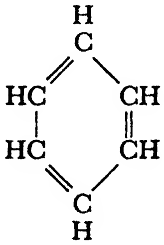
The Refining of Coal Tar. The coal-tar industry is a byproduct of the steel industry. The distillation of coal yields coke, gas, ammonia, and coal tar. Coke is essential in the winning of iron from its ores and would be prepared for this purpose whether or not the coal tar were collected and utilized. From 100 lb of coal there is obtained 6 lb of coal tar, and this furnishes only about $\frac{1}{2}$ lb of aromatic hydrocarbons. In spite of this very low yield, **benzene, toluene,** and **naphthalene** are cheap raw materials because an enormous amount of coal is converted each year into coke.

Name	*Formula*	*Boiling Point*	*Melting Point*	*Solubility*
Benzene	C_6H_6	80°	+6°	All insoluble in water
Toluene	$C_6H_5CH_3$	111°	−95°	
o-Xylene	$C_6H_4(CH_3)_2$	144°	−27°	
m-Xylene	$C_6H_4(CH_3)_2$	139°	−54°	
p-Xylene	$C_6H_4(CH_3)_2$	138°	+13°	
Naphthalene	$C_{10}H_8$	218°	+80°	
Anthracene	$C_{14}H_{10}$	342°	+218°	
Phenanthrene	$C_{14}H_{10}$	340°	+101°	

Coal tar is refined by distillation and by chemical treatment. The eight most important hydrocarbons thus obtained are listed in the table on page 255. In addition to these hydrocarbons, many other aromatic and heterocyclic compounds are present in coal tar. Some of them are separated in the refining, and others could be separated if a demand for them arose. The bulk of the coal tar, however, is left after refining as a black mass of pitch of unknown composition which is used for roofing and for roads.

BENZENE

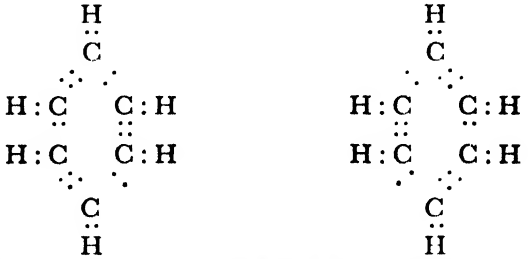
The simplest aromatic compound is benzene, C_6H_6, for which we can write the following structural formula.



The most characteristic chemical property of benzene is its ability to undergo substitution reactions — reactions in which a hydrogen atom is replaced by some other atom or group of atoms. For example, benzene and bromine yield bromobenzene, C_6H_5Br. All the methods of preparing a given monosubstitution product such as bromobenzene lead to the same substance, which means that all six hydrogen atoms in benzene are equivalent. This is consistent only with the symmetrical structure written above.

The next striking feature of the chemistry of benzene is the fact that the compound does not undergo the addition reactions shown by the group —CH=CH in aliphatic compounds. Benzene neither decolorizes bromine water nor reduces potassium permanganate solution. This lack of reactivity of the double bond toward addition reactions is best explained in terms of *resonance*, and a few words about resonance are therefore in order.

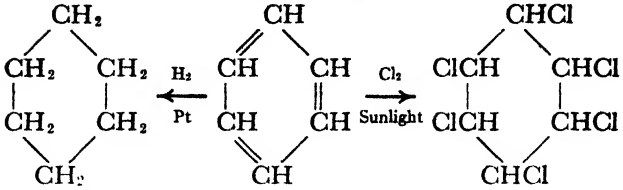
We can write two structural formulas for benzene which differ only in the location of certain valence electrons.



(The first of these formulas corresponds to the one written above. In the second formula the double and single bonds have shifted places.)

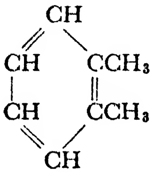
Isomers which differ from each other only in the location of certain valence electrons are called *electromers*. Such isomers have never been isolated, and we believe them to be incapable of existence. When, however, it is possible to write two or more electromeric structures for a compound, the compound is believed to have a structure intermediate between them. The intermediate structure, which is difficult to write in terms of our ordinary structural conventions, is known as a **resonance hybrid.** The resonance hybrid of benzene has a completely symmetrical structure in which each of the carbon-carbon bonds is intermediate in nature between a single and a double bond. Measurements show that all the bonds between the carbon atoms in benzene are of the same length, 1.39 Å, intermediate between the length of a C—C bond (1.54 Å) and a C=C bond (1.34 Å).

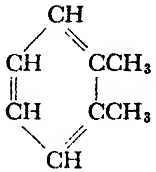
Resonance is accompanied by increased stability and lowered reactivity. As we have seen, the benzene structure persists in substitution reactions and benzene does not show typical ethylenic addition reactions. Benzene does undergo a few addition reactions; they always lead to completely saturated products. The addition of hydrogen furnishes cyclohexane, and the addition of chlorine furnishes the hexachloride which is an important insecticide.



Cyclohexane

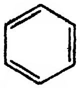
The formula for benzene written on page 256 apparently predicts the existence of two isomeric disubstitution products in which the substituents are attached to adjacent carbon atoms.



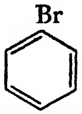


These two products, however, differ from each other only in the location of certain valence electrons. They are electromers and the structure of the single disubstitution product obtained is that of the resonance hybrid.

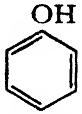
The difficulty of writing a structural formula for the resonance hybrid of benzene has already been mentioned. We therefore ordinarily use the simple formula shown on p. 256 recognizing its inadequacies. For most purposes an even simpler representation is employed: a hexagon in which neither the carbon nor the hydrogen atoms are shown. It is assumed that the group CH constitutes each corner. If a group or atom has replaced a hydrogen, this group or atom is shown. The following examples will make this convention clear.



Benzene
C_6H_6



Bromobenzene
C_6H_5Br



Phenol
C_6H_5OH

Aromatic Properties. The chemical properties which are characteristic of benzene and its derivatives are spoken of as aromatic properties. They include: (1) the ready substitution of hydrogen by other atoms or groups; (2) the failure to add reagents which usually add to unsaturated compounds; (3) resistance to oxidation; (4) acidic properties of the hydroxyl derivatives (to be discussed later).

The first characteristic is of special importance and needs amplification. The more important substitution reactions are:

1. **Halogenation,** the substitution of hydrogen by chlorine or bromine.

$$C_6H_6 + \underset{(\text{or } Br_2)}{Cl_2} \xrightarrow{\text{Iron as a catalyst}} \underset{(\text{or } C_6H_5Br)}{C_6H_5Cl} + \underset{(\text{or HBr})}{HCl}$$

2. **Nitration,** the substitution of hydrogen by the nitro group.

$$C_6H_6 + HNO_3 \xrightarrow{H_2SO_4} C_6H_5NO_2 + H_2O$$

A mixture of concentrated nitric and sulfuric acids is used.

3. **Sulfonation,** the substitution of hydrogen by the sulfonic acid group.

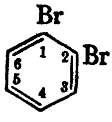
$$C_6H_6 + H_2SO_4 \longrightarrow C_6H_5SO_3H + H_2O$$

4. **Friedel and Crafts reaction,** the introduction of an alkyl or acyl group by means of the halide and aluminum chloride.

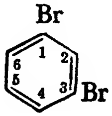
$$C_6H_6 + C_2H_5Br \xrightarrow{AlCl_3} C_6H_5C_2H_5 + HBr$$

$$C_6H_6 + CH_3COCl \xrightarrow{AlCl_3} C_6H_5COCH_3 + HCl$$

Number of Substitution Products. We have seen that it has been experimentally established that all the positions in the benzene ring are equivalent. There are only three isomers of a compound $C_6H_4X_2$. The nomenclature of these isomers may be illustrated by the dibromobenzenes, $C_6H_4Br_2$.



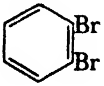
Ortho
dibromobenzene
or 1,2-dibromobenzene



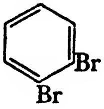
Meta
dibromobenzene
or 1,3-dibromobenzene

Para
dibromobenzene
or 1,4-dibromobenzene

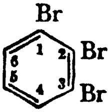
The terms *ortho*, *meta*, and *para* should be noted. It is, of course, only the relative positions of the groups which are important, and the ortho compound, for example, may also be written:



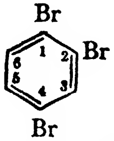
or



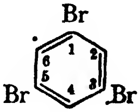
There are three isomers of a trisubstituted benzene of the formula $C_6H_3X_3$. Thus, there are three tribromobenzenes.



1,2,3-Tribromobenzene
(vicinal form)



1,2,4-Tribromobenzene
(asymmetric form)



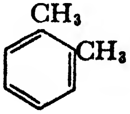
1,3,5-Tribromobenzene
(symmetric form)

The nomenclature used with benzene derivatives containing more than two groups involves the numbering of the ring as indicated above. The disubstitution products are also sometimes referred to in this way; thus, ortho dibromobenzene is 1,2-dibromobenzene, and the para compound 1,4-dibromobenzene.

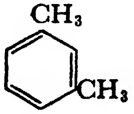
ALKYL DERIVATIVES OF BENZENE

The alkyl derivatives of benzene are very similar to the parent substance in their general behavior. Toluene, $C_6H_5CH_3$, and the isomeric xylenes are readily obtained from coal tar. We shall have many occasions to refer to toluene since it can be transformed into a variety of important substances. The structures of toluene and of the three isomeric xylenes are as follows:

Toluene



Ortho xylene

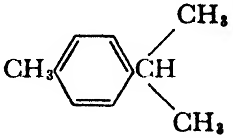


Meta xylene

Para xylene

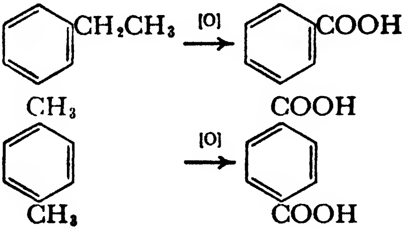
The boiling points of the three isomeric xylenes lie so near together that it is difficult to separate the one from the other. Commercial xylene is a mixture of all three.

Cymene (or para cymene), 1-methyl-4-isopropylbenzene,



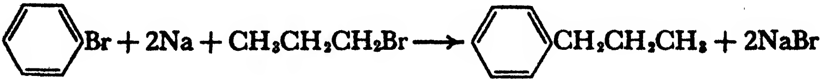
is closely related to a number of the terpenes which are considered in Chap. 21. Many terpenes may be converted into this hydrocarbon which occurs in a variety of essential oils.

The alkylbenzenes show even more strikingly than benzene itself the resistance of the aromatic nucleus to oxidation. Many alkylbenzenes, regardless of the length of the alkyl group, can be oxidized to aromatic acids (p. 303); in this process the saturated aliphatic side chain, not the unsaturated aromatic ring, is attacked.

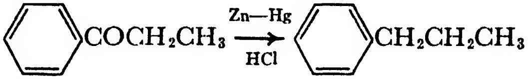


Methods of Preparing Aromatic Hydrocarbons. Although benzene, toluene, and the xylenes are obtained from coal tar, it is important to have general methods of preparing aromatic hydrocarbons. The two most satisfactory laboratory methods are the Wurtz-Fittig reaction and the reduction of ketones.

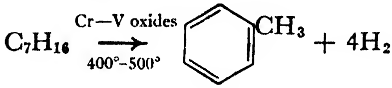
The Wurtz-Fittig reaction differs from the Wurtz reaction (p. 44) only in that an alkyl halide and an aromatic halide are employed.



Ketones containing an aromatic and an aliphatic group are available through the Friedel-Crafts synthesis (pp. 259, 301). When these ketones are reduced by means of amalgamated zinc and hydrochloric acid, alkylbenzenes are formed.



Preparation of Aromatic Hydrocarbons from Aliphatic Compounds. When *n*-heptane is heated in the presence of suitable catalysts, conversion to toluene and hydrogen occurs. The same process is applicable, of course, to heptene, whereas hexane and hexene yield benzene.



This process, whereby paraffin hydrocarbons are converted to aromatic hydrocarbons, attained extraordinary importance in World War II, and petroleum as a source of toluene for nitration to TNT (p. 281) far outstripped coal tar. In 1940 no commercial production of nitration-grade toluene from petroleum was reported; by 1944 the toluene obtained from petroleum amounted to 70 per cent of all that produced in this country. The fact that there was an adequate supply of toluene for TNT during World War II is the direct result of the development of the process we have been considering.

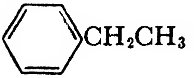
The use of petroleum as a raw material for the preparation of aromatic hydrocarbons is another example of the way in which the development of chemistry has made for the interchangeability of raw materials.

Nomenclature of Aryl Groups. Just as we have names for the alkyl groups, so it is convenient to have names for the groups corresponding to an aromatic radical — aryl groups. The aryl group, C_6H_5—, is known as the *phenyl group.* The name originated from the fact that the corresponding hydroxyl compound, C_6H_5OH, is known as *phenol.* It must be noted that the name of this aryl group does not suggest the name of the corresponding hydrocarbon. However, the nomenclature of the aryl groups corresponding to the alkyl derivatives of benzene usually follows that of the hydrocarbon. Thus, $CH_3C_6H_4$— is the tolyl group (ortho, para, or meta), $(CH_3)_2C_6H_3$—, the xylyl group, and $(CH_3)_3C_6H_2$—, the mesityl group. The group, $CH_3C_6H_4$—, is also sometimes called the *cresyl group*, the name being derived from that of the hydroxyl compound, $CH_3C_6H_4OH$, cresol.

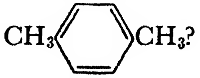
QUESTIONS AND PROBLEMS

1. Write structural formulas for all the dichlorobenzenes and the trichlorobenzenes.

2. What reactions would you use to show that an organic compound was either



or



?

3. Describe briefly the refining of coal tar.

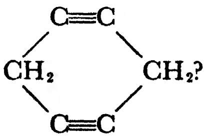
4. Define and illustrate with examples the following terms: (*a*) *homocyclic*, (*b*) *orientation*, (*c*) *alicyclic*, (*d*) *aryl*, (*e*) *heterocyclic*.

5. Write equations indicating what occurs when the following are allowed to react: (*a*) *o*-bromotoluene, isopropyl bromide, and sodium; (*b*) benzene, acetyl chloride, and aluminum chloride; (*c*) benzene, chlorine, and sunlight.

6. Write structural formulas for ortho xylene, 1,2,4-trimethylbenzene, 2-bromo-1,3-dimethylbenzene, vicinal trichlorobenzene, para bromotoluene, meta chlorobromobenzene, and para cymene.

7. What facts make it necessary to write a symmetrical structural formula for benzene?

8. What simple chemical tests would enable you to distinguish between $CH_3CH_2C\equiv C—C\equiv CH$ and



?

9. Name and give examples of the characteristic substitution reactions of benzene.

10. Given ethyl alcohol, benzene, and any inorganic chemicals necessary, how would you prepare ethylbenzene?

11. Discuss resonance as found in benzene. What are (*a*) resonance hybrids, (*b*) electromers?

CHAPTER 17

Aryl Halides, Sulfonic Acids, and Phenols

ARYL HALIDES

One of the characteristic reactions of aromatic compounds is the replacement of a hydrogen atom on the ring by chlorine or bromine. The resulting compounds are **aryl halides.** Unlike the alkyl halides, the simple aryl halides are almost never prepared from the corresponding hydroxyl compounds. They are usually prepared from the hydrocarbons.

Chlorobenzene (bp 132°) and **bromobenzene** (bp 156°) may be taken as typical representatives of the aryl halides. They are prepared by the action of chlorine or bromine on warm benzene in the presence of some catalyst. Iron is almost always the catalyst employed.

$$C_6H_6 + Br_2 \xrightarrow{Fe} C_6H_5Br + HBr$$

The product is purified by distillation. In addition to the monohalogen compound, some dichloro- or dibromo-benzene is also formed. Further halogenation furnishes the dihalogen derivatives. One of these, para dichlorobenzene, is used extensively as a moth and caterpillar repellent.

Unlike bromine and chlorine, iodine, by itself, does not directly replace a hydrogen atom attached to an aromatic ring. Iodobenzene, however, can be made by the action of iodine and boiling nitric acid on benzene.

$$2C_6H_6 + 2I + [O] \xrightarrow{HNO_3} 2C_6H_5I + H_2O$$

Halogenation of Alkyl Derivatives of Benzene. The alkyl derivatives of benzene such as toluene and ethylbenzene may react in two different ways when treated with chlorine or bromine. A hydrogen atom of the nucleus or a hydrogen atom of the alkyl group (the "side chain") may be replaced. The nuclear halogenation is accelerated by such catalysts as metallic iron or ferric salts; the introduction of a halogen atom into the side chain is favored by strong light and high temperature.

$$C_6H_5CH_3 + Cl_2 \xrightarrow[\text{FeCl}_3]{\text{Catalyst}} \underset{\substack{\text{Mixture of}\\ \text{ortho and}\\ \text{para isomers}}}{ClC_6H_4CH_3} + HCl$$

$$C_6H_5CH_3 + Cl_2 \xrightarrow{\text{Light}} \underset{\text{Benzyl chloride}}{C_6H_5CH_2Cl} + HCl$$

It will be noticed that the product of the side-chain chlorination, **benzyl chloride** (bp 179°), does not contain the halogen atom directly attached to the aromatic ring. It is, therefore, not an aryl halide like ortho and para chlorotoluene but an alkyl halide (methyl chloride) in which one hydrogen atom has been replaced by an aromatic group (C_6H_5).

The chlorination of the side chain of toluene proceeds further to give **benzal chloride** (bp 207°), $C_6H_5CHCl_2$, and finally **benzotrichloride** (bp 213°), $C_6H_5CCl_3$. Unlike the chlorination of methane (p. 45), the side-chain reaction of toluene with chlorine can be controlled so that any one of the three chlorination products can be obtained in a good yield.

$$C_6H_5CH_2Cl + Cl_2 \longrightarrow \underset{\text{Benzal chloride}}{C_6H_5CHCl_2} + HCl$$

$$C_6H_5CHCl_2 + Cl_2 \longrightarrow \underset{\text{Benzotrichloride}}{C_6H_5CCl_3} + HCl$$

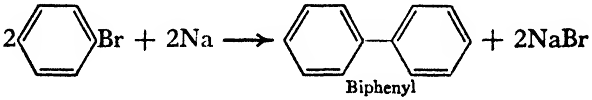
Chemical Behavior of Aryl Halides. In comparison with the alkyl halides, the aryl halides are very unreactive; for example, they do not react with potassium cyanide, silver hydroxide, or, under the usual conditions employed in the laboratory, with sodium hydroxide or ammonia. When heated under pressure to 200° to 300° with these last two reagents and copper salts, the halogen atom may be replaced by the hydroxyl and amino groups respectively.

Aryl halides react with magnesium to form a Grignard reagent which is similar to the aliphatic Grignard reagents.

$$C_6H_5Br + Mg \xrightarrow[\text{ether}]{\text{Dry}} C_6H_5MgBr$$

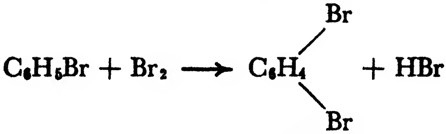
Aryl halides react with metallic sodium in the Wurtz-Fittig reaction considered in the preceding chapter. If no alkyl halide is employed two molecules of the aryl halide join together.

$$C_6H_5Br + C_2H_5Br + 2Na \longrightarrow \underset{\text{Ethylbenzene}}{C_6H_5C_2H_5} + 2NaBr$$



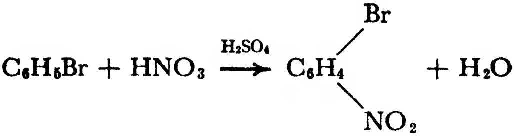
Formation of Ortho, Meta, and Para Isomers. In the preparation of the disubstitution products of benzene, three isomers are possible. For example, the further bromination of bromobenzene might yield the ortho or the meta or the para isomer. Actually, the product is a mixture of the ortho and para compounds. By contrast, the bromination of nitrobenzene, $C_6H_5NO_2$, yields meta bromonitrobenzene. Some rules for predicting the isomers are obviously needed.

The Directive Influence of Substituents. An exhaustive study of the preparation of disubstituted benzenes has led to *two important generalizations*. These are subject to certain reservations but are nevertheless of great value as an approximate guide in predicting the course of substitution reactions. The first generalization is as follows: *The position of the entering group is determined by the nature of the atom or group already present* and is independent of the nature of the entering group. For example, the bromination of bromobenzene yields a mixture of the ortho and para compounds, and the nitration of bromobenzene proceeds in the same way.



$$C_6H_5Br + Br_2 \longrightarrow C_6H_4\begin{array}{l}\diagup Br\\ \diagdown Br\end{array} + HBr$$

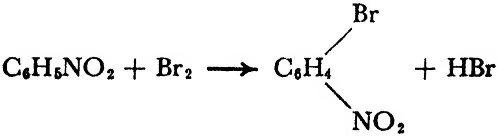
Ortho and para



$$C_6H_5Br + HNO_3 \xrightarrow{H_2SO_4} C_6H_4\begin{array}{l}\diagup Br\\ \diagdown NO_2\end{array} + H_2O$$

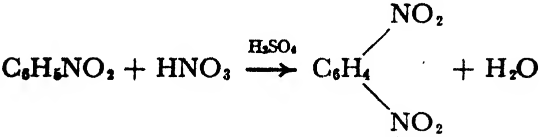
Ortho and para

On the other hand, the nitration of nitrobenzene yields only the meta compound, and similarly the bromination of nitrobenzene yields only meta bromonitrobenzene.



$$C_6H_5NO_2 + Br_2 \longrightarrow C_6H_4\begin{array}{l}\diagup Br\\ \diagdown NO_2\end{array} + HBr$$

Meta



$$C_6H_5NO_2 + HNO_3 \xrightarrow{H_2SO_4} C_6H_4\begin{array}{l}\diagup NO_2\\ \diagdown NO_2\end{array} + H_2O$$

Meta

Rules of Orientation. It will be seen from the above examples that the directing influences of the bromine atom and the nitro group are different. One causes the formation of a mixture of ortho and para isomers, the other only of the meta compound. It has been found that all the atoms or groups which are common substituents in the benzene ring may be divided into two categories according to whether they have a directive influence like that of the bromine atom or like that of the nitro group. This is the second great generalization in regard to substitution in aromatic compounds.

A list of the groups is given below.

Class I. (Directs the entering group into the ortho and para positions.) OH, NH_2, OCH_3, $N(CH_3)_2$, $NHCOCH_3$, Cl, Br, I, CH_3 and other alkyl groups, CH_2COOH.

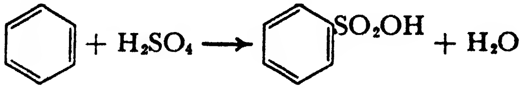
Class II. (Directs the entering group into the meta position.) NR_3^+, NO_2, $C{\equiv}N$, COOH, SO_3H, $COOC_2H_5$, CHO, COR, NH_3^+.

Those atoms and groups in Class I are spoken of as *ortho and para orienting atoms or groups;* those in Class II as *meta orienting groups.* It will be convenient to remember that all those groups which contain a double linkage *connected to the first atom* fall in Class II as do those which carry a positive charge on the atom directly attached to the ring. In general, the introduction of a second substituent into a molecule is easier (i.e., proceeds more rapidly at a lower temperature) if the substituent already present belongs to Class I, and is more difficult when the substituent present is of Class II.

Limitations of the Rules. Several important exceptions to these rules of orientation will be noted even in this elementary presentation of the subject; if a greater number of aromatic compounds were considered, the exceptions would be more numerous. Not only are there certain cases where the facts are exactly contrary to the simple rules of orientation, but, in general, the *rule only predicts the major product of the reaction.* There is, almost always, at least a few per cent of the other isomers formed. In spite of these limitations, the rules of orientation are of invaluable assistance in the practical matter of devising syntheses of aromatic compounds with several groups. We shall repeatedly refer to them.

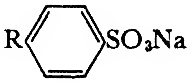
ARYL SULFONIC ACIDS

Aryl Sulfonic Acids. One of the characteristic reactions of aromatic compounds mentioned in the previous chapter is sulfonation.



The product of this reaction is an aryl sulfonic acid, which is usually isolated as a salt. The aryl sulfonic acids are of importance in the preparation of other compounds since the sulfonic acid group may be replaced by other groups. The sulfonic acid group is also often introduced into a molecule in order to make the compound soluble in water. The aryl sulfonic acids of low molecular weight and most of their salts are soluble in water. Even some aromatic hydrocarbons of very complex structure and high molecular weight may be changed into water-soluble products by the introduction of a number of sulfonic acid groups.

One group of detergents (p. 132) is made by chlorinating high-boiling petroleum fractions and treating the resulting alkyl chlorides with benzene and aluminum chloride. This furnishes alkylbenzenes containing a long-chain alkyl group, R. When these substances are sulfonated, the sodium salts of the sulfonic acids are detergents.



Reactions of Sulfonic Acids and Sulfonates. The sulfonic acid group may be replaced by the hydroxyl group, the nitrile group, or hydrogen. All these reactions are of importance in the preparation of aromatic compounds. They are illustrated by the following representative equations.

1. **Replacement by OH.**

$$C_6H_5SO_3Na + \underset{\text{Molten}}{2NaOH} \xrightarrow[300^\circ]{} C_6H_5ONa + Na_2SO_3 + H_2O$$

$$C_6H_5ONa + H_2SO_4 \longrightarrow \underset{\text{Phenol}}{C_6H_5OH} + NaHSO_4$$

2. **Replacement by C≡N.**

$$C_6H_5SO_3Na + NaCN \longrightarrow \underset{\text{Benzonitrile}}{C_6H_5CN} + Na_2SO_3$$

3. **Replacement by H.**

$$C_6H_5SO_3H + H_2O \xrightarrow[\substack{\text{On heating at about 150°}\\ \text{with dilute acid}\\ \text{under pressure}}]{} C_6H_6 + H_2SO_4$$

The acid chlorides of the aryl sulfonic acids are formed by the action of the chlorides of phosphorus on the free acids or the sodium salts.

$$C_6H_5SO_3Na + PCl_5 \longrightarrow C_6H_5SO_2Cl + NaCl + POCl_3$$

Aryl Sulfonamides. The action of ammonia on the aryl sulfonyl chlorides yields the unsubstituted aryl sulfonamides. These are crystalline solids; benzene and toluene sulfonamides are somewhat soluble in organic solvents and in water. The para toluene sulfonamide, $CH_3C_6H_4SO_2NH_2$, is a byproduct of the manufacture of saccharin (p. 311). The sulfonamides which contain a replaceable hydrogen atom dissolve in aqueous sodium hydroxide, forming salts.

$$C_6H_5SO_2NH_2 + NaOH \longrightarrow C_6H_5SO_2NHNa + H_2O$$

On acidifying, the sulfonamide is precipitated. The aryl sulfonyl group (e.g., $C_6H_5SO_2$—), is very acidic in its influence. The corresponding OH compounds (the sulfonic acids) are strong acids and the —NHR derivatives are strong enough acids to dissolve in aqueous sodium hydroxide. (It will be recalled that the amides of the organic acids were not acidic enough to manifest this property in aqueous solution, p. 153.)

The **chlorosulfonamides** are an interesting group of compounds prepared by the action of sodium hypochlorite on the sulfonamides.

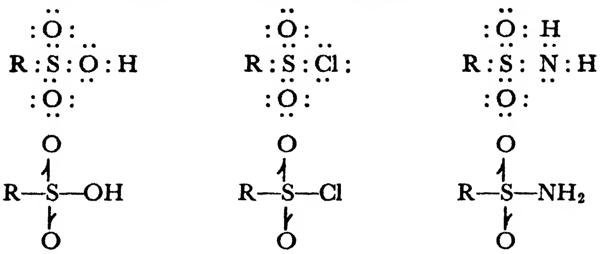
$$CH_3C_6H_4SO_2NH_2 + NaOCl \longrightarrow CH_3C_6H_4SO_2NHCl + NaOH$$

They are crystalline solids which in water solution slowly liberate hypochlorous acid.

$$CH_3C_6H_4SO_2NHCl + H_2O \xrightarrow[\text{Slowly}]{} CH_3C_6H_4SO_2NH_2 + HOCl$$

For this reason they have been used as effective antiseptic agents for wounds. Chloramine T is a sodium salt, $CH_3C_6H_4SO_2NClNa$, and is soluble in water: dichloramine T is $CH_3C_6H_4SO_2NCl_2$, and is soluble in organic solvents.

Structure of Sulfonyl Compounds. The electronic structures of a sulfonic acid, a sulfonyl chloride, and a sulfonamide are shown below, together with formulas using the convention we have adopted for representing a coordinate covalence (p. 163).



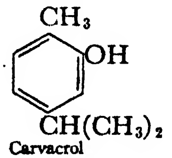
(The electronic structure of the aryl group R is not written except for the one link joining the carbon atom to the sulfur.) It is probably not worth while to try to represent the special sulfur to oxygen linkage in these compounds every time the formula is written. With suitable mental reservations, such noncommittal formulas as $C_6H_5SO_2OH$, $C_6H_5SO_2Cl$, and $C_6H_5SO_2NH_2$ are sufficient.

PHENOLS

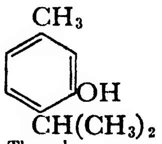
The hydroxyl derivatives of aromatic hydrocarbons which have the OH group directly attached to the ring are called *phenols*. **Phenol,** or **carbolic acid,** C_6H_5OH, is the most important representative of the class. It is a colorless, crystalline substance which melts at 41°. Small amounts of water dissolved in phenol lower the melting point below room temperature.

The phenols which are derivatives of toluene are called *cresols*.

Thymol, mp 51°, and *carvacrol*, a liquid at room temperature, are hydroxyl derivatives of para cymene which occur in many essential oils. Thymol is used in medicinal preparations as an antiseptic. It is much less poisonous than phenol.



Carvacrol



Thymol

Reactions of Phenols. All the simple phenols (with the exception of the nitrophenols) are very weak acids but are sufficiently acidic to dissolve in sodium hydroxide.[1]

$$C_6H_5OH + NaOH \longrightarrow \underset{\text{Sodium phenoxide}}{C_6H_5ONa} + H_2O$$

[1] The dissociation constant of phenol is about 1.7 × 10^{-10}. (Cf. p. 106.)

They will not, however, dissolve in sodium bicarbonate solution, thus differing from organic acids which contain the carboxyl group. Since they are weaker acids than carbonic acid, the following reaction takes place when carbon dioxide is passed through a water solution of their salts.

$$C_6H_5ONa + CO_2 + H_2O \longrightarrow C_6H_5OH + NaHCO_3$$

The hydroxyl group in phenols is very different from that in alcohols. The acyl derivatives (the esters) cannot be made by direct esterification. They are prepared by the use of acid anhydrides or acid chlorides.

$$C_6H_5OH + (CH_3CO)_2O \longrightarrow \underset{\text{Phenyl acetate}}{C_6H_5OCOCH_3} + CH_3COOH$$

The aryl halides cannot be readily prepared from phenols either by the action of the phosphorus trihalides or by the action of halogen acids. With phosphorus pentachloride or bromide, however, phenols yield the corresponding halides, but in poor yields.

In general, phenols are to be contrasted with alcohols and also with acids. They form a separate class and are most closely related to the enols (p. 182). If we compare the Kekulé formula for phenol with the formula for an enol the analogy is evident; both compounds contain the grouping —C═C(OH)—. *The hydroxyl group directly attached to an unsaturated carbon atom is acidic.*

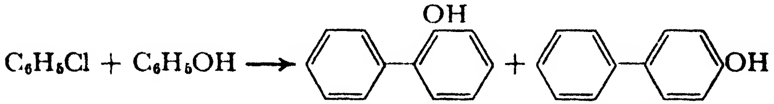
Production of Phenol. For many years phenol was obtained solely from coal tar. In refining, this substance is obtained by extraction with aqueous sodium hydroxide. During World War I enormous quantities of phenol were needed to make the explosive **trinitrophenol (picric acid)**, and to meet this demand synthetic phenol was produced. This synthetic method involves the preparation of sodium benzenesulfonate by the method previously described (p. 268). This salt is then fused with sodium hydroxide, and sodium phenoxide is formed. On dissolving the melt in water and acidifying, the phenol separates. It can then be purified by distillation. (The equations for the reactions involved in this process are given on p. 269.)

In more recent years, the demand for an abundant and cheap supply of phenol became so great that a new method of preparation from chlorobenzene was developed. Chlorobenzene is heated with dilute sodium hydroxide under very high pressure in a continuous tubular system of copper.

$$C_6H_5Cl + 2NaOH \longrightarrow C_6H_5ONa + NaCl + H_2O$$

At the same time some diphenyl ether and some 2-hydroxybiphenyl and 4-hydroxybiphenyl are formed.

$$C_6H_5ONa + C_6H_5OH \rightleftharpoons \underset{\text{Diphenyl ether}}{C_6H_5OC_6H_5} + NaOH$$



2-Hydroxybiphenyl 4-Hydroxybiphenyl

The reaction which furnishes diphenyl ether is, it will be noticed, reversible. Consequently, by adding diphenyl ether to the initial reaction mixture of chlorobenzene and sodium hydroxide, the formation of this byproduct can be suppressed.

Industrial Uses of Phenol. The increased demand for phenol is largely due to the growth of the synthetic resin industry. Synthetic resins are used in the manufacture of fountain pens, phonograph records, pipestems, and as an insulator in electrical equipment. **Bakelite** is a synthetic resin formed by the action of formaldehyde on phenol in the presence of ammonia. This industry requires not only large amounts of phenol but also of formaldehyde. (Bakelite and other phenol-formaldehyde resins are discussed later in Chap. 19.) Great quantities of phenol are also used in the manufacture of drugs, photographic developers, and dyes. Phenol itself is an excellent antiseptic, and dilute water solutions of phenol (usually called *carbolic acid*) are widely used for this purpose.

In 1924, 5200 tons of phenol were produced in the United States; in 1947 some 100,000 tons were produced, of which about 90% was prepared by synthetic methods.

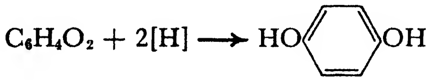
POLYHYDROXYL COMPOUNDS

The derivatives of benzene with two or more hydroxyl groups attached to the ring resemble phenol in their chemical behavior. They are very weak acids and give characteristic colors with ferric chloride. As would be expected from the number of hydroxyl groups, they are readily soluble in water.

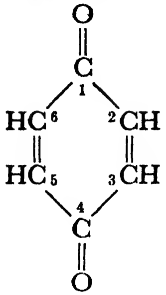
Hydroquinone, $C_6H_4(OH)_2$ (1,2), *p*-dihydroxybenzene, is a colorless crystalline solid which melts at 171°. It finds extensive use as a photographic developer.

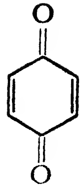
Hydroquinone is prepared from aniline, $C_6H_5NH_2$ (p. 284). When aniline is oxidized with potassium dichromate and sulfuric acid, a yellow, volatile solid, **quinone** or **benzoquinone,** $C_6H_4O_2$, is formed. This compound on reduction with sulfur dioxide yields hydroquinone. In the preparation of hydroquinone on a large scale no effort is made to separate the intermediate compound; it is at once distilled with steam from the reaction mixture and reduced with iron and acid. The hydroquinone is obtained as a crystalline mass on concentrating the solution.

$$C_6H_5NH_2 + 2[O] \xrightarrow{K_2Cr_2O_7} \underset{\text{Quinone}}{C_6H_4O_2} + NH_3$$



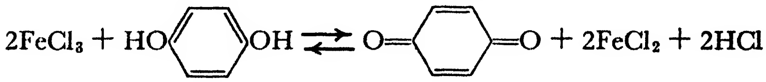
Quinone (1,4-Benzoquinone). If we examine the intermediate substance, quinone, we find that it is a yellow, crystalline solid (mp 116°) with a penetrating odor. It does not behave like an aromatic compound. On the contrary, it shows the typical reactions of an olefin hydrocarbon and an aliphatic ketone. For example, it combines with four atoms of bromine to form a tetrabromide, and reacts with hydroxylamine forming a dioxime. Taking into account these facts and its easy conversion into para dihydroxybenzene (whose structure is definitely established by other syntheses), we can write the following formula with considerable confidence. (The outline formula on the right is frequently employed.)



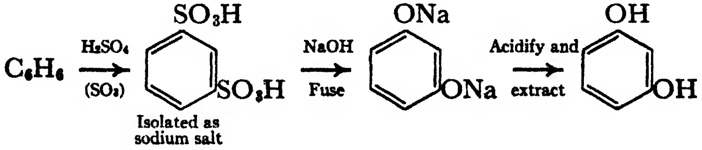


It will be noted that in this compound the double linkages are indicated as being definitely in the 2,3 and 5,6 positions, and that, unlike benzene and its derivatives, two of the six carbon atoms are attached to a divalent atom (oxygen). Although quinone is formed by the oxidation of an aromatic compound and passes into a member of this class on reduction, it is itself *not a typical aromatic substance.* **Quinone is an unsaturated, cyclic ketone,** an alicyclic compound.

Reversibility of the Reduction of Quinone. The change from quinone to hydroquinone can easily be reversed in acid solution by treating hydroquinone with an oxidizing agent. The reduction of quinone to hydroquinone and the reoxidation of the latter are extraordinarily rapid processes and are strictly reversible. This is one of the relatively few oxidation and reduction reactions of organic chemistry which is rapid and reversible like the oxidation and reduction of inorganic ions.



Resorcinol. 1,3-Dihydroxybenzene, resorcinol, is prepared industrially by alkaline fusion of the corresponding disulfonic acid. Starting with benzene, the steps involved are the following:



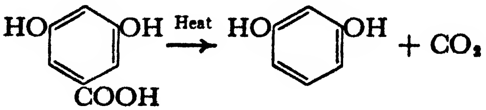
Resorcinol is a colorless solid which melts at 110°. A number of alkyl derivatives of resorcinol which contain an alkyl group in the 4 position are valuable antiseptics. Hexylresorcinol, $C_6H_3(OH)_2(CH_2CH_2CH_2CH_2CH_2CH_3)$ (1,3,4), may be mentioned as an example.

Pyrocatechol. The ortho dihydroxybenzene, $C_6H_4(OH)_2$ (1,2), a colorless solid which melts at 105°, is known as *pyrocatechol* or *catechol*. It can be prepared from ortho chlorophenol by hydrolysis of the compound in an aqueous solution of sodium and strontium hydroxides in the presence of copper. It is easily oxidized in alkaline solution, yielding complex products. When oxidized with silver oxide under special conditions pyrocatechol yields ortho benzoquinone.

The pyrocatechol grouping occurs in a great variety of natural products; sometimes with both phenolic groups free, sometimes partially methylated, and sometimes combined with a methylene group. A number of such natural products, including the substance lignin present in wood, will be discussed in the following chapters.

Guaiacol, $C_6H_4(OCH_3)(OH)$ (1,2), is the monomethyl ether of catechol. It was first obtained by the destructive distillation of gum guaiacum (a resin), and occurs in large quantities in wood tar. It can be synthesized from phenol or benzene by a variety of processes. Guaiacol is a low-melting, colorless solid (mp 28°) with a characteristic, pleasant odor. It is used in medicine and pharmaceutical preparations. It can be converted into catechol by boiling with hydrobromic or hydriodic acid.

Pyrogallol from Gallic Acid. Pyrogallol, or pyrogallic acid, $C_6H_3(OH)_3$ (1,2,3), is one of the few aromatic compounds which is *not prepared from coal tar*. It has been synthesized from benzene in the laboratory, but the process is too difficult and expensive to be used industrially. **Gallic acid,** $C_6H_2(OH)_3COOH$, is a substance which is readily prepared from tannic acid (p. 308). On heating, gallic acid loses carbon dioxide and forms pyrogallol.



This trihydroxybenzene thus owes its importance to the fact that it can be readily obtained from a natural product (tannic acid). It is used as a developing agent and as a dye intermediate. Its alkaline solutions are very easily oxidized even by atmospheric oxygen. They are often used as an absorbent for oxygen in gas analysis.

Polyhydroxy Aromatic Compounds in Nature. The hydroxyl derivatives of benzene are widely distributed in the plant world, often as glycosides (p. 205) in which the phenolic group is attached to a glucose or other sugar molecule. A number of more or less complicated substances derived from the polyhydroxy compounds are found in the tannins (p. 308). Pyrocatechol, hydroquinone, and phloroglucinol (symmetrical trihydroxybenzene) have been isolated as glucosides from many species of plants. The glucoside of hydroquinone, known as *arbutin*, is very common in the plant kingdom.

QUESTIONS AND PROBLEMS

1. Write structural formulas for *p*-chlorophenol, meta benzenedisulfonic acid, para iodotoluene, benzyl chloride, *p*-bromobenzenesulfonic acid, *p*-toluenesulfonamide, and meta cresol.

2. Compare by means of equations the behavior of phenol and *n*-hexanol toward the following reagents: (*a*) NaOH; (*b*) H_2SO_4; (*c*) HBr; (*d*) CH_3COOH and a small amount of sulfuric acid; (*e*) $(CH_3CO)_2O$.

3. How would you prepare the following substances starting with benzene or toluene: (*a*) iodobenzene; (*b*) benzyl chloride; (*c*) *p*-nitrotoluene; (*d*) *p*-bromotoluene; (*e*) *m*-bromobenzenesulfonic acid?

4. Write balanced equations for the reactions which take place when (*a*) *p*-toluenesulfonic acid and water are heated together, (*b*) sodium *p*-toluenesulfonate is heated with sodium cyanide.

5. State briefly the rules describing the positions taken by substituents introduced into benzene derivatives.

6. Applying the rules stated in question 5, predict what products will be formed in the following reactions: (*a*) ethylbenzene and nitric acid, (*b*) ethylbenzene and bromine in the presence of ferric bromide,

(*c*) nitrobenzene and sulfuric acid, (*d*) para cresol and sulfuric acid, (*e*) benzenesulfonic acid and bromine.

7. Write structural formulas for benzenesulfonic acid, benzenesulfonyl chloride, and benzenesulfonamide.

8. Describe two industrial methods of synthesizing phenol and explain why phenol is of such importance in the chemical industry.

9. What chemical tests would you use to distinguish between $CH_3C_6H_4OCH_3$, $C_2H_5C_6H_4OH$, and $CH_3C_6H_4CH_2OH$?

10. How could you separate by chemical methods a mixture of phenol and *n*-valeric acid?

11. How is quinone prepared? What is the relationship between quinone and hydroquinone?

CHAPTER 18

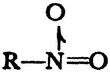
Aromatic Nitro Compounds, Amines, Diazonium Salts, and Azo Dyes

The Nitration of Aromatic Compounds. The hydrogen atoms which are attached to the aromatic ring are readily replaced by the nitro group. This is one of the characteristic reactions of aromatic compounds. The nitration is usually carried out by treating the substance with a mixture of concentrated nitric and sulfuric acids. The sulfuric acid itself does not react, but provides the experimental conditions under which the nitric acid is most effective. Some compounds like phenol are nitrated even by dilute nitric acid.

The **nitro compounds** are quite distinct from the esters of nitrous acid. A comparison of the structural formulas of **nitrobenzene** (formed by the nitration of benzene), $C_6H_5{-}NO_2$, and ethyl nitrite, $C_2H_5{-}O{-}N{=}O$, makes this evident. In the nitro compounds there is a carbon to nitrogen linkage. Unlike esters, *nitro compounds are not hydrolyzed.*

The **electronic formula** for a nitro compound RNO_2 is given below together with its representation in ordinary valence terms.

$$\mathrm{R:\overset{:\ddot{O}:}{\underset{}{\overset{\cdot\cdot}{N}}}::\underset{\cdot\cdot}{\ddot{O}}}$$



$$\mathrm{R{-}\overset{\overset{\textstyle O}{\uparrow}}{N}{=}O}$$

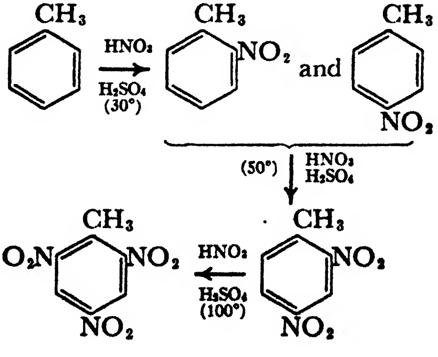
Importance of Nitro Compounds. Aromatic nitro compounds are of importance because of their use as explosives, and because they may be readily reduced to the corresponding

primary amines. These in turn are the starting materials for the manufacture of many dyes. The presence of one or more nitro groups in an aromatic nucleus markedly influences the chemical properties of other atoms or groups in the molecule; this is particularly true if the groups are in the ortho and para positions. The nitro group is almost unique in the extent of this influence which it exerts. For this reason we shall often have occasion to refer to the special properties of nitro phenols, nitro amines, and nitro halogen compounds.

Nitrobenzene is a slightly yellow liquid with a characteristic odor somewhat reminiscent of almonds. It is prepared on a very large scale chiefly for use in the preparation of aniline. The nitration of benzene is accomplished by agitating a mixture of the hydrocarbon with sulfuric and nitric acids. The product is insoluble in the nitrating mixture and may be readily separated. It is purified by washing with water and then distilling.

The introduction of a second nitro group into benzene is more difficult than the introduction of the first. This fact illustrates the general rule that the presence of a meta-orienting group makes substitution more difficult than in benzene itself. In order to prepare **meta dinitrobenzene,** a higher temperature is required and fuming nitric acid is employed. The introduction of a third nitro group into benzene is very difficult.

Toluene may be nitrated in a stepwise manner to 2,4,6-trinitrotoluene.



Since toluene contains the methyl group which orients ortho and para, its nitration is more readily accomplished than is the nitration of benzene. This contrast is particularly evident in the formation of 2,4,6-trinitrotoluene without difficulty. The nitration is done in three stages, each at a somewhat higher temperature than its predecessor; and the spent acid from the trinitration is used for the dinitration, and so on.

Aromatic Nitro Compounds as High Explosives. Trinitrotoluene, usually called **TNT,** was prepared in enormous quantities during both World Wars and was used in shells as a high explosive. It is relatively insensitive to shock and can, therefore, be used in filling projectiles which are fired from guns and which could not contain the more sensitive nitrates of cellulose (p. 212). It is detonated by means of a special charge called a *booster*, which is ignited by a time fuse or on impact. The explosion of aromatic nitro compounds, like that of glycerin trinitrate, is a rapid combustion in which the oxygen comes from *within* the molecule itself. Because the nitro groups supply this oxygen, the explosive force increases with the number of nitro groups. Although trinitrobenzene is an excellent explosive, it is so difficult to introduce the third nitro group into benzene that the manufacture is out of the question. A military high explosive is made from benzene by first preparing phenol (p. 271), which is then nitrated to picric acid (**PA**), see below. This differs from TNT only in having a hydroxyl group in place of a methyl.

NITROPHENOLS

Nitration of Phenol. The ortho and para nitrophenols may be prepared by the nitration of phenol with dilute nitric acid. The fact that dilute acid may be employed is another illustration of the accelerating influence of a group of Class I (p. 267) on substitution reactions.

Further nitration of ortho and para nitrophenol yields **2,4-dinitrophenol,** $C_6H_3(OH)(NO_2)_2$ (mp 112°), and eventually 2,4,6-trinitrophenol, $C_6H_2(OH)(NO_2)_3$ (mp 123°), **picric acid (PA)**, an important high explosive. The nitrophenols are only slightly soluble in water.

Picric Acid. In the industrial preparation of picric acid, phenol is dissolved in concentrated sulfuric acid and then treated with nitric acid, first at 0° and then

100°. The process probably involves first the formation of para phenolsulfonic acid, $C_6H_4(OH)SO_3H$, and then the replacement by the nitro group of both the sulfonic acid group and the ortho hydrogen atom, yielding 2,4-dinitrophenol. The final nitration at 100° introduces the third nitro group.

The salts of picric acid with the heavy metals (the picrates) are sensitive explosives when dry and easily detonate when subjected to mechanical shock. Picric acid itself, however, like TNT, is not sensitive and can be used in filling shells. Picric acid is often used in the laboratory in the isolation of bases since its salts with organic bases are often but slightly soluble and usually nicely crystalline. Picric acid forms loose molecular addition compounds with many aromatic hydrocarbons, particularly those containing a number of rings. These crystalline **molecular compounds** are sometimes useful in separating the complex aromatic hydrocarbons.

Sulfur Dyes. Picric acid is a yellow solid and its solutions will color wool and silk, but it is not of importance as a dye. From it, however, by heating with sodium polysulfide solution is obtained the important dye **sulfur black.** (The United States production of this dye in 1940 exceeded 16,000 tons.) The structure of sulfur black, which can also be prepared from 2,4-dinitrophenol and sodium sulfide, is not known.

Sulfur black is the most important member of the group of sulfur dyes prepared by heating various aromatic nitrophenols, aminophenols, or amines with sodium polysulfide. The sulfur dyes are usually applied by dissolving them in sodium sulfide solution and dyeing the cloth in this solution. They are used with cotton.

The Acidic Properties of the Nitrophenols.

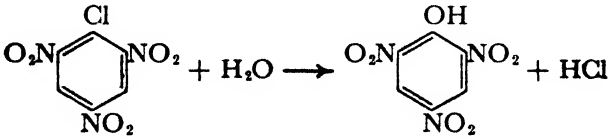
The remarkable influence of the nitro group is strikingly shown by a comparison of the acidic properties of phenol and its nitro derivatives.

Phenol and most of its simple derivatives are such weak acids that they will not dissolve in sodium bicarbonate. 2,4-Dinitrophenol, however, will dissolve in an aqueous solution of this reagent because it is as strong an acid as formic acid and readily replaces carbonic acid from its salts. Trinitrophenol (picric acid) is nearly as strong as the mineral acids. The dissociation constants are as follows:

Phenol	1.7×10^{-10}
p-Nitrophenol	6.4×10^{-8}
2,4-Dinitrophenol	1.0×10^{-4}
Picric acid	1.6×10^{-1}

The dissociation constants of carbonic acid are: $H_2CO_3 \rightleftarrows HCO_3^- + H^+$, 1×10^{-7} and $HCO_3^- \rightleftarrows CO_3^{=} + H^+$, 5×10^{-11} (p. 106). Many phenols may be separated from acids and nitrophenols by the difference in solubility in sodium bicarbonate solution. The solubility of an acid in a given alkaline solution (with the formation of a salt) depends on two factors: (1) the strength of the acid group and (2) the solubility. Phenols of high molecular weight are often only very slightly soluble and will not dissolve even in dilute sodium hydroxide. Similar considerations apply to acids. However, as a general rule, acids of low molecular weight may be extracted from an ether solution by sodium bicarbonate or sodium carbonate while phenols require sodium hydroxide. The nitrophenols, however, are often extracted by sodium carbonate since they are stronger acids if the nitro groups are in the ortho or para position to the hydroxyl. Like the phenols, many highly enolic substances are soluble in dilute sodium hydroxide and may be extracted by this reagent.

Reactivity of Nitro Aryl Halides. We have just seen the marked effect of a nitro group in the ortho or para position on the acidity of a phenol. The nitro group modifies the molecule so that the hydroxyl group is more acidic. The influence of the nitro group is not confined to a hydroxyl group, but also extends to a halogen atom in the ortho or para position. Here, the effect of the nitro group is to make the halogen atom much more readily replaced by such groups as OH, NH_2, and OCH_3. The effect is cumulative. 2,4,6-Trinitrochlorobenzene (picryl chloride) is converted to picric acid when it is boiled with water alone.



AROMATIC AMINES

Classification. The aromatic amines, like the aliphatic amines, are divided into three classes: (1) **primary amines,** (2) **secondary amines,** and (3) **tertiary amines.** As an example of each class we may mention: (1) **aniline, $C_6H_5NH_2$,** (2) **diphenylamine, $(C_6H_5)_2NH$,** and (3) **triphenylamine, $(C_6H_5)_3N$.** Mixed aliphatic-aromatic amines are also known; for example, **monomethylaniline,** $C_6H_5NHCH_3$, and **dimethylaniline,**

$C_6H_5N(CH_3)_2$. The primary aromatic amines and the mixed amines are usually weak bases which form salts with mineral acids; the secondary and tertiary aromatic amines are too weak to form salts which are stable in water solution.

Physical Properties. The physical properties of some common aromatic amines are given in the table below. All the substances listed in the table except the last two are soluble in dilute hydrochloric or sulfuric acid because they form water-soluble salts with these acids.

Name	*Formula*	*Boiling Point*	*Melting Point*	*Solubility Grams per 100 Grams of Water*
Aniline	$C_6H_5NH_2$	184°	−6°	3.5 at 25°
o-Toluidine	$CH_3C_6H_4NH_2$	201°	−21°	1.5 at 25°
m-Toluidine	$CH_3C_6H_4NH_2$	203°	−32°	Slightly soluble
p-Toluidine	$CH_3C_6H_4NH_2$	201°	+44°	0.730 at 21°
Monomethylaniline	$C_6H_5NHCH_3$	196°	−57°	Very slightly soluble
Dimethylaniline	$C_6H_5N(CH_3)_2$	194°	+2°	Very slightly soluble
Diphenylamine	$(C_6H_5)_2NH$	302°	53°	Insoluble
Triphenylamine	$(C_6H_5)_3N$	365°	127°	Insoluble

Preparation of Aniline, a Primary Amine. Aniline, $C_6H_5NH_2$, is prepared by the reduction of nitrobenzene.

$$C_6H_5NO_2 + 6[H] \longrightarrow C_6H_5NH_2 + 2H_2O$$

In the laboratory, tin and hydrochloric acid are usually employed; industrially, the cheaper scrap iron replaces the tin and only a little acid is employed. The industrial process, thus, is essentially the reduction of nitrobenzene by iron and water, the products being aniline and ferric hydroxide; these are separated by steam distillation (Fig. 12). Nitro compounds are smoothly reduced to amines by catalytic hydrogenation.

Aniline is also made commercially by heating chlorobenzene and ammonia at about 200° with a mixture of cuprous oxide and cuprous chloride. The latter is a catalyst while the cuprous oxide participates in the reaction.

$$2C_6H_5Cl + 2NH_3 + Cu_2O \xrightarrow{Cu_2Cl_2} 2C_6H_5NH_2 + Cu_2Cl_2 + H_2O$$

The recovered cuprous chloride is treated with alkali to convert most of it to the oxide, and the mixture is then used for the next charge.

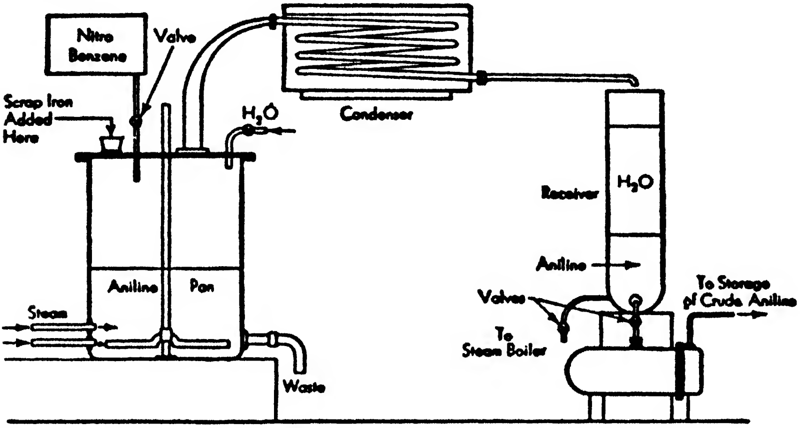


Fig. 12. Diagram illustrating the essential equipment used in the industrial preparation of aniline. The nitrobenzene, water and a little acid are first introduced into the reaction vessel. Scrap iron is dropped in through a manhole and the mixture stirred. After the reduction is complete, steam is introduced; the vapors are condensed and the distillate allowed to settle in tall tanks. The crude aniline is drawn off, the water goes to the steam generator.

Monomethylaniline and Dimethylaniline. These amines are formed when aniline is heated with methyl alcohol and hydrochloric acid under pressure. The apparatus in which such reactions are carried out under pressure is called an *autoclave* (Fig. 13). The methyl alcohol and hydrogen chloride first form methyl chloride which then reacts with the primary amine (p. 158), yielding the hydrochloride of monomethylaniline.

$$C_6H_5NH_2 + CH_3Cl \longrightarrow C_6H_5NHCH_3 \cdot HCl$$

By varying the temperature and proportions of reacting materials either monomethylaniline or dimethylaniline may be prepared. Both are important substances in the manufacture of dyes.

Aniline and its alkyl derivatives such as monomethyl- and dimethyl-aniline are weak bases with basic dissociation constants of about 3×10^{-10}. It will be recalled that ammonia has the value of 2×10^{-5} and the aliphatic amines about 5×10^{-4} (p. 157).

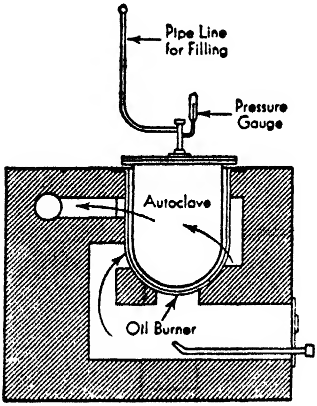
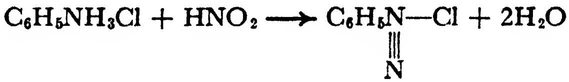


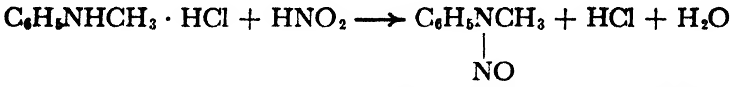
Fig. 13. Autoclave employed in the industrial preparation of dimethylaniline.

Reaction with Nitrous Acid. Primary, secondary, and tertiary amines differ in their reaction with nitrous acid. This may be illustrated by comparing the action of this reagent with aniline, monomethylaniline, and dimethylaniline. With the first, a water-soluble **diazonium salt,** $C_6H_5N_2Cl$, is formed. This compound will be further considered shortly.



$$C_6H_5NH_3Cl + HNO_2 \longrightarrow C_6H_5\underset{\underset{N}{|||}}{N}—Cl + 2H_2O$$

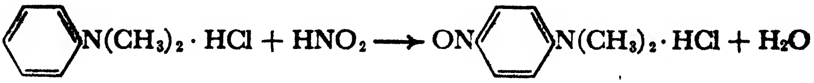
With monomethylaniline, a yellow, oily **nitroso compound** is produced.



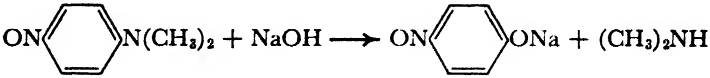
$$C_6H_5NHCH_3 \cdot HCl + HNO_2 \longrightarrow C_6H_5\underset{\underset{NO}{|}}{N}CH_3 + HCl + H_2O$$

This substance is such a weak base that it will not dissolve in aqueous acid solutions. When treated with alcoholic hydrogen chloride, the nitroso group migrates from the nitrogen to the para position of the nucleus.

The para hydrogen atom in the nucleus of dimethylaniline is unusually reactive and is replaced by the **nitroso group** when the compound is treated with dilute nitrous acid. The product is the hydrochloride of ***p*-nitrosodimethylaniline** which is a yellow, crystalline solid.

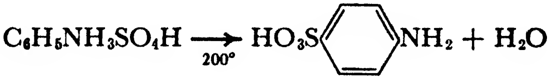


The nitroso group, like the nitro group, profoundly affects an atom or group attached to the ortho or para position of the aromatic nucleus. For this reason, *p*-nitrosodimethylaniline, on boiling with alkali, decomposes forming dimethylamine and the salt of the corresponding hydroxyl compound (nitroso phenol).



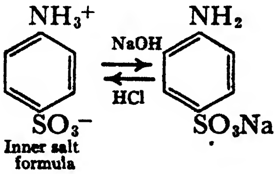
This is probably the best method of preparing pure dimethylamine.

Sulfanilic Acid. Aniline may be sulfonated, producing the para sulfonic acid. The amine is first neutralized with concentrated sulfuric acid, forming the solid **aniline acid sulfate,** $C_6H_5NH_3SO_4H$. This, on baking in an oven at 200°, forms sulfanilic acid and water.



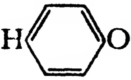
Sulfanilic acid is a solid only slightly soluble in organic solvents and in water. It is nonvolatile and has no definite melting point; in these respects it resembles an inorganic salt rather than an organic compound. It is soluble in sodium carbonate or sodium hydroxide, forming a sodium salt; acidification precipitates sulfanilic acid. It has such weak basic properties that it does not dissolve even in concentrated hydrochloric acid.

Inner Salt Formula for Sulfanilic Acid. All the facts mentioned in the last paragraph are best represented by the inner salt formula already encountered in amino acids (Chap. 14).



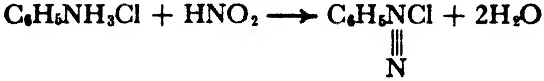
This formula is written to indicate that an internal neutralization has occurred. In this process the acid hydrogen of the sulfonic acid group has added to the NH_2 group. The "linkage" between the NH_3^+ group and the SO_3^- group is of the sort which we meet in inorganic salts such as sodium chloride and ammonium sulfate. This linkage we are quite certain is not a linkage in the sense of the ordinary valence formulas used in organic chemistry; it merely represents an electrical field between two charged atoms or molecules.

In the inner salts, we imagine that the positive and negative charges are localized on particular groups of the large molecule. The simple formula, $NH_2C_6H_4SO_3H$, is often written for sulfanilic acid, but the representation, $NH_3^+C_6H_4SO_3^-$, is to be preferred. Inner salts differ from salts such as sodium chloride in that the positive and negative ions are not free to part company in solution. Inner salts are ionized but not dissociated.

Acetanilide, $CH_3CONHC_6H_5$, is the acetyl derivative of aniline. It is a substance of considerable importance both as an intermediate in the preparation of organic compounds and as a drug. It is one of the oldest of the so-called coal-tar medicinals. It has an effect on the human system which causes the lowering of the temperature of a patient suffering with fever. A substance which has this action is said to be an *antipyretic* or *febrifuge.* Acetanilide has been used less extensively in recent years for this purpose because more efficient and relatively less harmful drugs have been synthesized (e.g., phenacetin, CH_3CONHOC_2H_5).

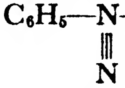
THE DIAZONIUM SALTS

Diazotization. The synthesis of aromatic compounds is greatly facilitated by the easy conversion of aromatic primary amines into **diazonium salts.** These compounds are very reactive, and from them many different types of products may be prepared. The process of converting the salt of a **primary aromatic amine** into the **diazonium salt** is called **diazotization.** It is usually carried out by dissolving the amine in dilute aqueous acid and adding a solution of sodium nitrite. It is necessary to keep the temperature low, as otherwise both the nitrous acid and the diazonium salt may decompose.

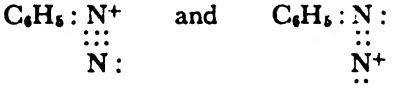


$$C_6H_5NH_3Cl + HNO_2 \longrightarrow C_6H_5\underset{\substack{|||\\ N}}{N}Cl + 2H_2O$$

Structure of Diazonium Salts. The diazonium salts may be represented as ArN_2X, in which Ar is an aryl group, such as phenyl, and X, an acid group. In solution, they are dissociated into the ions $ArN_2^+ + X^-$. The formula $C_6H_5—\underset{\substack{|||\\ N}}{N}—Cl$ is usually preferred to $C_6H_5N{=}N—Cl$. The substance, $C_6H_5N_2Cl$, is called *benzenediazonium chloride*. The reactions of a diazonium salt are thus essentially the reactions of the diazonium ion. This ion is very unstable and reactive and undergoes varied transformations which depend on the conditions.



The problem of the structure of the diazonium salts is the problem of the position of the positive charge on the diazonium ion. In other words, the location of an electron is involved. The two formulas



$$C_6H_5:\underset{\substack{\cdots\\ \cdots\\ N:}}{N^+} \qquad \text{and} \qquad C_6H_5:\underset{\substack{\cdot\cdot\\ \cdot\cdot\\ N^+\\ \cdot\cdot}}{N}:$$

represent two resonating structures and the ion is a resonance hybrid.

Reactions of Diazonium Salts. The following reactions of diazonium salts are of great synthetic value. Although they will be illustrated by considering benzenediazonium chloride, it is important to bear in mind that *a diazonium salt from any primary aromatic amine* will behave in the same manner.

1. The Replacement of N_2X by OH.

This is brought about by heating an aqueous solution of the diazotized amine. The solution should be strongly acid to avoid the coupling reaction between phenol and undecomposed diazonium salt, a reaction which is discussed on p. 291.

$$C_6H_5N_2Cl + H_2O \longrightarrow C_6H_5OH + N_2 + HCl$$

2. The Replacement of N_2X by H.

Some diazonium salts are converted to the corresponding hydrocarbon by heating them with ethyl alcohol.

$$C_6H_5N_2Cl + C_2H_5OH \xrightarrow{\text{Heat}} C_6H_6 + N_2 + HCl + CH_3CHO$$

This method is not general since very frequently an ether is formed.

$$C_6H_5N_2Cl + C_2H_5OH \longrightarrow C_6H_5OC_2H_5 + N_2 + HCl$$

With benzenediazonium chloride a mixture of the hydrocarbon and ether is formed. The course of the reaction of diazonium salts with alcohols depends largely on the nature of the alcohol, the diazonium salt, and on the conditions of experiment.

A more general procedure for the conversion of a diazonium salt to the corresponding hydrocarbon is treatment with hypophosphorous acid.

$$C_6H_5N_2Cl + H_3PO_2 + H_2O \longrightarrow C_6H_6 + H_3PO_3 + HCl + N_2$$

3. The Replacement of N_2X by Halogens.

In this reaction the solution is kept as concentrated as possible and 1 mole of cuprous salt and a considerable amount of halogen acid are added. A complex compound between the cuprous salt and the diazonium salt is first formed and often precipitates. This slowly decomposes and yields the aryl halide and nitrogen.

$$C_6H_5N_2Cl + \underset{\text{Where X = Cl or Br}}{Cu_2X_2} + HX \longrightarrow C_6H_5X + N_2 + HCl + Cu_2X_2$$

The introduction of an iodine atom does not require the use of a cuprous salt. Hydrogen iodide or its salts may be used.

4. Replacement of N_2X by CN.

This reaction takes place when sodium cyanide and cuprous cyanide are used.

$$C_6H_5N_2Cl + Cu_2(CN)_2 + NaCN \longrightarrow C_6H_5CN + N_2 + NaCl + Cu_2(CN)_2$$

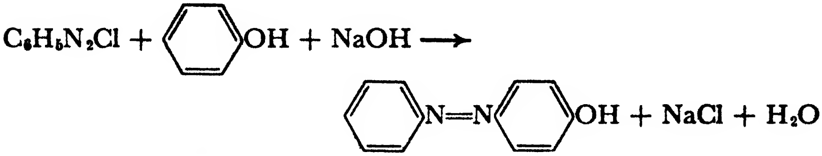
The preceding two reactions are often called the *Sandmeyer reaction*. If finely divided copper is used as the catalyst, the reaction is known as the *Gattermann reaction*.

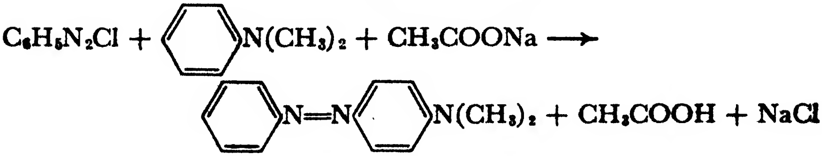
Phenylhydrazine, $C_6H_5NHNH_2$. When an aqueous solution of benzenediazonium chloride is reduced, the hydrochloride of phenylhydrazine is formed.

$$C_6H_5N_2Cl + 4[H] \longrightarrow C_6H_5NHNH_3Cl$$

Stannous chloride in hydrochloric acid or sodium sulfite are the usual reducing agents employed. The free base can be prepared from the salt in the usual manner. Phenylhydrazine may be considered as the phenyl derivative of the inorganic base **hydrazine,** NH_2NH_2. It has been of great value in the laboratory because it reacts with ketones and aldehydes forming crystalline compounds called *phenylhydrazones.* These have proved very useful in the identification and isolation of ketones and aldehydes (p. 95). Indeed, the discovery of phenylhydrazine by Emil Fischer in 1875 enabled him to make great advances in our knowledge of the carbohydrates (p. 204).

The Coupling of Diazonium Salts. The usefulness of the diazonium salts is not exhausted with the replacement reactions we have just considered. This remarkable class of compounds is also the basis of one branch of the synthetic coal-tar dye industry. All the azo dyes are prepared by the so-called coupling of diazonium salts. This coupling reaction takes place when a *phenol* or *aryl amine* is treated with a diazonium salt solution. Sodium acetate, sodium carbonate, or sodium hydroxide is added to make the mixture less acid.



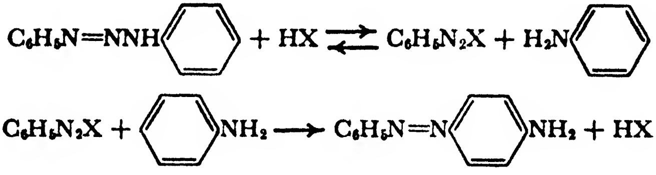


It will be noted, in the examples given above, that the coupling reaction has taken place in the para position. The ortho and para hydrogen atoms in phenols and tertiary amines are reactive and, therefore, the process takes place with these compounds. Hydrocarbons, with only a few exceptions, will not couple with diazonium salts. If a primary or secondary aryl amine is used, the coupling takes place on the nitrogen atom.

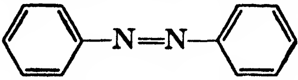
$$C_6H_5N_2Cl + C_6H_5NH_2 + CH_3COONa \longrightarrow C_6H_5N{=}NNHC_6H_5 + NaCl + CH_3COOH$$

On heating the resulting compound in weakly acid solution or with aniline hydrochloride, a rearrangement occurs, and a product is formed, $C_6H_5N{=}NC_6H_4NH_2$, which corresponds to that produced by direct para coupling with the tertiary amine.

The mechanism of this process involves the hydrolysis of the diazoamino compound back to the diazonium salt and amine which then slowly couple the other way round.



Ordinarily, the coupling of primary and secondary amines is carried out in slightly acid medium. Under these conditions direct para or ortho coupling occurs.

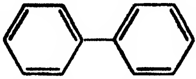
Nomenclature of Azo Compounds. The substances produced by coupling a diazotized aryl amine and a phenol or tertiary amine are derivatives of **azobenzene**, a compound which is prepared by the partial reduction of nitrobenzene and has the structure . Thus, the product of the interaction of diazotized aniline and phenol is called *p-hydroxyazobenzene;* the compound from dimethylaniline and benzenediazonium chloride is *p-dimethylaminoazobenzene*. The compound first formed in the coupling of aniline and diazotized aniline, $C_6H_5N_2NHC_6H_5$, is known as *diazoaminobenzene*. In general, *diazo compounds* contain the grouping $ArN{=}N{-}Z$, where Ar is any aryl group and Z any group not linked through carbon to the nitrogen. The *azo compounds* contain the group —N=N— with a carbon to nitrogen linkage on both sides as in azobenzene itself.

THE AZO DYES

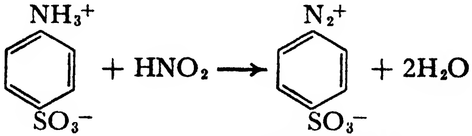
All aromatic azo compounds are colored. Some can be applied to fabrics so as to give the fabric a color that is resistant to washing with soap and water. The members of this second and smaller group are dyes: more specifically, azo dyes.

The azo dyes constitute just one of several large classes of synthetic dyes. Almost all these dyes are aromatic compounds and, consequently, they are referred to collectively as *coal-tar dyes*. We shall have occasion later to mention other groups of organic dyes: the phthaleins (p. 312) and the triphenylmethane dyes (p. 319). The first synthetic dye was a triphenylmethane dye, and when we discuss this group of dyes we shall say something about the origin and development of the coal-tar dye industry.

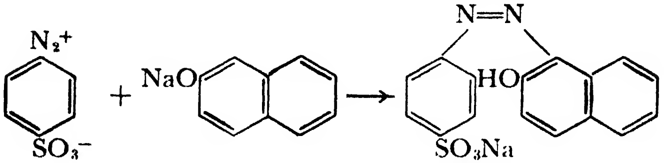
The useful azo dyes are *direct* to wool and silk; that is, they will dye these fibers when the cloth is kept for a short time in a boiling solution of the dye. Wool and silk are proteins which contain both acid and basic groups. Direct dyes for these fibers also contain acid or basic groups. Acid azo dyes usually contain the sulfonic acid group, which also makes the dye soluble in water; basic azo dyes usually contain the dialkylamino group.

The azo dyes are prepared by the coupling reaction described above, but starting with more complex diazonium salts, amines, and phenols. As a result the industrially important azo dyes are fairly complex substances. The *intermediates* used in their preparation (the amines to be diazotized, and the amines or phenols with which the coupling takes place) are highly substituted aromatic compounds, often derivatives of naphthalene (p. 325), or biphenyl, , and they go under trivial names since their scientific names are so cumbersome. This is even more true of the final products, the dyes themselves.

A typical acid dye is Orange II (note the name!), prepared by coupling diazotized sulfanilic acid with β-naphthol (a hydroxyl derivative of naphthalene quite analogous to phenol).

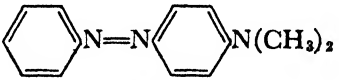


Inner diazonium salt



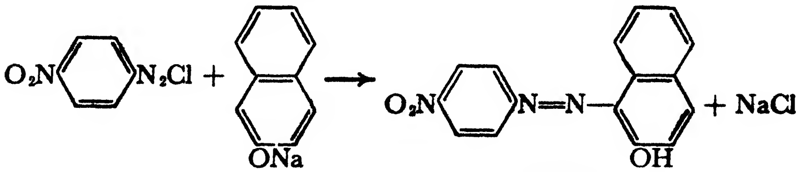
Orange II

A typical basic azo dye is *butter yellow*, prepared by coupling benzenediazonium chloride with dimethylaniline. Its scientific name is *p*-dimethylaminoazobenzene.



Butter yellow

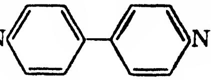
Azo Dyes for Cotton. Cotton, essentially cellulose, is a neutral substance, and the acid and basic dyes which are direct to silk and wool are not direct to cotton. They can be made direct to cotton by a special method of application in which the coupling reaction to form the dye is carried out in the fibers of the cloth. This may be done by impregnating the cloth with an alkaline solution of a phenol or amine and then passing the cloth through a solution of the diazonium salt. Dyes produced in this way are known as *ingrain colors*. If cloth is impregnated with an alkaline solution of β-naphthol and then passed through a solution of diazotized para nitroaniline the ingrain dye, *para red*, is formed.



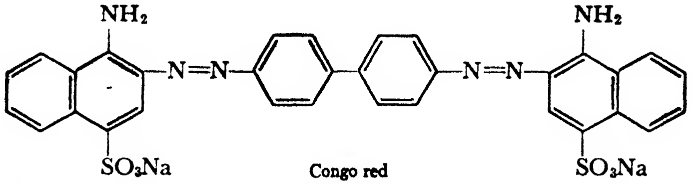
Para red

A variant of this procedure leads to the **developed dyes.** A cloth is dyed with a dye which contains a primary amino group. The cloth is then led through a cold dilute solution of nitrous acid, and then at once through an alkaline solution of a phenol or an amine. The nitrous acid diazotizes the primary amine which then couples with the phenol or amine.

One group of acid azo dyes is for some unknown reason direct to cotton. The members of the group are also direct to wool and silk by virtue of being acid dyes. For this reason, they may be used on mixed materials and are sometimes called *union colors*. The dyes which are sold for household use usually belong to this class since they are designed for use as direct dyes for wool, silk, or cotton.

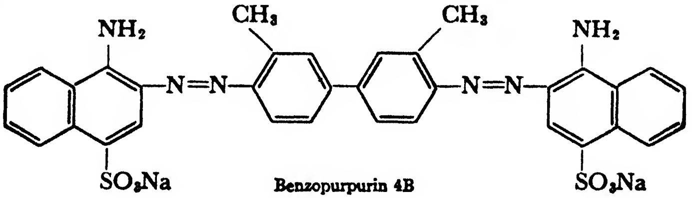
Practically all these direct cotton dyes have two or more azo linkages and two or more sulfonate groups. They are prepared by the double diazotization and coupling of certain diamines. One of the most important of the diamines which will form direct cotton dyes is **benzidine,** H_2NNH_2.

The two primary amino groups in this compound can be diazotized in the usual way, and the *bis*-diazonium salt coupled with sulfonated phenols or amines to give dyes. One of the simplest of these compounds is *Congo red,* which has the formula:



Congo red

The closely related Benzopurpurin 4B is one of the most important direct cotton colors.



Benzopurpurin 4B

QUESTIONS AND PROBLEMS

1. What is the inner salt formula for sulfanilic acid? Why is this formula written for the compound? What other substances which exist as inner salts have you encountered earlier in this course?

2. Write structural formulas for 2-hydroxy-4-nitrotoluene, benzidine, *p*-nitroazobenzene, 2,4,6-trinitroaniline, 3,5-dinitrochlorobenzene, diazoaminobenzene.

3. Write balanced equations for the action of nitrous acid on $C_6H_5NHCH_3$, $CH_3NHC_2H_5$, $CH_3CH_2CONH_2$, $CH_3NHCOOC_2H_5$, $C_6H_5N(C_2H_5)_2$, CH_3NH_2, *p*-$BrC_6H_4NH_2$, and $(CH_3)_2NC_2H_5$.

4. Write structural and electronic formulas for benzenediazonium chloride. How are diazonium salts prepared?

5. Write equations for the replacement reactions of *p*-nitrobenzenediazonium chloride.

6. Why is *p*-hydroxyazobenzene not a dye, though it is a deeply colored compound?

7. What types of azo dyes are fast to wool and silk? Can you offer an explanation for the fact that these dyes are fast to wool and silk, but not to cotton?

8. What group of azo dyes are fast to cotton? How can other groups of azo dyes not ordinarily fast to cotton be applied so that they are fast to that fabric?

9. Write balanced equations and specify the experimental conditions for two methods of reducing nitro compounds to amines.

10. Write the equations for the preparation of phenylhydrazine from aniline and for the reaction between phenylhydrazine and (*a*) acetone, (*b*) *n*-butyraldehyde, and (*c*) glucose.

CHAPTER 19

Aromatic Alcohols, Aldehydes, Ketones, and Acids

In this chapter we shall consider a variety of compounds which occur in plants and which are related to aromatic aldehydes, alcohols, and acids. One group consists of volatile sweet-smelling materials present in the essential oils; another is related to the amorphous material called lignin that is present in wood fiber together with cellulose. We shall likewise study a few simple benzene derivatives in which a single functional group such as the aldehyde or carboxyl group is attached to the ring. Certain aromatic acids are prepared on a large scale for industrial use; one, in particular, phthalic acid, is the basis of the preparation of an important class of synthetic resins. Therefore the chapter concludes with a discussion of modern plastics.

AROMATIC ALDEHYDES

It is usual to limit the term *aromatic aldehyde* to those compounds in which the aldehyde group is directly attached to the aromatic nucleus. The aromatic aldehydes are similar in their carbonyl group reactions to the aliphatic aldehydes considered in Chap. 6. However, since the aromatic aldehydes do not contain alpha hydrogen atoms and do contain an aromatic nucleus, they differ in some reactions from the typical aliphatic aldehydes. These similarities and differences can best be illustrated by considering in detail the simplest aromatic aldehyde which is also the most important from the industrial standpoint.

Benzaldehyde, C_6H_5CHO. This aldehyde (bp 180°) is much used in the synthesis of compounds which contain aromatic groups. It is also employed as a perfume and flavoring material under the name of *oil of bitter almonds*. Before the development of the coal-tar dye industry it was prepared by crushing bitter almonds with water. These nuts contain a glucoside, **amygdalin**, and an enzyme which causes its hydrolysis to glucose, hydrocyanic acid, and benzaldehyde.

Benzaldehyde is now prepared industrially from toluene directly or from its chlorination products, benzyl chloride, $C_6H_5CH_2Cl$ or benzal chloride, $C_6H_5CHCl_2$ (p. 265).

The oxidation of toluene to benzaldehyde is brought about by the use of manganese dioxide and sulfuric acid with the addition of copper sulfate as catalyst.

$$C_6H_5CH_3 + [O] \xrightarrow[H_2SO_4]{MnO_2} C_6H_5CHO + H_2O$$

It is obvious that the production of an aldehyde by oxidation procedures must involve the use of special oxidizing agents and controlled conditions, as otherwise the aldehyde will be further oxidized to the corresponding acid.

The conversion of benzyl chloride to benzaldehyde is accomplished by oxidation with an aqueous solution of lead or copper nitrates. Benzal chloride is readily transformed into benzaldehyde by boiling with water containing a small amount of alkali.

$$C_6H_5CH_2Cl + [O] \xrightarrow{Pb(NO_3)_2} C_6H_5CHO + HCl$$

$$C_6H_5CHCl_2 + H_2O \xrightarrow[CaCO_3]{100°} C_6H_5CHO + 2HCl$$

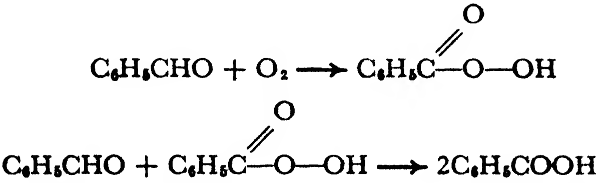
The above methods are applicable to the preparation of other aromatic aldehydes from the corresponding methyl compounds.

Characteristics of Aromatic Aldehydes. Benzaldehyde and its derivatives are similar to those aliphatic aldehydes which have *no hydrogen in the alpha position*, for example, $(CH_3)_3CCHO$ and HCHO (cf. p. 99). They give the fuchsine test, reduce ammoniacal silver nitrate solution, combine with sodium bisulfite, hydrocyanic acid, and the Grignard reagent; they readily form oximes and phenylhydrazones.

Because of the absence of an alpha hydrogen atom, they do not undergo an aldol condensation nor resinify when treated with alkali. Instead they undergo the Cannizzaro reaction (p. 99).

$$2C_6H_5CHO + NaOH \longrightarrow \underset{\text{Benzyl alcohol}}{C_6H_5CH_2OH} + \underset{\text{Sodium benzoate}}{C_6H_5COONa}$$

Autoöxidation. Benzaldehyde and certain of its derivatives absorb oxygen fairly rapidly when exposed to the air, forming derivatives of hydrogen peroxide. Benzaldehyde itself forms **benzoyl hydrogen peroxide,** C_6H_5COOOH, or **perbenzoic acid.** The peroxide then oxidizes another molecule of benzaldehyde to benzoic acid. The process is called *autoöxidation.*



$$C_6H_5CHO + O_2 \longrightarrow C_6H_5\overset{\overset{\displaystyle O}{/\!/}}{C}{-}O{-}OH$$

$$C_6H_5CHO + C_6H_5\overset{\overset{\displaystyle O}{/\!/}}{C}{-}O{-}OH \longrightarrow 2C_6H_5COOH$$

Although autoöxidation is a common reaction, only from benzaldehyde has an intermediate peroxide been isolated; however, peroxide formation probably is a necessary step in all autoöxidations. The reaction is autocatalytic; at the beginning the reaction is very slow and gradually it increases to a maximum velocity. The induction period (the time before the reaction is noticeable) indicates that either a certain concentration of peroxide must be formed before the rate becomes appreciable or minute amounts of impurities present as inhibitors must be removed. Generally autoöxidations are very sensitive to catalysts, either positive or negative. Those of the latter class probably react with the intermediate peroxide and thus destroy it. Among such negative catalysts, which are called *antioxidants,* are those polyhydroxy compounds which are readily dehydrogenated by very mild oxidizing agents (Chap. 17). As little as 0.001 per cent of hydroquinone in benzaldehyde will prevent its autoöxidation.

Quite frequently substances which are perfectly stable to oxygen are oxidized when added to a system capable of undergoing autoöxidation. A general equation for an autoöxidation may be written in which A is the substance which forms a peroxide AO_2, and B the substance which takes oxygen away from the peroxide (acceptor). The acceptor may be another molecule of A or another easily oxidized compound.

$O_2 + A \longrightarrow AO_2$ Peroxide formation

$AO_2 + B \longrightarrow BO + AO$ Peroxide oxidizes acceptor

It often happens that the substance B (the acceptor) is not directly oxidized by atmospheric oxygen. The substance A (e.g., benzaldehyde) thus serves to bring about the indirect oxidation of B. This is another example of a *coupled reaction* (pp. 141, 248), the oxidation of A being coupled to that of B. Since both oxidations are exothermic the coupling does not serve to provide energy to an otherwise endothermic process; instead it provides a special mechanism (peroxide formation) which increases the **rate** of oxidation of B.

Compounds which may polymerize often do so when they undergo autoöxidation, and peroxides are catalysts for many important polymerization processes. This probably means that the energy of the peroxide has been passed tole a mocule of the substrate which is now in an active state ready either to combine with oxygen (autoöxidation) or with another molecule (the first step in polymerization). The effect of peroxides on the addition of hydrogen bromide to ethylenic compounds (p. 56) is another example of a chain reaction. The discoloration and gum formation of cracked gasolines and the resinification of acrylic esters are catalyzed by autoöxidation. The addition of small amounts of inhibitors is essential in storing these substances since the antioxidants prevent autoöxidation and subsequent polymerization.

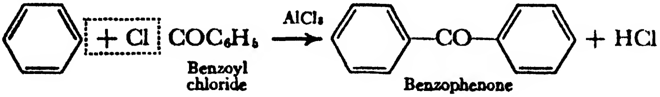
The drying of oil paints is another illustration of polymerization induced by autoöxidation. Positive catalysts are often added to speed up the autoöxidation process (quick-drying paints).

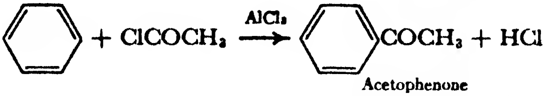
AROMATIC KETONES

Aromatic ketones may be divided into three classes on the basis of the relationship of the aryl groups to the carbonyl group. The first class may be represented by **benzophenone,** $C_6H_5COC_6H_5$; the second by **acetophenone,** $C_6H_5COCH_3$; and the third by **dibenzyl ketone,** $C_6H_5CH_2COCH_2C_6H_5$. The members of all three classes resemble the aliphatic ketones in most of their chemical properties. However, the immediate connection of an aryl group to a carbonyl group sets off the first two classes somewhat from the third, whose methods of preparation and whose reactions are those of the aliphatic ketones. We shall, therefore, consider a few representatives of the first two classes of ketones.

Methods of Synthesis. Aromatic ketones may be synthesized by most of the methods outlined in Chap. 6 for the preparation of aliphatic ketones: passing the vapors of the corresponding acids over metallic oxide catalysts, hydrolysis of dihalides, and oxidation of secondary alcohols.

In addition to these general methods of synthesizing aliphatic and aromatic ketones, there is one specific method for preparing aromatic ketones which contain the grouping ArCO—. This is the Friedel-Crafts reaction using an acid chloride, anhydrous aluminum chloride, and an aromatic hydrocarbon. It may be illustrated by the preparation of benzophenone (diphenyl ketone) and acetophenone (phenyl methyl ketone).

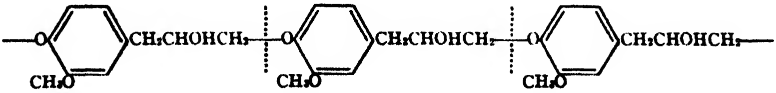




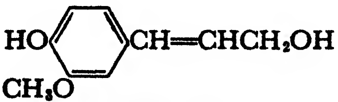
The aluminum chloride is a catalyst in this reaction. However, 1 mole of the catalyst must be employed because it usually combines with the product to form a loose addition compound, and thus is removed continuously from the reaction.

LIGNIN

It will be recalled that cellulose aggregates in wood fiber are associated with an amorphous material of high molecular weight known as lignin (p. 211). The probable fundamental unit of lignin is indicated in the following formula which must be regarded as tentative.

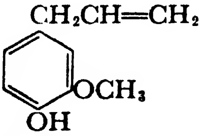


It will be noted that the units are joined together by an ether linkage between a primary hydroxyl group and a phenolic group. This unit is not found free in nature, but a closely related alcohol is found as a glucoside in the sap of coniferous trees. It is known as **coniferyl alcohol**; inspection shows that it may be regarded as a dehydration product of the hypothetical structural unit of lignin.

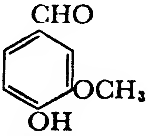


Coniferyl alcohol

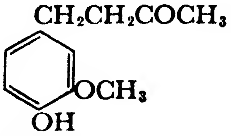
Phenolic Alcohols and Aldehydes in Plants. A number of the higher plants produce substances which seem to be related in one way or another to lignin. Coniferyl alcohol is an example. **Eugenol,** the chief constituent of oil of cloves, is another. **Vanillin,** the principal odoriferous constituent of the vanilla bean, is a third. **Zingerone,** one of the constituents of ginger which imparts a biting taste to this material, is a fourth. All these compounds contain an aromatic ring carrying two phenolic groups, one of which is found as a monomethyl ether.



Eugenol



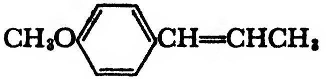
Vanillin



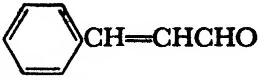
Zingerone

Vanillin can be obtained from the decomposition products of lignin found in waste sulfite liquors of the pulp industry (p. 211). It is usually prepared industrially from eugenol by heating that substance with alkali which furnishes *isoeugenol,* the isomer which contains the double bond adjacent to the ring. Oxidation of isoeugenol produces vanillin.

Essential Oils and Synthetic Perfumes. Almost all the higher plants contain fragrant volatile products which can be isolated by steam distillation. These are termed the **essential oils.** Many are of commercial importance. The essential oils are usually mixtures of compounds and include representatives of aliphatic, alicyclic, and aromatic compounds. The terpenes (p. 338) belong in this group as do the materials referred to in the preceding paragraph. Two aromatic compounds may be mentioned as being the chief constituents of certain important essential oils. Oil of anise is 90 per cent anethole, while oil of cinnamon and oil of cassia contain large quantities of cinnamic aldehyde.



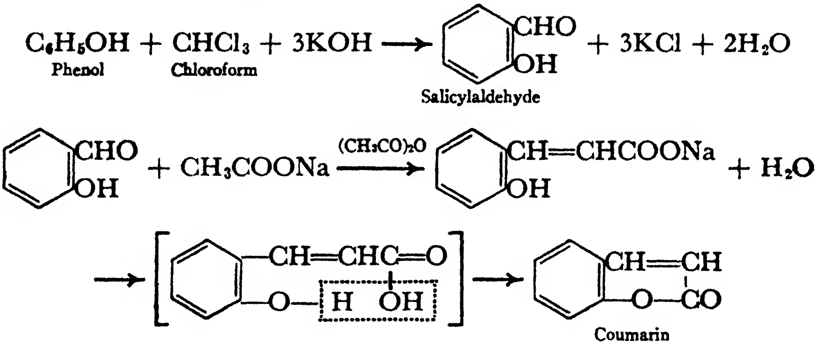
Anethole



Cinnamic aldehyde

Some aromatic aldehydes, esters of the higher aliphatic acids (p. 115), and certain compounds found in nature such as vanillin are now prepared synthetically for use in perfumes. One of the most interesting of these is *coumarin*, which has the odor of new-mown hay and is widely distributed in nature as a glucoside. It occurs particularly in tonka beans from which it may be readily extracted, but it is now prepared synthetically. To understand the synthesis one must realize that the structural formula of this substance corresponds to an inner ester or lactone of an ortho hydroxy acid. The aldehyde which is the starting point of the synthesis is salicylaldehyde. This in turn can be prepared from phenol by the action of chloroform and potassium hydroxide.

Synthesis of coumarin:



AROMATIC ACIDS

We shall now consider briefly those acids in which a carboxyl group is directly joined to an aromatic nucleus. On the whole, these acids differ less from the corresponding aliphatic compounds than do any other class of aromatic substances. For this reason, most of the chemical properties need be but briefly discussed. Three aromatic acids (benzoic, salicylic, and phthalic) are of industrial importance because they are used as intermediates in the preparation of dyes, drugs, and solvents. A number of aromatic acids and their derivatives occur in nature, and one large class of tannins is composed of condensation products of a trihydroxy benzoic acid.

Aromatic acids can often be prepared from alkylbenzenes if no other substituent which is sensitive to oxidation is present.

$$C_6H_5CH_2CH_3 + 6[O] \longrightarrow C_6H_5COOH + 2H_2O + CO_2$$

The Grignard reagent provides another route to aromatic acids. In this method an aryl halide is prepared, allowed to react with magnesium, and the organomagnesium compound treated with carbon dioxide. Obviously the method is not applicable if the molecule cannot be halogenated, or if it contains groups which react with the Grignard reagent (e.g., the carbonyl group).

$$C_6H_5Br \xrightarrow[\text{Ether}]{\text{Mg}} C_6H_5MgBr \xrightarrow{CO_2} C_6H_5COOMgBr \xrightarrow{H_2O} C_6H_5COOH$$

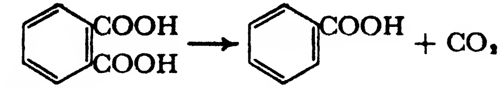
Benzoic Acid. This acid is a white, crystalline solid, melting at 122°, and is slightly soluble in water, easily sublimed, and volatile with steam. It occurs in the natural resin, gum benzoin, and in small amounts in cranberries. It is prepared on a large scale by hydrolysis of **benzotrichloride,** $C_6H_5CCl_3$, which is obtained by chlorinating toluene (p. 265).

$$2C_6H_5CCl_3 + 4Ca(OH)_2 \xrightarrow{\text{Boil}} (C_6H_5COO)_2Ca + 3CaCl_2 + 4H_2O$$

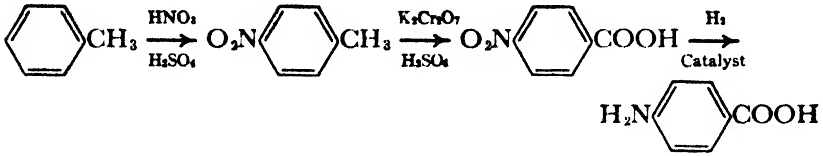
$$(C_6H_5COO)_2Ca + 2HCl \longrightarrow 2C_6H_5COOH + CaCl_2$$

Since benzoic acid is nearly insoluble in cold water, acidification of an aqueous solution of the salt produces a precipitate of the acid.

Benzoic acid is also manufactured by the catalytic decomposition of phthalic acid (p. 309) in the presence of steam. One carboxyl group is removed during this process.



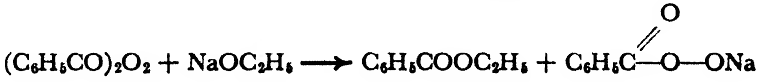
Derivatives of Benzoic Acid. The carboxyl group directs a second substituent into the meta position. The meta substituted derivatives of benzoic acid and its esters are therefore prepared by direct substitution, e.g., meta nitrobenzoic acid by the nitration of benzoic acid. Benzoic acid derivatives containing a substituent in the ortho or para position are generally prepared by synthesizing the corresponding ortho or para substituted toluene and then converting this to the acid by oxidizing the methyl group to a carboxyl group. Thus the important *p*-aminobenzoic acid is made by nitrating toluene to *p*-nitrotoluene, oxidizing this to *p*-nitrobenzoic acid, and reducing the nitro group to an amino group.



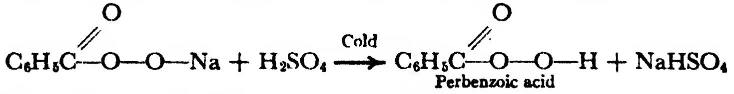
Benzoyl Peroxide. A very interesting compound, which finds use as a catalyst for many polymerization reactions, can be readily prepared by the action of benzoyl chloride on sodium peroxide.

$$2C_6H_5COCl + Na_2O_2 \longrightarrow C_6H_5\overset{O}{\overset{\|}{C}}-O-O-\overset{O}{\overset{\|}{C}}C_6H_5 + 2NaCl$$

Benzoyl peroxide (also known as *dibenzoyl peroxide*) is a colorless, crystalline solid which melts at 103°. It is a derivative of hydrogen peroxide (HOOH), in which both hydrogen atoms have been replaced by acyl groups. When it is treated with sodium ethoxide one benzoyl group is eliminated. The product is the sodium salt of monobenzoyl hydrogen peroxide or **perbenzoic acid.**



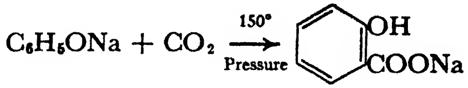
$$(C_6H_5CO)_2O_2 + NaOC_2H_5 \longrightarrow C_6H_5COOC_2H_5 + C_6H_5\overset{O}{\overset{/\!/}{C}}-O-ONa$$



$$C_6H_5\overset{O}{\overset{/\!/}{C}}-O-O-Na + H_2SO_4 \xrightarrow{\text{Cold}} \underset{\text{Perbenzoic acid}}{C_6H_5\overset{O}{\overset{/\!/}{C}}-O-O-H} + NaHSO_4$$

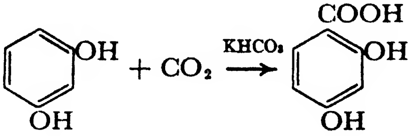
Unlike dibenzoyl peroxide, benzoyl hydrogen peroxide is unstable. It is a powerful oxidizing agent. It reacts with ethylene derivatives, adding one atom of oxygen to the double linkage forming an ethylene oxide derivative. It will be recalled that benzoyl hydrogen peroxide is the reactive intermediate in the autoöxidation of benzaldehyde (p. 299).

Salicylic Acid, $C_6H_4(OH)COOH$ (1,2). This hydroxy acid is a solid melting at 159°; it is more soluble in water than is benzoic acid. Sodium salicylate is prepared by a very remarkable reaction called the Kolbe synthesis which is illustrated by the following equation.



An intermediate phenol carbonate, $C_6H_5OCO_2Na$, is first formed; this then undergoes rearrangement.

The comparable reaction between resorcinol and bicarbonate ion to form β-resorcylic acid takes place in aqueous solution at atmospheric pressure.



Sodium Benzoate and Salicylate as Preservatives. Benzoic acid and salicylic acid in the form of their sodium salts are used as preservatives and very mild antiseptics. Enormous quantities of sodium benzoate are used each year in the preserving of fruits and vegetables, and in the manufacture of "ketchups." The legend "preserved with one tenth of one per cent of benzoate of soda" is probably familiar to all who have had occasion to scrutinize the labels on cans of preserved products. Sodium salicylate is used to a less extent. Sodium benzoate in the quantities used in preserving foods is generally believed to be noninjurious, although this has been a subject of some controversy and discussion. Both sodium benzoate and sodium salicylate are extensively used in the preparation of antiseptic medicinal preparations, such as tooth pastes and mouth washes.

Medicinal Products from Salicylic Acid. The chief use of salicylic acid is in the preparation of three compounds of great medical importance: salol, aspirin, and methyl salicylate. Sodium salicylate itself has valuable medicinal properties, particularly in treating rheumatism. However, when taken through the mouth it is very largely absorbed in the stomach, and this often leads to unpleasant symptoms. Chemists early endeavored to modify the salicylic acid molecule in some way so that these unpleasant effects would be overcome.

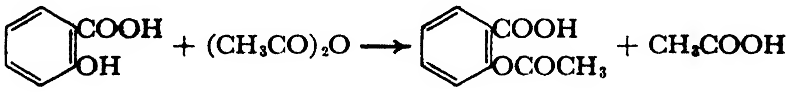
Salol. By esterifying salicylic acid with phenol the phenyl ester known as salol can be prepared.

$$3C_6H_4(OH)COOH(1,2) + 3C_6H_5OH + POCl_3 \xrightarrow{120^\circ} 3C_6H_4(OH)COOC_6H_5 + H_3PO_4 + 3HCl$$

It should be noted that, since salol is an ester of phenol, it cannot be prepared by the usual esterification method; a special procedure involving phosphorus oxychloride and a relatively high temperature is employed.

Salol, being an ester, passes unchanged through the stomach, which is acid, but is hydrolyzed in the intestines, which are alkaline. Phenol and salicylic acid are there liberated and absorbed. Salol is, therefore, a powerful intestinal antiseptic and is widely used as such. It is also employed as a coating for medicinal pills whose content is effective only if liberated in the intestines. Such pills pass through the stomach intact but disintegrate in the intestine. Salol is a crystalline solid melting at 42°.

Aspirin, $C_6H_4(OCOCH_3)COOH$ (1,2). This is another salicylic acid derivative, one of the most familiar of all coal-tar products. It is made by the acetylation of the phenolic group in salicylic acid.



Aspirin is a colorless solid melting at 134°; it is insoluble in water. Its physiological action is probably due to the fact that it is hydrolyzed in the intestines, liberating salicylic acid which is there absorbed by the system. Aspirin has become a popular remedy for all complaints. Over 6100 tons, the equivalent of more than 16,000,000,000 five-grain tablets, were manufactured in the United States in 1947, approximately 100 tablets per person per year!

Methyl Salicylate, C_6H_4 (OH)$COOCH_3$. This ester occurs in certain plants and is the chief constituent of oil of wintergreen. It is a colorless liquid which boils at 224° and has a pleasant wintergreen odor. It is made synthetically by esterifying salicylic acid in the usual manner with methyl alcohol. It is widely used in the flavoring industry and in the preparation of liniments and similar remedies for aches, sprains, and bruises. Methyl salicylate has the rather unusual property of penetrating the skin when rubbed on the surface. Probably hydrolysis takes place when the ester has penetrated, and the liberated salicylic acid has some physiological action which relieves the local pain.

GALLIC ACID AND TANNINS

Gallic Acid, $C_6H_2(OH)_3COOH$ (3,4,5-Trihydroxybenzoic Acid). Gallic acid is prepared by the hydrolysis of **tannins.** *It is not a coal-tar product.* It is a solid soluble in water and crystallizes from the aqueous solution with a molecule of water of crystallization, which it loses on heating. When heated above 200°, it loses carbon dioxide and forms pyrogallol (p. 276).

Tannins. A group of substances of vegetable origin have long been known as the *tannins.* They are amorphous powders, soluble in hot water and also in ether. Their solutions have a very astringent taste and are colored dark blue-black or greenish by the addition of ferric salts. This latter fact has led to the extensive use of tannins in the manufacture of writing inks. Tannins react with **proteins** (Chap. 14); if the protein is soluble, as is gelatine or white of egg, a voluminous precipitate is formed on adding a solution of a tannin. Insoluble proteins, such as the hide of animals, are changed by immersion in tannin solutions and the product is leather. The tanning of hides can also be brought about by using chromium compounds.

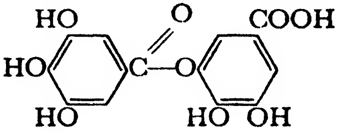
Tannins are widely distributed. For tanning hides, it is common to use the bark of such trees as oak and hemlock. Formerly, the bark and hide were soaked together in vats; the tannin gradually dissolved and acted on the protein material. The more modern practice uses extracts of vegetable material rich in tannins. Solutions of these extracts are prepared and used in treating the hides.

Gallotannin. The usual **tannic acid** of commerce is gallotannin. This is obtained principally from gallnuts, which are excrescences formed by the sting of insects on the branches of certain species of oak. Tannic acid is extracted from the powdered material with hot water. This material is used as a mordant in dyeing cotton cloth with basic dyes and also in the manufacture of inks. The commercial material may be further purified by extraction with ether or ethyl acetate; the tannin dissolves and is obtained by evaporation. Tannic acid is used in medicine as an astringent and for treatment of burns.

The study of carefully purified gallotannin has shown that it is a material of *high molecular weight*, which on hydrolysis with dilute sulfuric acid yields gallic acid and glucose. The relative amounts of the products as well as the general behavior of the tannin itself point to the following formula:

$$C_6H_7O[C_6H_2(OH)_3COOC_6H_2(OH)_2COO]_5$$

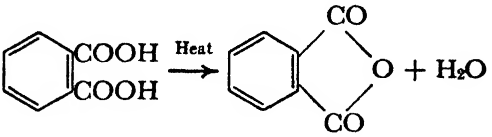
This is a penta-digalloyl-glucose. It is supposed that each hydroxyl group of glucose is esterified by **digallic acid.** A meta digallic acid has been synthesized which has the formula:



It will be noted that one hydroxyl group (in the meta position) of one molecule has formed an ester with the carboxyl group of the other molecule. A synthetic product obtained from glucose and the acid chloride of *m*-digallic acid resembles natural gallotannin in taste, solubility, optical activity, and the precipitation reactions. It is not identical with the natural material, however. Possibly the gallotannin itself contains para-digallic acid groups.

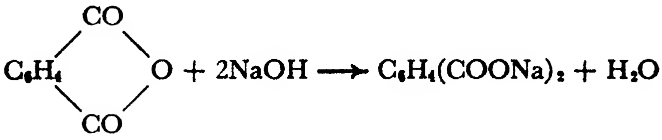
PHTHALIC ACID AND PHTHALIC ANHYDRIDE

The three isomeric dibasic acids, $C_6H_4(COOH)_2$, derived from benzene are phthalic acid (1,2), isophthalic acid (1,3), and terephthalic acid (1,4). All are colorless crystalline solids. **Phthalic acid** is the only one of importance. It is almost insoluble in water; it melts at 191°. On heating just above its melting point, phthalic acid loses a molecule of water and forms **phthalic anhydride, a** cyclic anhydride.



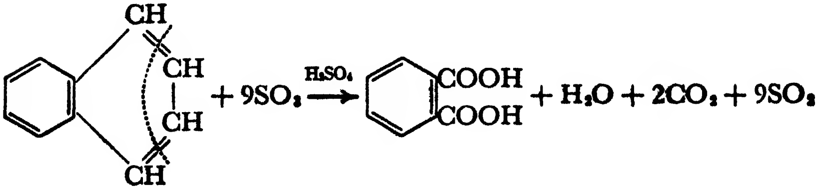
Like succinic anhydride (p. 170), this substance has a five-membered ring.

Phthalic anhydride melts at 131° and boils at 285°. It readily sublimes and is purified in this way. On treating with sodium hydroxide solution, the disodium salt of phthalic acid is formed, and on acidifying this solution phthalic acid precipitates.



$$C_6H_4(COONa)_2 + 2HCl \longrightarrow C_6H_4(COOH)_2 + 2NaCl$$

Preparation of Phthalic Anhydride. Phthalic anhydride is of great importance as an intermediate in the dye and resin industries. During 1947 almost 69,000 tons were produced in this country. It is prepared by oxidizing naphthalene, $C_{10}H_8$. For many years this was done by using fuming sulfuric acid as an oxidizing agent and mercury sulfate as a catalyst.

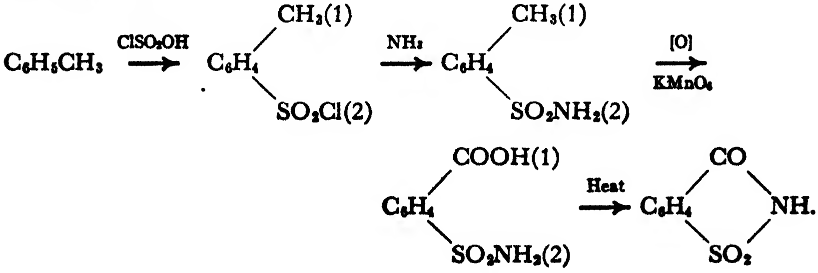


The enormous amount of sulfur dioxide evolved in the process was piped to a contact sulfuric acid plant. Here it was reoxidized to sulfur trioxide, and used again to make more fuming sulfuric acid.

The discovery that mercury sulfate is an essential factor in the oxidation was the result of an accident. The action of fuming sulfuric acid on naphthalene was being studied; in one experiment a thermometer used in stirring the mixture was broken. Much to the chemist's surprise, excellent yields of phthalic acid were obtained. The action of mercury salts seems to be quite specific in this case, and only in their presence will fuming sulfuric acid oxidize naphthalene.

Since 1918 there has been developed a process for oxidizing naphthalene with air at about 250°. A mixture of the oxides of certain rare metals is the catalyst. If the conditions are not carefully controlled, either complete combustion takes place or the naphthalene comes through unchanged. This catalytic process has very largely replaced the older sulfuric acid oxidation. Since phthalic acid very easily loses water, the actual product of the oxidation of naphthalene is not the acid but the anhydride.

Saccharin. An artificial sweetening agent 750 times as sweet as sugar is known as saccharin. Its sweet taste was discovered quite by accident in the course of purely scientific investigation. It is now manufactured for use as a sugar substitute for persons who are suffering from diabetes and cannot eat carbohydrates. It is used in very dilute solution in which the sweet taste is most evident; in moderately concentrated solutions it has a bitter taste. Unlike a real sugar, saccharin is not digested and has no food value: it is thus a sugar substitute only as far as its sweetening power is concerned. Saccharin is the **cyclic imide of ortho sulfobenzoic acid.** It is in no way connected with the sugars. The reason for its sweet taste is a mystery. It is synthesized from toluene by the following steps:



$$C_6H_5CH_3 \xrightarrow{ClSO_2OH} C_6H_4\begin{matrix} / CH_3(1) \\ \backslash SO_2Cl(2)\end{matrix} \xrightarrow{NH_3} C_6H_4\begin{matrix} / CH_3(1) \\ \backslash SO_2NH_2(2)\end{matrix} \xrightarrow[KMnO_4]{[O]}$$

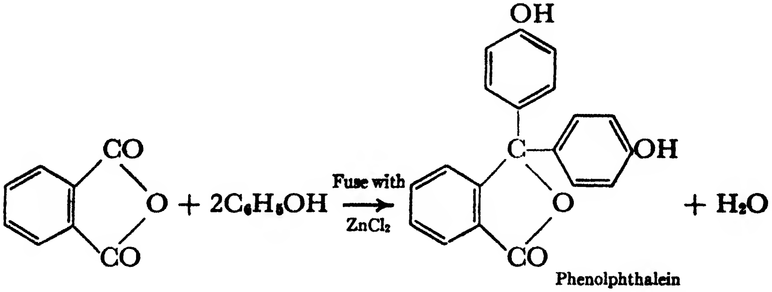
$$C_6H_4\begin{matrix} / COOH(1) \\ \backslash SO_2NH_2(2)\end{matrix} \xrightarrow{Heat} C_6H_4\begin{matrix} / CO \backslash \\ \backslash SO_2 / \end{matrix}NH.$$

In the first step in this synthesis chlorosulfonic acid ($ClSO_3H$) is used as the sulfonating agent, and the product is the acid chloride of the ortho sulfonic acid, instead of the sulfonic acid itself which is formed if sulfuric acid is used. The hydrogen of the >NH group in saccharin can be replaced by sodium if the compound is treated with sodium hydroxide. This sodium salt is much more soluble than the imide itself, and it is usually in this form that the substance is employed as a sugar substitute.

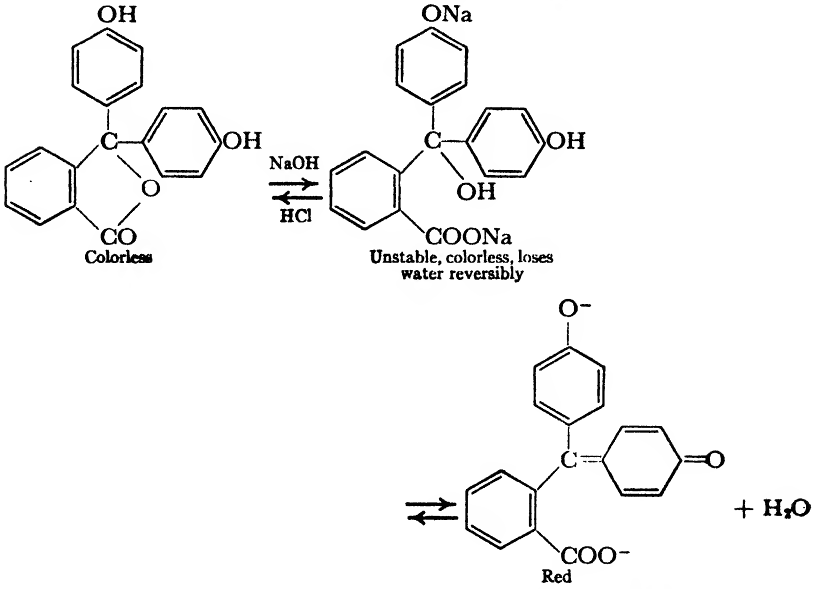
THE PHTHALEINS

Phenolphthalein. The carbonyl group in phthalic anhydride will react with aromatic compounds containing a reactive ortho or para hydrogen atom. The reaction takes place when phthalic anhydride, the aromatic compound, and a catalyst such as zinc chloride are heated together. Water is eliminated and a **phthalein** is formed. The phthaleins are dyes and indicators.

The simplest example is the reaction between phthalic anhydride and phenol. The product of this reaction is called *phenolphthalein.* It is a colorless solid which is used as a laxative and as an indicator.

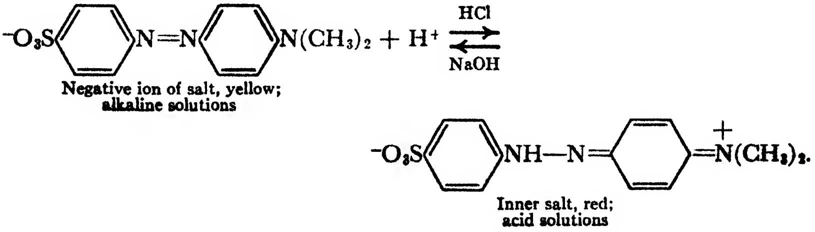


Phenolphthalein is a lactone of a gamma hydroxy acid. It will be recalled that certain hydroxy acids form lactones rapidly and that the reaction goes to completion; the free acids are unknown and only the sodium salts can be isolated. The free acid of which phenolphthalein is the lactone is also unknown. When the lactone ring in phenolphthalein is opened by alkali, the resulting salt loses a molecule of water forming a quinone-like structure in one ring; in addition the other phenolic group forms a salt. The resulting ion, which is stabilized by resonance, is highly colored.

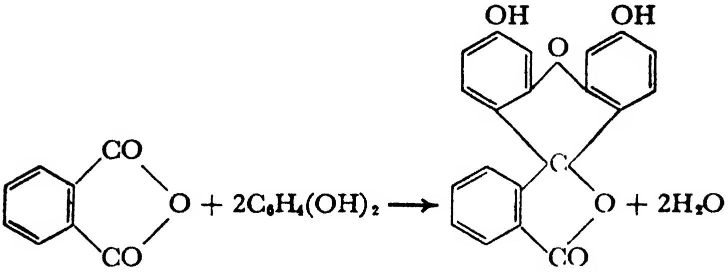


These changes are practically instantaneous, and they are reversed when the solution is acidified. Consequently phenolphthalein is red in alkaline solution, colorless in acid solution, and can be used as an indicator in the titration of acids and bases.

Other Indicators. There are a great many organic compounds which are used as indicators. Some of them are similar to phenolphthalein in structure, and the reason for the change in color is essentially the same. With others, an entirely different set of chemical reactions is involved. In every indicator, however, there is a practically instantaneous change (or changes) of structure in acid or alkaline solution which alters the structure and color of the molecule. As an example of another type of indicator, **methyl orange,** or **helianthin,** may be cited. This is a common indicator which turns in a somewhat more acid solution than phenolphthalein. The change is probably to be represented by the following formulas:



Fluorescein and Eosin. When phthalic anhydride is heated with resorcinol and a condensing agent (zinc chloride), a compound known as *fluorescein* is produced.



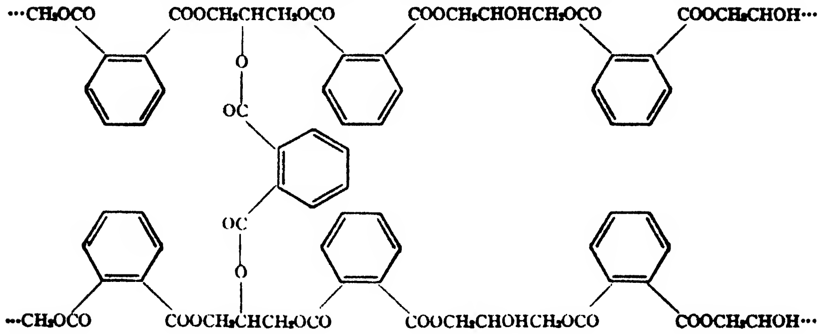
Fluorescein

This substance is an orange powder which is only very slightly soluble in water but dissolves in alkaline solution (as a salt). A dilute solution has a brilliant *green-red fluorescence.* The tetrabromo derivative of fluorescein is known as *eosin.* It is a red powder, soluble in alcohol, and insoluble in water ("spirit-soluble eosin"). Its disodium or ammonium salt is "water-soluble eosin." It is used as a direct dye for silk and as a biological staining material. **Red ink** is usually a dilute solution of water-soluble eosin.

Mercurochrome is a mercury derivative of dibromofluorescein. The group HgOH has replaced one of the hydrogen atoms attached to an aromatic ring. The introduction of a mercury atom is often spoken of as *mercuration;* it conveys strong antiseptic properties to the molecule. Mercurochrome is a bright red, water-soluble solid which is used in dilute solution as an antiseptic.

PLASTICS

Alkyd Resins. Phthalic acid is used in large quantities in the preparation of synthetic resins known as *alkyd* or *glyptal resins.* These are materials formed by heating the acid with glycerol. They are similar to the high-molecular-weight esters referred to earlier (p. 172), but, because glycerol has *three* hydroxyl groups, the long chains are *cross linked.* Thus the structure of a portion of the molecule may be represented in the following way.



The position and number of the cross links and the average molecular weight vary with the conditions under which the resin is prepared.

Maleic acid or abietic acid (p. 354) may be substituted for phthalic acid; the resins thus obtained are very similar to those from phthalic acid. They are used principally for protective coatings. In 1947 some 226,000 tons of resin were used in this way.

Classification of Plastics. A very large industry based on plastics has developed in the last twenty-five years, the output of plastics materials in the United States in 1947 reaching 625,850 tons. Under this heading of plastics one finds a variety of synthetic organic compounds of high molecular weight, all of which have the property of being plastic at temperatures somewhat above the boiling point of water (125° to 200°). This enables a great variety of articles to be manufactured by pressing the hot plastic into molds (pressures of 4 tons per square inch are commonly used); then cooling and extruding the product. Some plastics soften on reheating; they are known as *thermoplastics.* Others when once set are no longer fusible; they are known as *thermosetting* resins. The table on page 316 lists some of the common materials of each type.

High-boiling liquids known as *plasticizers* are usually incorporated in the thermoplastic resins. Butyl phthalate and butyl phosphate are typical plasticizers. These materials make the material plastic at a lower temperature and improve such properties as water resistance, toughness, and flexibility in the final product.

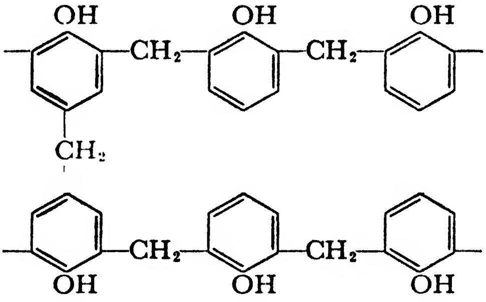
Classification of Plastics

A. Thermoplastics	
1. Cellulose acetate	p. 214
2. Ethenoid plastics	
Polythene	p. 58
Polystyrene	p. 324
Polyvinyl compounds	p. 143
Polyacrylic esters	p. 143
B. Thermosetting Plastics	
1. Glyptal resins	p. 314
2. Phenol formaldehyde resins (Bakelite)	p. 317
3. Urea formaldehyde resins	p. 317

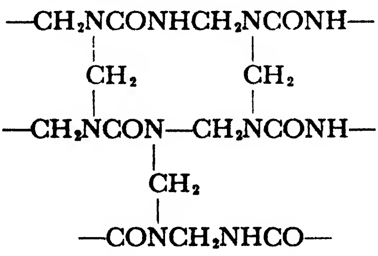
The difference between thermoplastic and thermosetting plastics in chemical terms is essentially the following: The molding operation does not change the molecular weight or chemical structure of the thermoplastic materials, but it does change the molecular weight and chemical structure of the thermosetting resins. At the molding temperature a further chemical reaction takes place, the average molecular weight of the material increases, and additional cross links form between the long chains. In the glyptal resins the chemical reaction is esterification; in the formaldehyde resins it is condensation. In both, cross linking is very important since it is the cross links in material of high molecular weight which make it soften less on heating and dissolve or swell less on treatment with a solvent. The student will recall that in the vulcanization of rubber the cross linking between molecules brings about great changes in physical properties. The process of vulcanization is very similar to the thermosetting of a plastic.

The final products of heating thermosetting plastics are hard, tough, very insoluble materials. It is interesting to compare such materials with the tough insoluble fibers of both natural and synthetic origin (cotton, silk, Nylon). In the fibers, a favorable arrangement of long-chain molecules with strong intermolecular forces binds many molecules together in a crystal-like pattern. The intermolecular forces in such high-molecular-weight materials largely determine their toughness and insolubility. In the thermosetting resins, by contrast, direct covalent links hold together chains of long molecules. The results are similar as far as toughness and insolubility are concerned, but the special properties of fibers are lacking in the thermosetting materials. In the thermoplastic resins, the amorphous material is composed of smaller molecules than in the thermosetting plastics, and, because there is only random orientation, the intermolecular forces are relatively weak. Hence the materials are *thermoplastic* and usually swell or dissolve in suitable solvents.

Formaldehyde Resins. A group of related plastics is formed by the condensation of formaldehyde with a variety of substances. The oldest of these is represented by Bakelite (p. 273), the condensation product of formaldehyde and phenol. The characteristic link in the phenolic resins may be represented in the following way.



As in the glyptal resins, long chains tied together by cross links give a very hard insoluble material as the final product. In the formaldehyde-urea resins the long chains are tied together with many methylene cross links.



$$\begin{array}{c}
\text{—CH}_2\text{NCONHCH}_2\text{NCONH—}\\
| \qquad\qquad\qquad |\\
\text{CH}_2 \qquad\qquad \text{CH}_2\\
| \qquad\qquad\qquad |\\
\text{—CH}_2\text{NCON—CH}_2\text{NCONH—}\\
|\\
\text{CH}_2\\
|\\
\text{—CONCH}_2\text{NHCO—}
\end{array}$$

The first condensation products of the formaldehyde type resins are of relatively low molecular weight and are prepared by heating the components for a short time with small amounts of alkali or ammonia as a catalyst. The result with the phenolic resins is an amorphous material which is insoluble in water but soluble in many organic solvents. Various fillers, such as wood pulp, are mixed with the powdered material, coloring matter is added, and the mixture is heated in molds under pressure. The resin then sets to the final product.

The first condensation products of the urea-formaldehyde type are water soluble. This enables one to apply them to various materials including textiles. On heating, the condensation proceeds further and water-insoluble products are formed.

QUESTIONS AND PROBLEMS

1. Write structural formulas for benzotrichloride, eugenol, benzoyl peroxide, saccharin, and salicylaldehyde.

2. How many products would you expect to obtain by the addition of bromine to cinnamic acid? Would they be optically active? Would they be resolvable?

3. What is an indicator? Using phenolphthalein as an example, explain in chemical terms the color changes that take place going from acid to alkaline solution and back.

4. Describe two commercial methods of preparing phthalic anhydride. What are some important industrial uses of this material?

5. Define and illustrate the following terms: *plasticizer*, *thermosetting plastic*, *thermoplastic resin*, *tannin*, *preservative*, *autoöxidation*.

6. Explain the chemical reactions involved in the formation of alkyd resins. When are these resins thermosetting and when thermoplastic?

7. Write equations for the reactions between benzaldehyde and (*a*) oxygen, (*b*) alkali, (*c*) methylmagnesium iodide, (*d*) hydroxylamine. Compare these reactions with those of the aliphatic aldehydes.

8. Describe and give examples of the Friedel-Crafts reaction.

9. What are the two general types of polymerization reactions? Give examples of both types.

10. Write structural formulas and names and indicate the uses of three important medicinal products prepared from salicylic acid.

11. Show the probable fundamental structural unit in lignin and write formulas for some closely related naturally occurring substances.

CHAPTER 20

Polynuclear Aromatic Compounds

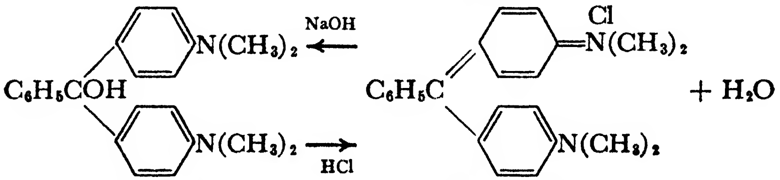
Many substances containing two or more aromatic nuclei are known; certain of them are of particular interest to us and will be considered in this chapter. The aromatic nuclei in these compounds may be separated, as in the triphenylmethane dyes and the hexaarylethanes which are arylated derivatives of the paraffin hydrocarbons; or they may be fused as in naphthalene, anthracene, and the other condensed polynuclear hydrocarbons.

THE TRIPHENYLMETHANE DYES

The first synthetic dye was a triphenylmethane dye, prepared quite unintentionally in 1856. William Henry Perkin, then a student, undertook a study of the oxidation of aniline as part of an attempt to synthesize quinine. He obtained from the oxidation a substance whose violet-colored solutions dyed wool and silk. Perkin started a factory for the manufacture of the new dye, which was called *mauve,* and thus started the coal-tar dye industry.

The manufacture of synthetic dyes has developed in the intervening years to an important industry. In the United States in 1947 some 106,000 tons of dyes with a value of about $150,000,000 were produced. The two most important groups of dyes in terms of volume of production were the azo dyes (p. 293), 39,000 tons; and the sulfur dyes (p. 282), 21,000 tons.

The structure of the triphenylmethane dyes was not established until 1876, twenty years after the first one was prepared. We can understand their structure and their chemistry best by considering their relation to triphenylmethane, $(C_6H_5)_3CH$, and triphenylcarbinol, $(C_6H_5)_3COH$. Derivatives of triphenylcarbinol in which two or three of the aromatic nuclei contain basic groups in the para positions react with hydrochloric acid to form chlorides which are not colorless nonpolar substances like triphenylmethane, but which are instead highly colored salts. These salts are the triphenylmethane dyes. For example, the colorless carbinol (I), di(*p*-dimethylamino)triphenylcarbinol, reacts with hydrochloric acid to form the chloride (II), which is the triphenylmethane dye **malachite green.**



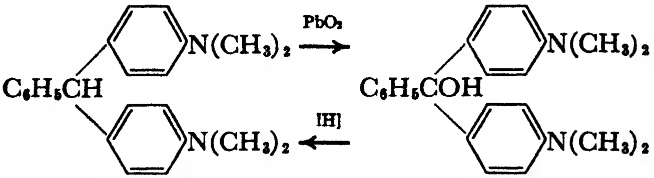
Colorless

I

Malachite green, a triphenylmethane dye

II

By treatment with alkali the dye is reconverted to the colorless carbinol, which is known as the *color base.* The carbinol, the color base, is readily reduced to the corresponding triphenylmethane derivative, the **leuco base.** On oxidation the leuco base regenerates the color base.



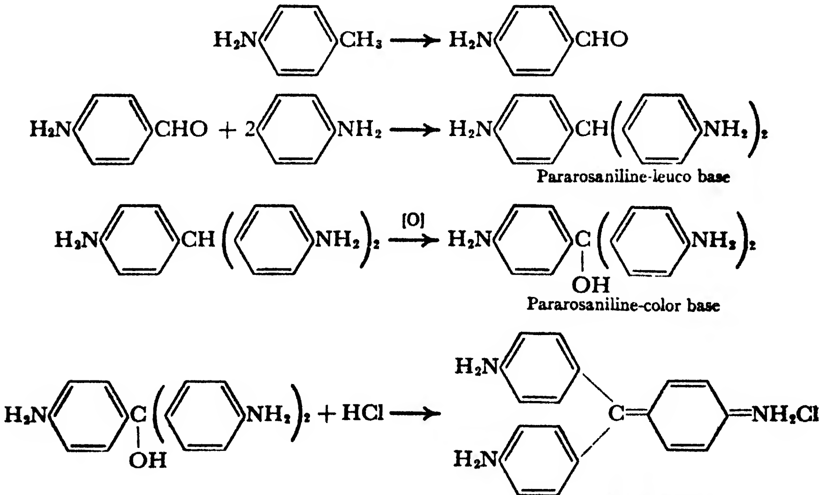
Leuco base, colorless triphenylmethane derivative

Color base, colorless triphenylcarbinol derivative

It is the relationship between the methane, the carbinol, and the dye, together with the fact that the synthesis of these dyes begins with the synthesis of the methanes, that led to the class name of *triphenylmethane dyes.* Thus the leuco base of malachite green is prepared by heating benzaldehyde and dimethylaniline in the presence of zinc chloride.

$$C_6H_5CHO + 2C_6H_5N(CH_3)_2 \longrightarrow C_6H_5CH[C_6H_4N(CH_3)_2]_2 + H_2O$$

Other Triphenylmethane Dyes. Fuchsine, or *magenta,* is a triphenylmethane dye prepared by oxidizing a mixture of aniline and the isomeric toluidines. The color base resulting from this oxidation forms the dye on treatment with hydrochloric acid. The principal constituent of magenta is the dye **pararosaniline.** It is formed by the oxidation of the para toluidine to para aminobenzaldehyde, condensation of para aminobenzaldehyde and aniline to the leuco base, oxidation of the leuco base to the color base, and conversion of the color base to the dye.



The leuco base of pararosaniline is triamino-triphenylmethane. When it is diazotized and boiled with alcohol (p. 290) the amino groups are replaced by hydrogen and triphenylmethane is formed. It was this reaction which established the structure of the triphenylmethane dyes.

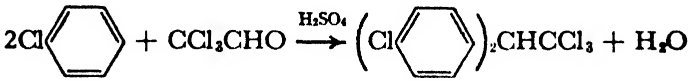
Crystal violet is the hexamethyl derivative of pararosaniline, the methyl groups being substituted for the hydrogen atoms of the amino groups. This substitution changes the color from a red to a bluish violet. **Methyl violet,** which contains only five methyl groups, is of a redder shade than crystal violet, as might be expected. These dyes can be made by methylating the parent dye, but are usually synthesized from the methylated anilines (p. 285).

Cotton Dyeing with Basic Dyes. The important triphenylmethane dyes are basic dyes and as such are direct to wool and silk but not to cotton. They may be made direct to cotton by treating the cloth with tannic acid (p. 309), followed by antimony tartrate (tartar emetic). The acid groups of the tannic acid combine with the basic groups of the dye forming an insoluble salt of high molecular weight, which adheres to the cotton. A substance like tannic acid which binds a dye to the fabric is known as a *mordant.* Cotton cloth soaked in a tannic acid solution can be dyed very satisfactorily with the basic dyes. At one time the use of the basic dyes with tannic acid as a mordant was the common method of dyeing cotton. This process has been largely replaced by the direct cotton dyes, the ingrain colors, sulfur dyes, and the vat dyes. Although the basic dyes may be applied to cotton by the use of mordants, they are not classified as mordant dyes. This name is restricted to those dyes which are applied to fabrics by means of a metallic hydroxide as a mordant.

Medical Uses of Dyes. In the nineteenth century, medical investigators were impressed with the selective action of dyes on living matter — properly chosen dyes stain certain types of organisms and not other types. From the time of this observation, dyes have played an important part in the development of chemotherapy (Chap. 23) and have themselves had important practical applications. A solution of methyl violet in water and aniline, the Gram stain, will divide bacteria into Gram-positive and Gram-negative groups according to whether the bacteria retain the dye after appropriate treatment.

ARYLATED ETHANES

Two aryl derivatives of ethane require our attention; one because of its practical importance, the other for its scientific interest. The first is *p,p′*-dichlorodiphenyl-trichloroethane, more generally known as DDT. It is prepared by the condensation of chlorobenzene with chloral, and it finds extensive use as an insecticide.



DDT

The second is hexaphenylethane, $(C_6H_5)_3CC(C_6H_5)_3$, a hydrocarbon in which the accumulation of phenyl groups has led to some remarkable properties.

Hexaphenylethane was first prepared in 1900 by Gomberg. The reaction he employed was similar to a Wurtz reaction.

$$2(C_6H_5)_3CCl + 2Ag \longrightarrow (C_6H_5)_3C{-}C(C_6H_5)_3 + 2AgCl$$

The resulting compound was a colorless, crystalline solid, as one would expect. But quite contrary to expectations *its solutions were orange*, and more surprising still *they absorbed oxygen* from the air with great rapidity. The oxygen absorption discharged the color of the solution, and a new, colorless, crystalline material separated. This compound on analysis proved to be a **peroxide,** $(C_6H_5)_3C{-}O{-}O{-}C(C_6H_5)_3$.

A careful study of hexaphenylethane and other hexaarylethanes has shown that the behavior of these substances is due to the fact that in solution they are dissociated into *free radicals.* Thus, in a solution of hexaphenylethane there is always a mobile equilibrium between hexaphenylethane itself and **triphenylmethyl,** $(C_6H_5)_3C{-}$, the free radical.

$$(C_6H_5)_3C{-}C(C_6H_5)_3 \rightleftarrows 2(C_6H_5)_3C{-}$$

This free radical is colored and extraordinarily reactive. It combines with oxygen and halogens.

$$2(C_6H_5)_3C{-} + Cl_2 \longrightarrow 2(C_6H_5)_3CCl$$

Other Free Radicals. Some hexaarylethanes are practically completely dissociated in solution at room temperature. Probably the crystalline solid even in such molecules, however, is the ethane and not the free radical. In solution, at least, a number of organic compounds exist in a form in which one of the carbon atoms is trivalent. These free radicals are exceptions to the general rule of the tetravalence of carbon, but their existence in no way affects the validity of the structural theory which was largely developed before their existence was discovered. The carbon to carbon linkage in ethane ($CH_3—CH_3$), butane ($C_2H_5—C_2H_5$), and biphenyl ($C_6H_5—C_6H_5$) is very different from that in hexaphenylethane. These simpler compounds do not dissociate into free radicals under ordinary conditions.

The difference between ethane and hexaphenylethane probably is connected both with the unsaturation of aromatic groups and with the fact that they occupy more space than simple alkyl groups. Neither tetraphenylmethane, tetraphenylethane, nor pentaphenylethane at room temperature shows any of the peculiarities of hexaphenylethane. On the other hand, derivatives of ethane with only four aryl groups and two *branched* alkyl groups have been prepared which, like hexaphenylethane, are dissociated into free radicals.

For many years all attempts to prepare free methyl and free ethyl radicals were without success. The products were always the well-known saturated or unsaturated hydrocarbons. However, evidence has been obtained that free methyl and free ethyl groups are formed at high temperatures by the thermal decomposition of hydrocarbons or metalloörganic compounds. Thus the vapor of tetramethyl lead, $Pb(CH_3)_4$, when passed rapidly through a hot tube decomposes with the formation of some **free methyl groups,** $CH_3—$. These very soon combine to form ethane, however, and their presence can only be detected by special methods. It is evidently quite out of the question to isolate free alkyl groups.

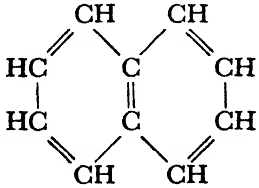
Styrene. One arylethylene, styrene or phenylethylene, $C_6H_5CH{=}CH_2$, is of great industrial importance because it furnishes valuable products when it is polymerized alone (polystyrene) or copolymerized with, for example, butadiene to form Buna S rubber (p. 76).

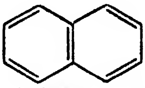
CONDENSED POLYNUCLEAR AROMATIC HYDROCARBONS

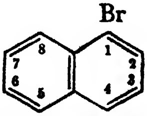
Naphthalene, anthracene, and phenanthrene are present in the higher fractions which are obtained in the industrial refining of coal tar. The production of the first two substances on a large scale has resulted in their use in the manufacture of a great number of very important dyes. The three high-boiling, solid hydrocarbons, as we shall see, are aromatic compounds, but differ in certain important respects from benzene.

Naphthalene. Naphthalene, $C_{10}H_8$, is a white crystalline solid which melts at 80° and boils at 218°. It has an appreciable vapor pressure even at room temperature and readily sublimes on warming. Naphthalene has a pungent odor, and is commonly sold in flakes or balls for use as a protection against moths. It is prepared from coal tar as outlined on p. 256. Since it occurs in relatively large amounts and is easily purified by distillation or sublimation, it is one of the cheap raw materials of the coal-tar chemical industry. In 1947 almost 157,000 tons of crude naphthalene were produced in the United States.

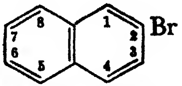
Naphthalene is very similar to benzene in many of its chemical properties. It can be nitrated, sulfonated, and halogenated; it yields *two isomeric monosubstitution products* and ten isomeric disubstitution products. It is represented by the following formula which adequately accounts for these isomers. The formula on the right is commonly employed. The mono-substitution products are divided into two classes, designated as *alpha* and *beta.*




Outline formula



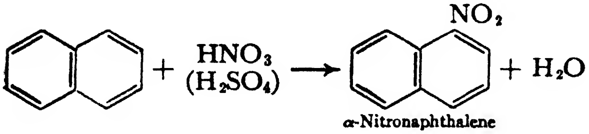
α-Bromonaphthalene or
1-Bromonaphthalene

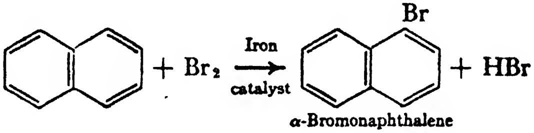


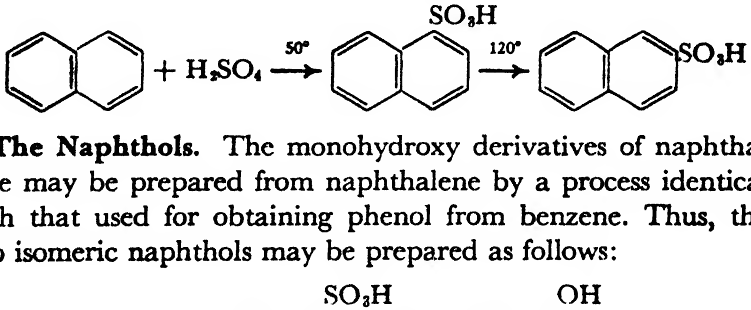
β-Bromonaphthalene or
2-Bromonaphthalene

The position of substituents is also often indicated by numerals, as shown above. Clearly the 1,4,5, and 8 positions are the alpha positions and 2,3,6, and 7 positions are the beta positions. All the alpha positions are equivalent to each other; the same is true of the beta positions. In other words, there are two and only two monosubstitution products.

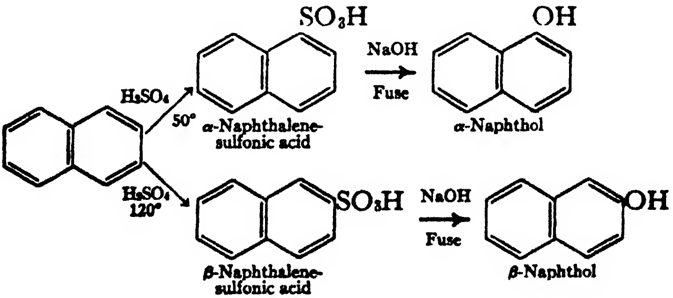
Substitution Reactions of Naphthalene Derivatives. The typical aromatic reactions of benzene are also characteristic of naphthalene. Halogenation and nitration of naphthalene produce the alpha isomer. Sulfonation also goes in the same way, but at a higher temperature the alpha isomer rearranges to the beta.







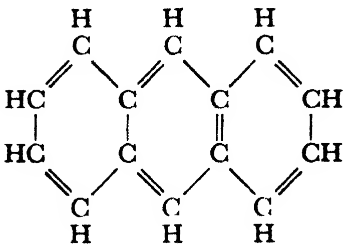
The Naphthols. The monohydroxy derivatives of naphthalene may be prepared from naphthalene by a process identical with that used for obtaining phenol from benzene. Thus, the two isomeric naphthols may be prepared as follows:

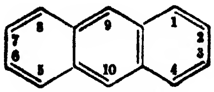


Alpha-naphthol, $C_{10}H_7OH$ (α), and **beta-naphthol,** $C_{10}H_7OH$ (β), are solids melting at 95° and 122° and boiling at 279° and 285° respectively. They resemble phenol in their general reactions; they are weak acids, soluble in sodium hydroxide solution but not in sodium bicarbonate solution. They are prepared in large quantities for use in the manufacture of azo dyes (p. 293). They readily couple with diazonium salts; α-naphthol couples in the 4 position, β-naphthol in the 1 position.

Anthracene. This hydrocarbon, $C_{14}H_{10}$, is present in the high-boiling fractions of the coal-tar distillate. It is difficult to isolate and purify. As a consequence a number of substances formerly prepared from anthracene are being synthesized from benzene derivatives in the United States, and the importance of the hydrocarbon itself as a raw material has diminished.

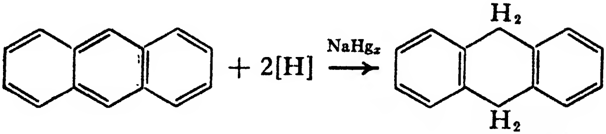
Anthracene is a colorless solid with a bluish fluorescence which is also weakly shown by solutions of the hydrocarbon. It melts at 216° and boils at 342°. In its chemical properties, it more nearly resembles an open-chain unsaturated hydrocarbon than does even naphthalene. For example, it readily combines with bromine or chlorine, is reduced to a dihydroanthracene by sodium amalgam, and is easily oxidized. At the same time, the typical substitution reactions of aromatic compounds can be brought about under certain conditions. The formula which best expresses the behavior of this interesting compound is the following, which is often written in outline as shown on the right.





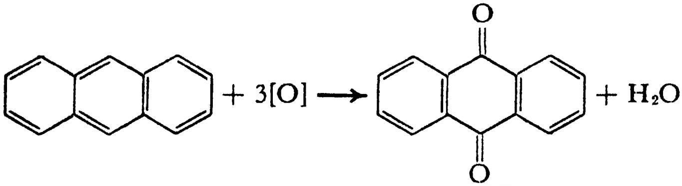
Outline formula

The method of numbering the ring is shown above. The two carbon atoms in the middle ring (9 and 10) are the points at which the anthracene molecule readily adds two atoms or groups. This may be illustrated by the reduction of anthracene to dihydroanthracene.



Dihydroanthracene

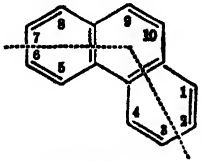
The oxidation to 9,10-anthraquinone is to be written as follows:



9,10-Anthraquinone

Phenanthrene. An isomer of anthracene is known as *phenanthrene;* it also occurs in coal tar and may be isolated from the higher fractions. Although it may be thus obtained without much difficulty, it is not usually separated because neither it nor its derivatives have been found to be of sufficient commercial value to warrant the expense of their manufacture. Unlike anthracene derivatives (or rather anthraquinone derivatives), the phenanthrene series of compounds seem to possess no characteristic which makes them more valuable industrially than the more accessible benzene and naphthalene compounds. The hydrogenated phenanthrene ring forms part of the structure of a number of important naturally occurring products (Chap. 21).

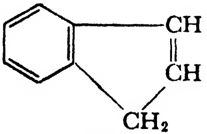
In phenanthrene three benzene rings are condensed together in what may be considered an angular manner as contrasted with the linear condensation in anthracene.



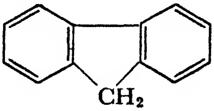
Phenanthrene

Phenanthrene, like anthracene, is a colorless solid with a slight fluorescence. It melts at 100° and boils at 340°.

Other Condensed Aromatic Hydrocarbons. A number of other polynuclear aromatic hydrocarbons occur in coal tar or may be prepared synthetically. Not only six-membered carbon rings, but also five-membered rings are found condensed with the benzene ring. Thus indene and fluorene are analogous to naphthalene and anthracene except that a five-membered ring replaces a six-membered ring. They both occur in coal tar.

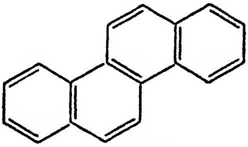


Indene



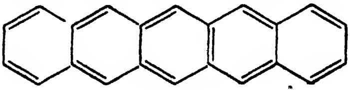
Fluorene

One of the hydrocarbons containing a very large number of condensed rings is chrysene, $C_{18}H_{12}$, which is found in coal tar. Chrysene melts at 255° and is important in elucidating the structure of certain sterols and bile acids (Chap. 21), since it is obtained from them as a degradation product.

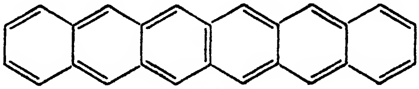


Chrysene

Two synthetic condensed polynuclear hydrocarbons, pentacene and hexacene, are of interest as higher homologs of a series of which the first three members are benzene, naphthalene, and anthracene. Pentacene and hexacene are colored blue and green, respectively. They are highly reactive in addition reactions and are easily oxidized.



Pentacene



Hexacene

Color and Chemical Constitution. The change from colorless to colored compounds in the series of hydrocarbons on ascending from benzene through pentacene raises the question of the relationship between color and chemical constitution — a relationship that is of practical importance in the dyes. Most organic compounds are colorless and yield colorless solutions. Such solutions appear to our eyes to be perfectly transparent to light, but this is only because the range of light which affects our eyes is so limited (Fig. 14). All organic compounds absorb light of short wavelengths (ultraviolet light). Such absorption may be studied by means of a photographic plate and a spectroscope which resolves the light transmitted by the liquid. The results (Fig. 14) are called *absorption spectra.* It is found that unsaturated compounds absorb light of longer wavelength (nearer the visible) than saturated compounds. Certain combinations of unsaturated groups cause the substance to absorb some of the light visible to the eye and the solution is then colored.

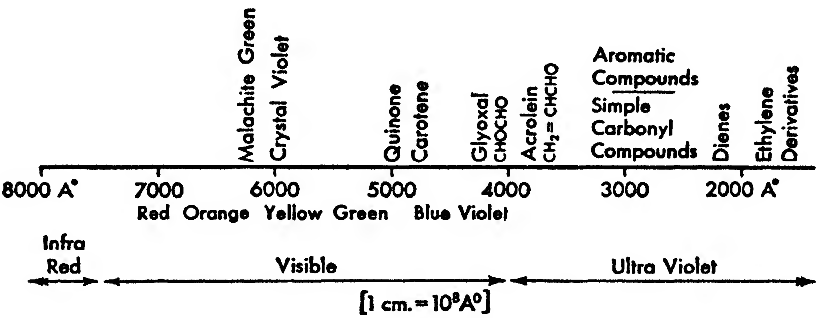
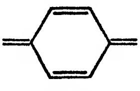


Fig. 14. Diagram showing absorption spectra in the visible and ultraviolet regions. The approximate position of the absorption band of *longest* wave length is indicated for each compound; many compounds have absorption bands in several positions.

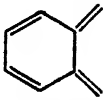
Certain unsaturated groupings are definitely associated with the absorption of visible light, and we can predict that compounds having such groupings will be colored. Such groups which confer color on a molecule are said to be *chromophoric* groups or chromophores. The following are usually regarded as important chromophores.

$—N{=}N—$

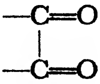
Azo group in aromatic compounds



Para quinoid linkage

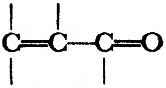


Ortho quinoid linkage



$$\begin{array}{l} —C{=}O \\ \quad | \\ —C{=}O \end{array}$$

Diketone



$$\begin{array}{cccc} | & | & & \\ C & {=}C & —C & {=}O \\ | & & | & \end{array}$$

Unsaturated ketone group in aromatic compounds

$—NO_2$

Nitro group in aromatic compounds

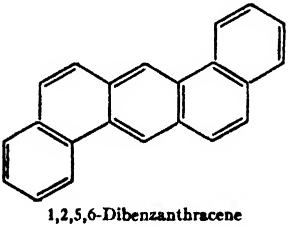
$—N{=}O$

Nitroso group even in aliphatic compounds

The presence of one or more aryl groups attached directly to the chromophoric group is usually essential; the introduction of such groups as —NH_2, —$N(CH_3)_2$, OH, OCH_3 in the aromatic nucleus intensifies the color.

Clearly any attempt to relate the color of a compound to its structure (chemical constitution) is only one aspect of the broader problem of the relation of structure and absorption spectrum. In a very rough way, we can recognize that certain groupings of atoms usually cause the absorption of a certain range of light, and can even foretell to some extent the absorption spectrum of a compound which contains several such groupings (although the effects are by no means simply additive). If the relation between structure and light absorption were completely understood, it might be possible to determine the constitution of many substances from an examination of their absorption spectra alone. Unfortunately, the absorption of light by the valence electrons of organic molecules is such a complex physical process that it has not been possible so far to subject it to a fundamental analysis. In a general way, it is evident that in saturated compounds the valence electrons absorb only very short wavelengths of light (extreme ultraviolet), because this light has a high energy content which can affect the tightly bound electrons (the shorter the wavelength of light, the richer it is in energy). Highly unsaturated compounds absorb in addition the longer wavelengths of visible light, since these contain only sufficient energy to affect the loosely bound electrons of the unsaturated linkages.

Carcinogenic Hydrocarbons. It has been known for many years that the workers in coal-tar refineries were susceptible to a skin cancer which came to be known as *tar cancer*. A series of systematic investigations on coal tar revealed that certain aromatic, condensed, polynuclear hydrocarbons are responsible for this disease. One of the most active **carcinogenic** (cancer-producing) compounds is 1,2,5,6-dibenzanthracene.

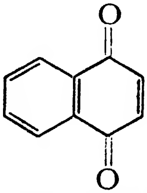


1,2,5,6-Dibenzanthracene

An inspection of the structure of 1,2,5,6-dibenzanthracene shows it is related to both anthracene and phenanthrene.

Polynuclear Aromatic Compounds in Nature. Although the chief interest and importance of naphthalene and anthracene derivatives center around the coal-tar dye industry, it would be a great mistake to believe that coal tar is the only source of these substances. Naphthalene, anthracene, and phenanthrene derivatives (or substances closely allied to them, as for example the corresponding quinones) have been found in the vegetable kingdom. Such substances, however, appear to occur less commonly than do the benzene derivatives, though this may be in part only a reflection of the greater difficulty of isolating them from the complex mixtures found in nature.

No simple naphthalene derivatives (such as the naphthols, for example) have been found in nature. Trihydroxynaphthalenes and derivatives of α-naphthoquinone occur in certain very restricted classes of plants.



α-Naphthoquinone

Derivatives of anthraquinone are quite widely distributed, though their occurrence is certainly much more specialized and localized than is the case of benzene derivatives. Certain naturally occurring hydroxy anthraquinones, e.g., alizarin, 1,2-dihydroxy-9,10-anthraquinone, are used as dyes. Hydroxyl derivatives of a methylanthraquinone occur as glucosides in a number of plants. Plant extracts containing such materials are known under the general name of *emodine*, and are used as drugs chiefly because of their laxative and purgative action. **Chrysophanic acid,** 1,8-dihydroxy-3-methyl-9,10-anthraquinone, may be cited as an illustration of the substances occurring in such drugs.

QUESTIONS AND PROBLEMS

1. Write structural formulas for 2,5-dibromonaphthalene, 3-chlorophenanthrene, anthraquinone, β-naphthol, dihydroanthracene, α-naphthalenesulfonic acid.

2. Show by means of equations the substitution reactions of naphthalene.

3. Discuss briefly the triphenylmethane dyes.

4. Write the structural formula and state the importance of DDT, styrene, chrysene, and hexacene.

5. Discuss the relationship between color and chemical constitution in organic compounds.

6. Define the term free radicals. Can you account for the difference in stability and reactivity between the methyl and the triphenylmethyl free radicals?

7. Write structural formulas for tri-*p*-aminotriphenylmethane, pararosaniline, tri-*p*-hydroxytriphenylmethane, malachite green, and crystal violet.

8. How can triphenylmethane dyes be made direct to cotton?

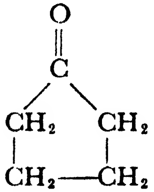
9. Define the following terms: *mordant*, *leuco base*, *carcinogenic hydrocarbon*, *chromophore*, *absorption spectrum*, *color base*.

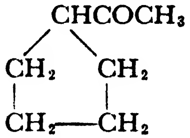
CHAPTER 21

Alicyclic Compounds and Related Natural Products

Several groups of natural products contain alicyclic rings. Among these natural products are the cyclic terpenes, a number of vitamins, and many hormones. The **cyclic terpenes** are a group of unsaturated compounds of the formula $C_{10}H_{16}$, together with their oxygen-containing derivatives, which are widely distributed in plants; some of them have important practical uses. The **vitamins** are accessory food factors in the diet of animals. Many careful experiments have shown that an animal may be fed on a diet which contains all the basal foods in a purified form, and yet the animal will fail to grow, become sick, and ultimately will die. This is true in spite of the fact that the components of the diet (purified proteins, fats, carbohydrates, mineral salts) are digested and metabolized by the animal. If now a few tenths of 1 per cent of certain materials are added to this diet, it becomes an entirely satisfactory ration and the animal survives. We have already mentioned vitamin C (p. 207); in this chapter we shall consider vitamins A, D, K, and E. **Hormones** are substances secreted internally by the ductless glands of the animal body. They are distributed by the blood or lymph to other portions of the body whose structure or function is thereby modified. The potency of the hormones is remarkable, a very small portion of a milligram often being effective. We shall consider certain of the sex hormones and those from the adrenal cortex. As an introduction to these groups of natural products we shall examine briefly the chemistry of some simple alicyclic compounds.

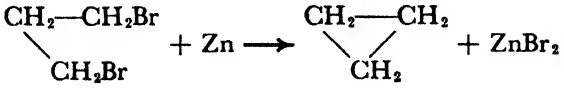
General Characteristics of Alicyclic Compounds. With the exception of cyclopropane (the first member of the series), the characteristic reactions of the alicyclic compounds are very close to those of the aliphatic; to a large extent we can transfer our knowledge gained in the one field to the other. We shall consider some peculiarities of cyclopropane compounds shortly, but shall first turn to the more general behavior of the other cycloparaffins and their derivatives. Just as we have alcohols, ketones, etc., which are derived from the paraffin hydrocarbons, so we have similar groups of alicyclic compounds. It should be recognized that functional groups which involve one or two valences can either be part of a ring or attached to a ring; thus we may have cyclopentanone and methyl cyclopentyl ketone. Functional groups, like carboxyl, which involve more than two valences naturally cannot be part of a ring.



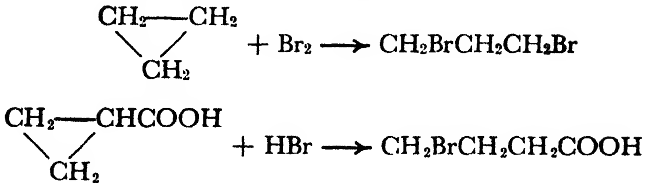


The various functional groups show the same reactions in the cycloparaffins as in the paraffins; the reactivity of the functional group is somewhat greater in the cycloparaffins, however. Cyclohexanone, for example, reacts more rapidly than diethyl ketone with such typical carbonyl reagents as bisulfite, hydroxylamine, and phenylhydrazine.

Cyclopropane (Trimethylene). Cyclopropane is made from trimethylene bromide and sodium or zinc. It has excellent anesthetic properties, but its high cost prevents its wider use.



In cyclopropane itself and many of its derivatives, the ring is opened even when the compounds are treated with such reagents as bromine and hydrobromic acid at room temperature.



Such cleavages of alicyclic rings occur less readily with cyclobutane and its derivatives, but not with the larger rings unless groups are present which cause the cleavage of even open-chain compounds.

Baeyer's Strain Theory. Somewhat more than fifty years ago, chemists were much impressed by the number of derivatives of cyclopentane and cyclohexane which were found in nature and which were readily prepared in the laboratory. They were also impressed by the ease with which five- and six-membered heterocyclic rings were formed. We have encountered a number of such instances in previous chapters; for example, only those dibasic acids whose cyclic anhydrides contain five- or six-membered rings form these anhydrides directly (p. 170).

As an explanation of all these facts, Baeyer in 1885 suggested his strain theory. He started with the regular tetrahedral carbon atom which had already provided an adequate explanation of stereoisomerism. In this atom the four valence forces are directed from the center to the corners of a regular tetrahedron, and therefore form an angle of 109° 28′ with each other (Fig. 15). In the union of two atoms, Baeyer assumed that these valence forces must lie joined in a straight line between the centers of the atom. If this assumption is correct, it is easy to see that a three-membered carbon ring can only be formed by a distortion of the valence angles of the carbon atoms. This is illustrated by the diagram shown in Fig. 16. The distortion or displacement of the valence angle can be calculated by simple geometry as 24° 44′;

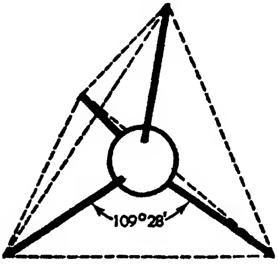


Fig. 15. Diagram showing normal valence angles of a carbon atom.

in the cyclobutane ring, the distortion is less (9° 44′), and in a cyclopentane ring, the distortion is less than a degree (44′). The cyclopentane ring can thus be closed without appreciable distortion; this is shown in the diagram (Fig. 17) of a model of a five-membered chain *so manipulated as to bring the terminal atoms as near together as possible.* It is clear that the ends of a five-carbon chain can approach very close to each other without any distortion of the valence bonds; this, of course, is not so with a four- or three-membered chain. Baeyer supposed that the distortion of the valence angles in the three- or four-membered rings caused a *strain* in the molecule and that this strain was responsible for the fact that many of these compounds combined with various reagents: in so doing the ring is opened and the strain is relieved. No better explanation has yet been given.

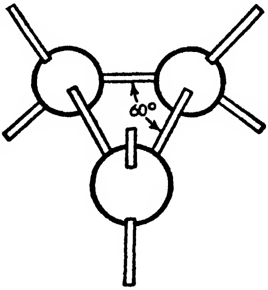


Fig. 16. Drawing of a model representing a cyclopropane ring.

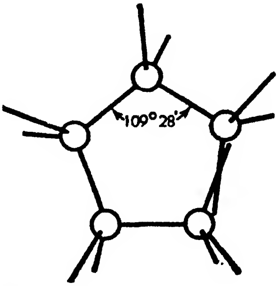


Fig. 17. Diagram showing the close approach of the terminal atoms of normal pentane when all the carbon atoms lie in a plane.

Baeyer also assumed that all the atoms in a ring are in the same plane: in this assumption he was in error. In rings larger than six carbon atoms this would require expansion of the valence angles, and, in very large rings it would result in almost incredible strain. We know now that saturated rings containing more than five atoms are not planar. This is shown for cyclohexane in Fig. 18.

Many-Membered Rings. A development of recent years has been the preparation and the study of the properties and reactions of alicyclic compounds containing up to thirty-four carbon atoms in the ring. In this work the cyclic ketones were prepared by heating the salts of the dibasic acids. These many-membered cyclic ketones show no essential differences from aliphatic compounds. From the ketones by reduction, the corresponding secondary alcohols and finally the cyclic hydrocarbons may be prepared. In this way, for example, cyclotriacontane, $C_{30}H_{60}$, a solid melting at 56°, may be prepared from the corresponding cyclic ketone.

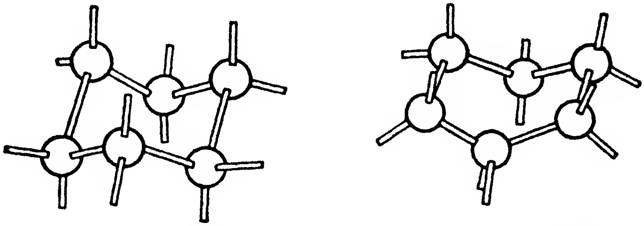
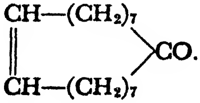


Fig. 18. Drawing of models representing two phases of a strainless cyclohexane ring. (The two phases are readily interconvertible by oscillation of the atoms and, therefore, do not represent isomeric forms.)

When the compounds with large rings are once formed, they are perfectly stable, and the ring cannot be opened any more readily than an open chain can be cleaved.

A very interesting cyclic ketone with a seventeen-membered ring occurs in nature as the chief constituent of the natural, odoriferous material known as *civet*. This ketone is known as *civetone*, and has been proved to have the following formula:

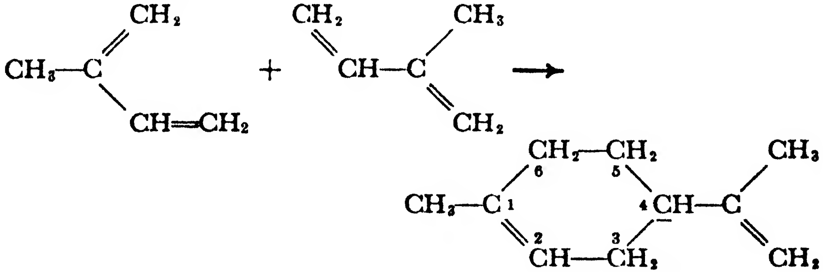


$$\begin{array}{l} CH-(CH_2)_7 \\ \| \qquad\qquad\quad \rangle CO. \\ CH-(CH_2)_7 \end{array}$$

CYCLIC TERPENES

The cyclic terpenes occur in essential oils (p. 302) particularly those obtained from citrus fruits. They also occur in oil of turpentine and similar materials made from coniferous trees. Certain cyclic alcohols and ketones closely related to the cyclic terpenes are also found in the plant world.

Limonene. Limonene, $C_{10}H_{16}$, occurs in two optically active forms, a dextro compound which is present in many essential oils from citrus fruits, and a laevo limonene which can be obtained from the leaves of certain pines. The racemic compound, known as *dipentene*, can be prepared in the laboratory either by a complete synthesis or by a transformation of certain other terpenes. Dipentene is also formed along with other products by heating isoprene at 300°; in this reaction, which is a diene synthesis, two isoprene molecules combine with each other. These compounds are liquids (bp 177°). As the formula shows, they are derivatives of cyclohexene; one methyl group and an unsaturated side chain containing three carbon atoms are attached to the opposite extremities of the ring. The asymmetric carbon atom is underlined. As would be expected, the two double bonds react with a variety of reagents.

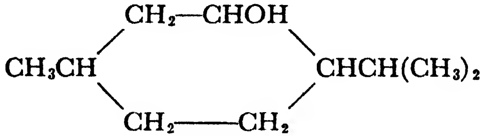


Limonene (dipentene)

The nature of the carbon skeleton in limonene was first established by converting it into the aromatic hydrocarbon known as *para cymene* (p. 261). Subsequently, dipentene itself was synthesized from a cyclohexanone derivative of known structure.

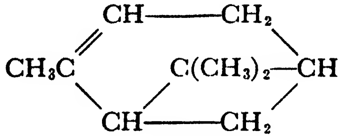
Menthone and Menthol. Two oxygen-containing substances closely related to limonene occur in certain essential oils. One of these is a saturated alcohol, **menthol**, $C_{10}H_{20}O$, which is the chief constituent of peppermint oil. Associated with it is the corresponding ketone, **menthone**, $C_{10}H_{18}O$. Menthol is a solid melting at 43.5°, while menthone is a liquid boiling at 207°.

Both of these substances have a strong peppermint odor and are laevorotatory. It will be noted that menthol is a hydroxyl derivative of the completely hydrogenated limonene molecule. The characteristic reactions of the hydroxyl group and the ketonic group are shown by menthol and menthone respectively.



Menthol

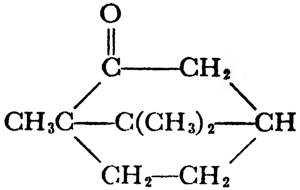
Pinene. Pinene, $C_{10}H_{16}$, is the principal constituent of turpentine oil. It occurs in two forms, the dextro in American turpentine and the laevo in European turpentine. **Turpentine** is manufactured from the sap of coniferous trees by a distillation process. It is widely used as a solvent in the paint industry.



Pinene

Pinene contains two rings and is thus a **dicyclic compound.** One of the rings is a cyclobutane ring, the other a cyclohexene ring. Pinene is a colorless oil boiling at 156°. It combines with one molecule of hydrochloric acid, yielding a crystalline solid known as *pinene hydrochloride*, $C_{10}H_{17}Cl$. This name is unfortunate, as the compound is not a hydrochloride in the sense in which this term is used to describe the salts of bases; it is really a chloro derivative of a saturated dicyclic compound. During the addition of hydrogen chloride a rearrangement of the cyclobutane ring to a cyclopentane ring occurs. This rearrangement was for a long time the cause of a great deal of confusion in regard to the structure of pinene and its derivatives. Pinene hydrochloride has a camphorlike odor and is known as artificial camphor. It is not to be confused, however, with true synthetic camphor.

Camphor. Camphor, $C_{10}H_{16}O$, is a ketonic derivative of a saturated dicyclic hydrocarbon.

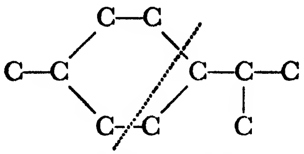


Camphor

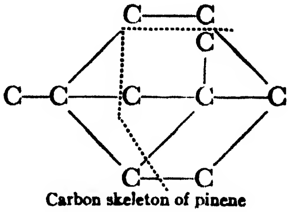
Camphor (often called *Japan camphor*) is obtained by the steam distillation of the wood, twigs, and leaves of the camphor tree (*laurus camphora*). It is produced almost entirely in the Orient. The form which occurs in the camphor tree is dextrorotatory, and it is obtained as colorless crystals with a very characteristic odor (mp 175°, bp 204°). It has been used in medicine in small amounts for a great many years and is now used in very large quantities in the manufacture of celluloid (p. 213). It may be prepared by a series of chemical transformations from pinene; the material thus prepared is the racemic form. The commercial synthesis of camphor from oil of turpentine produces a product which competes with the natural product.

The alcohol which corresponds to camphor is **borneol,** $C_{10}H_{18}O$, mp 206°. It is found naturally in certain trees in the Orient. It can be prepared by the reduction of camphor. The chemical preparation of camphor from pinene involves the preparation of bornyl chloride, the hydrolysis of this to the racemic borneol, and subsequent oxidation to the ketone.

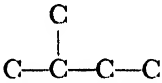
Relation of Terpenes to Isoprene. A very significant relationship exists between cyclic terpenes and isoprene. This unsaturated hydrocarbon, $CH_2{=}C(CH_3)CH{=}CH_2$, we have already encountered as being the fundamental building stone of the rubber molecule. If we examine the structure of the cyclic terpenes it will be seen that they all may be regarded as containing two isoprene nuclei joined together in different ways. This is illustrated below with the limonene and the pinene skeletons by the broken line separating the isoprene units. The reader can easily convince himself that a similar situation exists in regard to camphor. It will be clear that it is the occurrence of the carbon chain of isoprene which is of importance, and that different degrees of hydrogenation are obviously involved in the different terpene compounds.



Carbon skeleton of limonene and menthol



Carbon skeleton of pinene



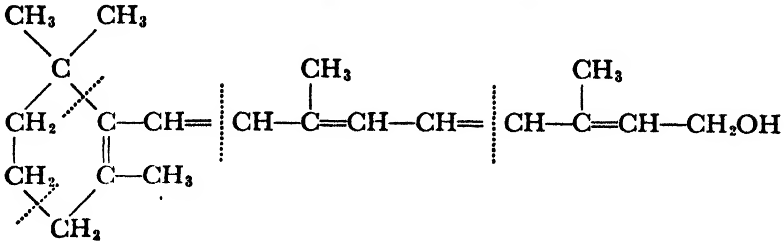
$$\mathrm{C{-}\overset{\overset{C}{|}}{C}{-}C{-}C}$$

Carbon skeleton of isoprene

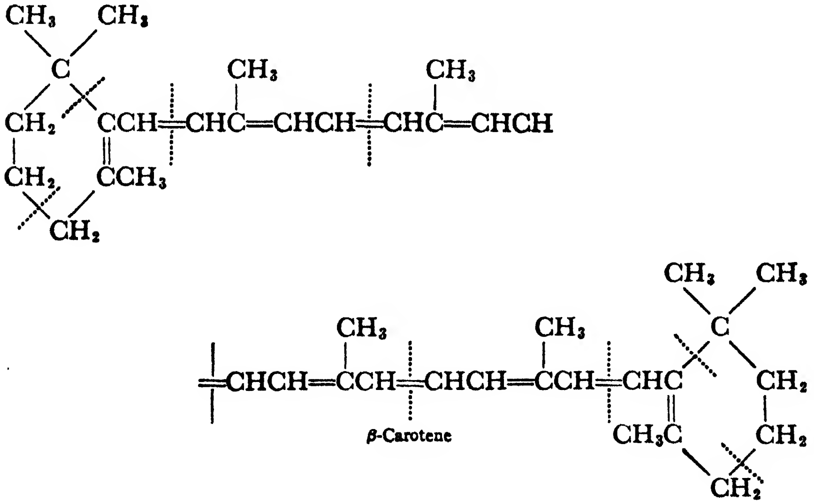
The terpenes themselves are often defined as naturally occurring substances of the formula $(C_5H_8)_n$, that is, multiples of the isoprene unit; those having the formula $C_{10}H_{16}$ are known as the *terpenes* proper and include both open-chain and alicyclic compounds. Higher terpenes are also known; those with the molecular formula $C_{15}H_{24}$, that is, $(C_5H_8)_3$, are called *sesquiterpenes.*

The Isoprene Rule. Vitamin A. The occurrence in natural products of structures which can be considered to be built up of isoprene units is so frequent that chemists making preliminary decisions between alternative formulas for a naturally occurring compound will choose the structure that is composed of isoprene units. Vitamin A and a few related compounds will serve to illustrate the importance of the isoprene unit in natural products.

Vitamin A can be isolated from the unsaponifiable residue from fish oils. Its absence from an otherwise normal diet leads to a state of ill-health characterized by a degeneration in the structure of the eye, a condition known as *xerophthalmia.* The structure of vitamin A is shown below, with dotted lines to indicate the isoprene residues.

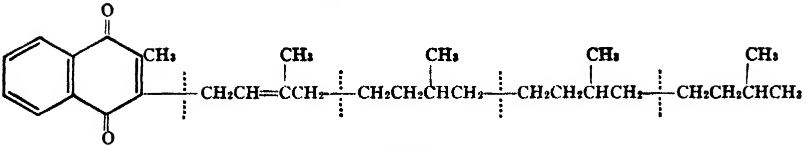


Vitamin A can be replaced in the diet of animals by the carotenes, three isomeric compounds which are transformed into vitamin A in the liver and which are, therefore, provitamins. The structure of one of the isomers, **β-carotene,** is shown below. Again the isoprene units are obvious.

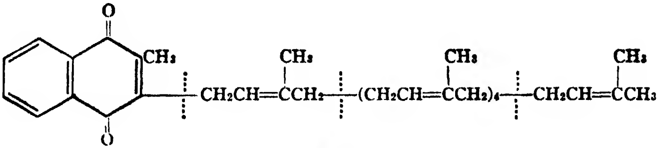


β-Carotene

Vitamins K and E. These two vitamins will serve to illustrate the application of the isoprene rule to a portion of the structure of a natural product. Two naturally occurring antihemorrhagic factors, vitamins K_1 and K_2, are derivatives of α-naphthoquinone (the naphthalene analog of benzoquinone). In both the side chain is composed of isoprene units.

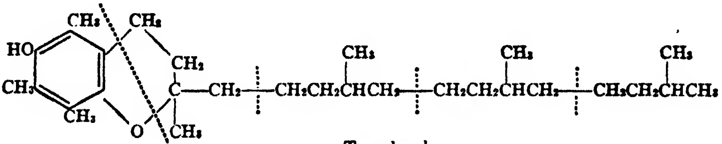


Vitamin K_1



Vitamin K_2

Vitamin E, obtained from seed-germ oils, is necessary for reproduction in rats. It consists of three closely related compounds known as α-, β-, and γ-tocopherol in which the side chain and part of the ring itself are made up of isoprene units.



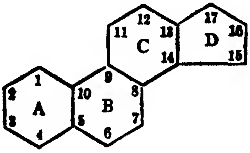
α-Tocopherol

STEROLS AND BILE ACIDS

The sterols are a group of complex alicyclic alcohols. They are colorless, crystalline solids, soluble in organic solvents, and usually found in the unsaponifiable portion of fats (p. 137). The commonest example is **cholesterol,** which occurs widely distributed in animals, particularly in relatively large quantities in the spinal cord and in human gallstones. The sterols which occur in plants are known as the **phytosterols;** there are a great many of these known. Esters of the sterols, as well as the free sterols, occur in plants and animals. **Lanolin,** or wool fat, is a very complicated mixture of sterols and sterol esters.

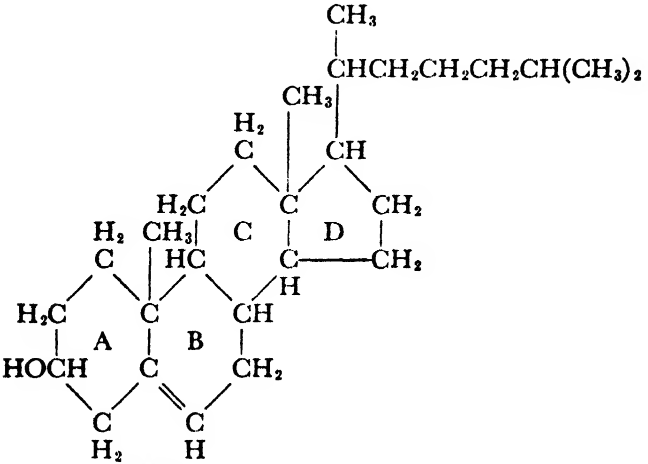
Cholesterol. Cholesterol is a colorless, crystalline solid which melts at 148° to 151°. Like all the sterols, it is difficult to purify when it is contaminated with similar substances. The molecular formula of cholesterol is $C_{27}H_{46}O$. The oxygen atom is present in a secondary hydroxyl group, and there is one double bond in the molecule. The saturated parent hydrocarbon which may be obtained from it is **cholestane,** $C_{27}H_{48}$. As shown by its empirical formula, this hydrocarbon contains four alicyclic rings. The corresponding paraffin would be $C_{27}H_{56}$; therefore, there is a deficiency of 8H or $4H_2$, indicating four alicyclic rings.

It has taken many years of patient labor by many chemists to determine the size and relative positions of the four alicyclic rings in cholesterol and the many other sterols. Only within recent years has the goal been reached, namely, the establishment of a satisfactory structural formula. One of the important lines of evidence was furnished by an x-ray study of the crystals of certain sterols and sterol derivatives in 1932. The dimensions of the molecule thus revealed were inconsistent with the arrangement of rings which had been favored until then. They corresponded closely, however, with those of a molecule which contained a hydrogenated phenanthrene ring to which an additional alicyclic ring had been fused. In the next few years it was clearly established that all the sterols and, as we shall see, many other classes of interesting compounds as well contain the following carbon skeleton:



This arrangement of carbon atoms corresponds to that of a hydrocarbon in which a phenanthrene nucleus (rings A, B, C) and a cyclopentane ring (D) have been fused together. Such a hydrocarbon, if the first three rings are aromatic and ring D a cyclopentene ring (CH_2 at 15,16,17, double bond at 13,14) is known as *cyclopentenophenanthrene.* Since in the sterols all the rings are alicyclic, they may be regarded as derivatives of the completely saturated compound, **perhydrocyclopentanophenanthrene.** This parent hydrocarbon can also be considered as consisting of a perhydrophenanthrene ring and a cylopentane ring fused together; an alternative name is therefore *cyclopentanoperhydrophenanthrene.*

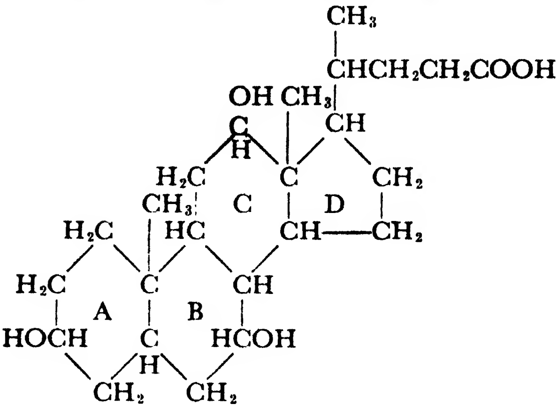
Constitution of Cholesterol. The structural formula of cholesterol is:



Cholesterol

It will be noted that this formula contains the fused, hydrogenated phenanthrene-cyclopentane skeleton with methyl groups substituted at positions 10 and 13, a branched aliphatic chain at 17, a hydroxyl group at 3, and a double bond between atoms 5 and 6 in ring B. Almost all the sterols so far investigated differ from cholesterol only in regard to (1) the degree and position of the unsaturation (some are saturated); (2) the nature of the side chain on position 17; and (3) their stereochemical configuration.

Cholic Acid. This acid occurs in large quantities in the bile of man as one of the constituents of the bile salts (p. 226). The close relationship between cholic acid and cholesterol can be seen by comparing the structural formula of cholic acid shown on the next page with that of cholesterol shown above.

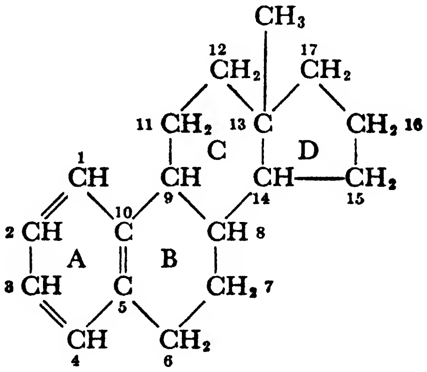


Like the sterols, cholic acid and all the other bile acids contain the cyclopentanoperhydrophenanthrene skeleton. Furthermore, like the sterols, there are methyl groups in positions 10 and 13, a branched side chain in position 17 (which in this case carries a carboxyl group) and position 3 carries a hydroxyl group. Unlike cholesterol, there is no unsaturation and there are two additional hydroxyl groups in positions 7 and 12, respectively.

SEX HORMONES, CORTIN, AND VITAMIN D

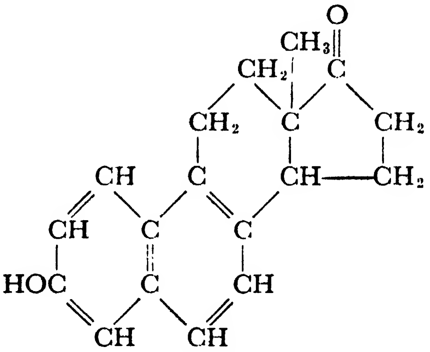
The group of substances known as the *sex hormones* are closely related to cholesterol and the bile acids. Structurally, they may be considered as derived from cholesterol by oxidation. Indeed, it may be that cholesterol is the actual precursor of these hormones; but on this point we are still uncertain, and the way the animal body prepares these hormones is as yet unknown. The physiologist has recognized for years that the glands of the genital systems produce hormones. It is only recently, however, that by the combined labors of the physiologist, biochemist, and organic chemist the sex hormones have been isolated and their structure determined. Three different types of sex hormones originate in the gonads (testes and ovaries). They are (1) the estrogenic hormones; (2) the hormone produced by the corpus luteum which is essential for pregnancy; and (3) the male hormones that cause changes in the accessory sexual organs of the male. The production of all these hormones appears to be regulated in turn by other substances (the gonadotropic hormones produced in the anterior lobe of the pituitary). The structure of these pituitary hormones is not now known. Those of the sex hormones have been established and examples are given below.

The Female Sex Hormones. The hormones concerned with the estrogenic cycle and the hormone of the corpus luteum (a small yellow body in the ovary) are often designated as the *female sex hormones.* The estrogenic hormones (more than half a dozen have been isolated) may all be regarded as derived from the following hypothetical parent hydrocarbon.



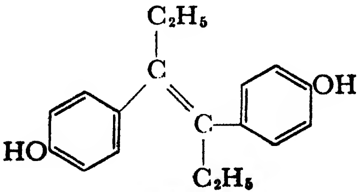
For example, one of the most potent of these hormones is **estriol,** which can be isolated from the urine of pregnant women. This substance is a trihydroxy derivative of the hydrocarbon shown above, the OH groups being at positions 3, 16, and 17. In a closely related ketone, **estrone,** which occurs along with estriol, there is a ketonic oxygen attached to carbon atom 17, and a hydroxyl at 3. (If the reader will write these formulas, it will become evident that on dehydration estriol should readily lose water between 16 and 17, yielding the enolic form of estrone. Actually, estrone is readily formed by dehydrating estriol.) Unlike the sterol and bile acid nucleus, that of the estrogenic hormones contains one aromatic ring. The hydroxyl group in position 3 is, therefore, phenolic (weakly acidic).

A group of estrogenic hormones similar in structure to estrone has been isolated from mare's urine. One of these hormones, **equilenin,** has been synthesized. The hormone contains two asymmetric carbon atoms. The synthesis, of course, furnished only inactive material, but this material was resolved (p. 194) into the four active forms, one of which was identical with naturally occurring equilenin.

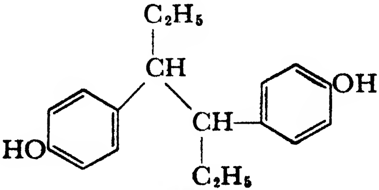


Equilenin

Estrone has been isolated not only from urine and placenta, but also from a variety of vegetable sources. It is interesting, in view of this lack of specificity of origin of estrone, that estrogenic activity is not specifically connected with the estrone type of structure. Thus the two synthetic compounds, **diethylstilbestrol** and **hexestrol,** only remotely related structurally to estrone, have estrogenic properties.



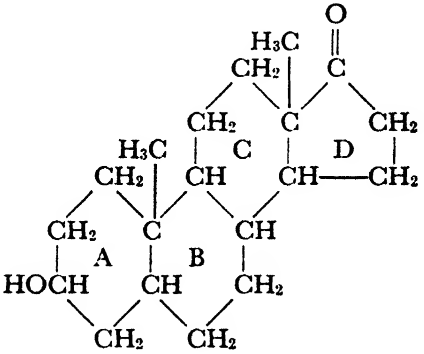
Diethylstilbestrol



Hexestrol

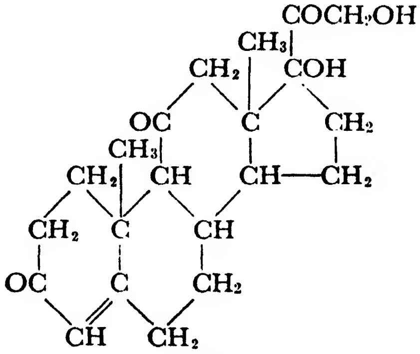
Progesterone, the hormone produced by the corpus luteum, is more closely related to cholesterol than the other female hormones. In this substance ring A is still alicyclic and the methyl group at position 10 intact. A ketonic oxygen is at position 3 and a double bond between 4 and 5; the other rings are saturated. At position 17 there is an acetyl group, $CH_3CO—$, representing a residuum of the side chain of cholesterol and the bile acids.

Male Sex Hormones. The two most important male hormones which can be isolated from urine and testicular extracts are **androsterone** and **testosterone.** Like progesterone, these compounds are more closely related to cholesterol than the female hormones. Androsterone contains the cholesterol structure with all four rings saturated, a hydroxyl group at 3 (secondary alcohol), and a ketonic oxygen at 17. In testosterone, a ketonic oxygen is at 3 and a hydroxyl (secondary alcohol) at 17 with a double linkage between atoms 4 and 5 in ring A. The male hormone structure seems to be much more specific than that of the estrogenic hormone.



Cortin. The crude extract obtained from the adrenal cortex which contains many hormones closely related to the sex hormones is known as *cortin.* Almost thirty hormones have been isolated from cortin. In these hormones the four alicyclic rings of cholesterol and the two methyl groups at positions 10 and 13 are intact. In most of them there is a side chain of two carbon atoms attached at position 17; this chain carries two hydroxyl groups or a hydroxyl and a ketonic group. Usually there are two other oxygen atoms in the molecule, at positions 3 and 11.

Currently the interest in these hormones centers about 17-hydroxy-11-dehydrocorticosterone, **cortisone,** which has given spectacular results in the treatment of rheumatoid arthritis and rheumatic fever and which gives promise of other important applications.



Cortisone

For use and further study of cortisone a source of supply other than cortin is essential. Cortisone has been synthesized from cholic acid (p. 346) and desoxycholic acid which differs from cholic acid only in having a hydrogen in place of the hydroxyl group in position 7. The synthesis, however, requires over thirty separate chemical reactions and a new method of synthesis must be developed before cortisone will be generally available at reasonable cost.

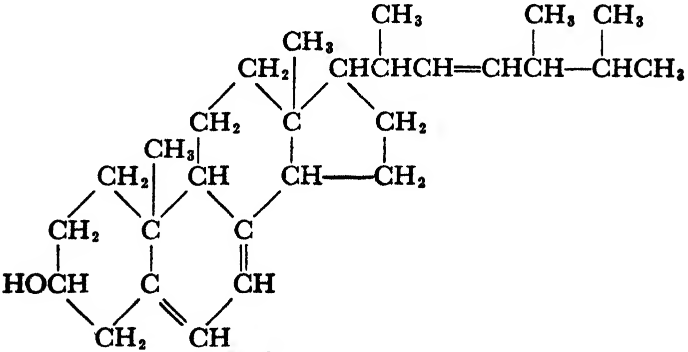
A hormone of as yet unknown structure, the adrenocorticotrophic hormone (ACTH) from the anterior pituitary is similar to cortisone in physiological action. It is believed to act by stimulating the production of hormones by the adrenal glands.

Vitamin D. This vitamin is known as the antirachitic vitamin. Its absence in the diet interferes with the proper formation of bone tissue and continued vitamin D-free diet thus leads to rickets.

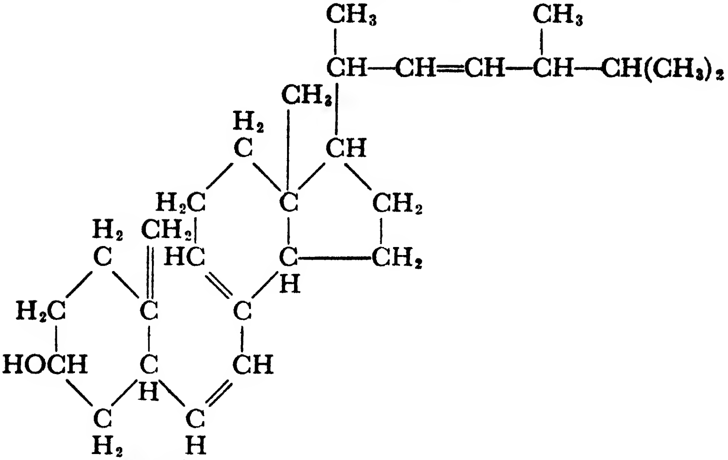
The first clue as to the nature of vitamin D was provided by the discovery that irradiation with ultraviolet light was beneficial to rickets. It was next found that the foodstuff might be irradiated instead of the patient. As soon as this fact was established, a chemical investigation of the foods was begun to discover what particular constituent was turned into vitamin D by the action of ultraviolet light. This substance proved to be **ergosterol,** which can thus be considered as a provitamin D. This sterol on irradiation with ultraviolet light of rather long wavelength (250 to 300 mμ) was transformed into a very active vitamin D. It was subsequently discovered that a still more important provitamin D is 7-dehydrocholesterol. This substance on irradiation, can be transformed into a slightly different vitamin D (vitamin D_3).

Vitamin D_2 from Ergosterol. The conversion of ergosterol to vitamin D_2 proceeds in a series of steps. The first two products which are formed are biologically inactive. Further irradiation of the vitamin produces still other compounds which are inactive. The active compound which can be isolated from the irradiated ergosterol under the most favorable circumstances is known as *vitamin D_2* or *calciferol.*

Calciferol is isomeric with ergosterol. Investigations of the structure of calciferol have showed that it differs from ergosterol in that ring B of the sterol system has been opened, the methyl group at position 10 has been transformed to a methylene group ($=CH_2$), and the two ring double bonds in positions 5–6 and 7–8 in ergosterol are in positions 6–7 and 8–9 in calciferol. These differences can best be seen by comparing the formulas of the two compounds as they are given below.



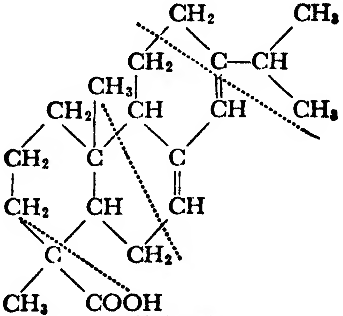
Ergosterol



Calciferol
(vitamin D_2)

Vitamin D_3. It was at first thought that the vitamin D which occurs naturally in such materials as cod-liver oil was identical with the crystalline material obtained by irradiating ergosterol. This has turned out not to be so, however. The true vitamin in fish oils has been isolated and identified as being the compound prepared by irradiating a cholesterol transformation product called 7-*dehydrocholesterol.* (*Dehydro* indicates less hydrogen.) 7-Dehydrocholesterol is, therefore, a provitamin D. 7-Dehydrocholesterol has a saturated side chain identical with that of cholesterol, saturated rings A, C, and D and, like almost all the sterols, a secondary alcohol group at position 3. There are two conjugated double bonds in 7-dehydrocholesterol just as there are in ergosterol, and it is for that reason that it undergoes the same type of transformation with ultraviolet light. The vitamin D which is thus formed and which occurs in nature is called *vitamin D_3*. If one substitutes the saturated eight-carbon side chain of cholesterol for the unsaturated nine-carbon chain of vitamin D_2, the structural formula of vitamin D_3 results. (The name *vitamin D_1* was given to a substance which later proved to be a mixture; only two pure vitamin D's are known, D_2 and D_3.)

Rosin. The residue left behind in the manufacture of turpentine by distillation (p. 340) is a solid known as *rosin* or *colophony*. It is a mixture of **abietic acid,** $C_{19}H_{29}COOH$, and its anhydride. Abietic acid contains a partially hydrogenated phenanthrene nucleus. It is thus related to the sterols and, because the molecule can be divided into four isoprene residues (p. 342), to the terpenes. Since abietic acid has a high molecular weight, its sodium and potassium salts have soaplike properties, and it is frequently used in connection with the manufacture of soap. It is also used in the manufacture of varnishes and, with alum, it is employed as sizing for paper.



Abietic acid

QUESTIONS AND PROBLEMS

1. Write structural formulas for isoprene, cholesterol, limonene, abietic acid, and menthol.

2. What is the relationship between the size of alicyclic rings and the ease with which the rings are opened?

3. Define and illustrate the following terms: alicyclic compounds, terpenes, sterols, hormones, and vitamins.

4. Discuss briefly the Baeyer strain theory.

5. State the isoprene rule and give examples of its usefulness.

6. Compare the structure of the alkali salts of abietic acid with the structures of other detergents encountered earlier in the book. Can you account for the fact that these salts are detergents?

7. Write equations for the reactions you would expect to take place when cyclohexanone was treated with (*a*) hydroxylamine and (*b*) methylmagnesium iodide.

8. Name and write structural formulas for two synthetic substances which have marked estrogenic activity. Compare their structures with that of estrone.

9. What reactions would you use to show that cholesterol contains (*a*) an ethylenic linkage and (*b*) a hydroxyl group?

10. What structural features do the sterols, bile acids, sex hormones, and the adrenal cortex hormones have in common?

11. Outline the changes that take place in conversion of ergosterol to vitamin D_2. What is the difference between vitamins D_2 and D_3?

CHAPTER 22

Heterocyclic Compounds

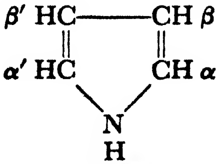
Cyclic compounds which contain two or more different elements in the ring are known as **heterocyclic compounds.** The elements which are commonly found in ring systems in addition to carbon are oxygen, sulfur, and nitrogen. We have already had occasion to introduce certain heterocyclic compounds in connection with our study of aliphatic compounds. Thus the cyclic forms of the sugars, the cyclic anhydrides, and the lactones are, strictly speaking, heterocyclic compounds; so too are the nitrogen analogs of the cyclic anhydrides known as the cyclic imides. In all these compounds, however, the heterocyclic ring system is readily transformed into an open-chain system by hydrolysis. Indeed, it is difficult to avoid opening the ring in these compounds and only rarely are we concerned with a series of chemical changes in which the ring system remains intact. Because the cyclic anhydrides, lactones, and the cyclic forms of the sugars are so readily converted into open-chain compounds, these heterocyclic compounds are usually considered in connection with aliphatic chemistry.

Another type of heterocyclic ring is present in certain amino acids (Chap. 14). The five-membered rings containing nitrogen in proline, hydroxyproline, tryptophane, and histidine persist through a great variety of chemical changes. Earlier, in presenting the amino acids and proteins we treated these heterocyclic groupings very much as we did the benzene rings in phenylalanine and tyrosine; from the point of view of the reactions of the α-amino group and the carboxyl group, these cyclic arrangements were almost like hydrocarbon residues. One may speak of compounds whose behavior is like proline or histidine and unlike the cyclic anhydrides as having a *persistent* heterocyclic structure.

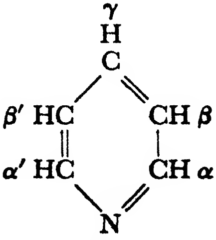
In this chapter, we shall be concerned with a few types of **persistent heterocyclic rings** which occur in substances of importance to the biologist and biochemist. As is already clear from the study of the proteins, heterocyclic compounds containing nitrogen play a very important role in nature. Unfortunately for the student some of them have rather complicated heterocyclic structures. We shall start by a consideration of the simple substances which contain only one nitrogen atom in the ring.

PYRROLE AND PYRIDINE DERIVATIVES

Five- and six-membered rings containing only *one* nitrogen atom are frequent units in the structure of natural products. It is convenient to regard all such groupings of atoms as relatives of the two parent substances pyrrole and pyridine which have the maximum degree of unsaturation and no substituents. As in the case of benzene and its derivatives, some compounds can be considered as substitution products, one or more hydrogen atoms of the ring being replaced by substituents; other substances contain hydrogenated pyrrole or pyridine rings and are related to the parent structures as are cyclohexane or cyclohexene derivatives to benzene.

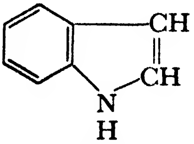


Pyrrole

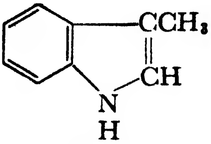


Pyridine

An examination of the structure of the two amino acids proline and hydroxyproline (p. 221) will show that a tetrahydropyrrole ring is present in each. Tryptophane contains a pyrrole ring fused with a benzene ring in a fashion similar to the condensation of two benzene rings in naphthalene. The simplest substance which contains this arrangement of atoms is *indole.*



Indole



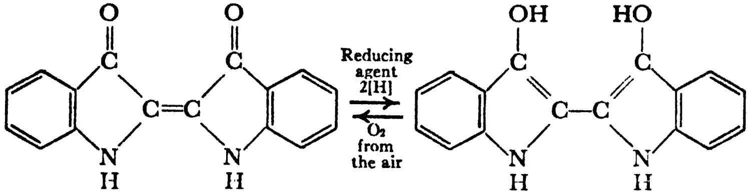
Skatole

Indole and its methyl derivative skatole (see above) are formed by the decomposition of tryptophane as a result of bacterial action in the large intestine. Both substances have appreciable vapor pressure at room temperature and very disagreeable odors; they are largely responsible for the odor of feces.

Nomenclature. It is common practice to indicate the position of substituents in pyrrole and pyridine derivatives by the use of Greek letters. The position nearest the nitrogen is designated alpha or alpha prime as shown in the diagrams. Skatole is β-methylindole. A compound with two methyl groups substituted for the hydrogen atoms on the carbon atoms adjacent to the nitrogen in pyrrole would be α,α'-dimethylpyrrole. Substituents on nitrogen are often designated by the letter N before the substituent. Another method of nomenclature involves numbering the rings counterclockwise starting with the nitrogen atom. Thus skatole is also correctly named 3-methylindole. The reader should convince himself that 1,2,3-trimethyl-4-ethylpyrrole is the same substance as N-methyl-α,β-dimethyl-β'-ethylpyrrole; further that 2,6-dimethyl-3-ethoxypyridine is the same as α,α'-dimethyl-β-ethoxypyridine.

Indigo. Indigo, one of the oldest known dyes, is a derivative of indole. Cloth is immersed in an alkaline solution of the reduced dye and then exposed to air, at which time the dye is formed in the fibers by oxidation. This process is known as *vat* dyeing.

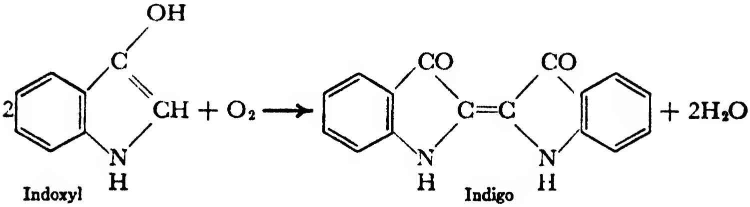
Dyeing with indigo may be represented by the following equation.



Indigo blue, insoluble

Indigo white, soluble

A number of semitropical plants contain the glucoside **indican.** On hydrolysis, indican furnishes glucose and indoxyl. This latter substance is oxidized to indigo by exposure to atmospheric oxygen.



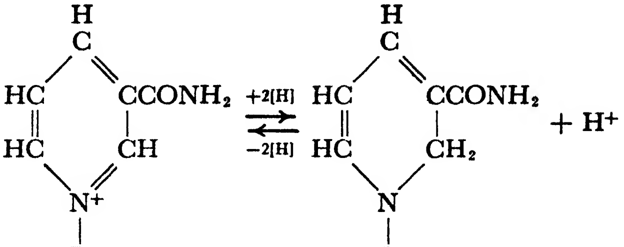
Indoxyl

Indigo

Indigo was obtained from plants for hundreds of years. In 1882, however, Baeyer established the structure of indigo, and methods of synthesis were soon developed. Over 2500 tons of synthetic indigo were produced in the United States in 1947.

Nicotinic Acid. The pyridine derivative corresponding to benzoic acid is nicotinic acid. The position of the carboxyl group is indicated by a Greek letter; nicotinic acid is pyridine-β-carboxylic acid. Combined with a pentose sugar and a complex phosphoric acid ester, nicotinic acid amide is present in the prosthetic group of at least two of the enzymes, Coenzymes I and II, which are involved in carbohydrate metabolism (p. 251) and whose structure is considered later on p. 375. A study of these enzymes indicates that their role is to act as an intermediate in the transfer of hydrogen from the carbohydrate derivative which is being oxidized to other enzymes which eventually react with atmospheric oxygen. The ability of this particular enzyme to act as a reversible dehydrogenating agent depends on the fact that a dihydropyridine ring containing a substituent on the nitrogen atom can be reversibly oxidized and reduced with ease.

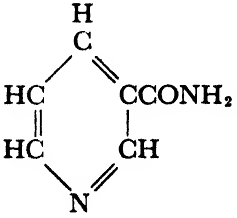
In simplified form the reaction may be illustrated by the following equation.



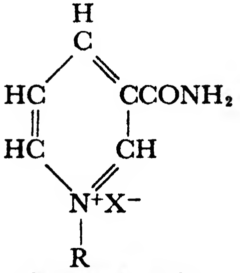
Oxidized prosthetic group
(Note positive charge on N)

Reduced prosthetic group

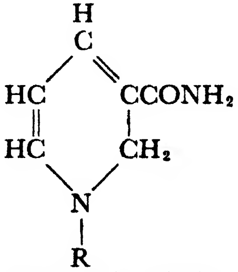
In these formulas R_{PA} stands for a pentose residue carrying the complex phosphoric acid residue known as adenylic acid (to be described later). It should be noted that the prosthetic group in the oxidized form is related to the simple quaternary ammonium salts formed by the addition of an alkyl halide to pyridine; in the reduced form it is a derivative of a dihydropyridine. The significant chemistry of these complex substances depends on the ability of pyridinium salts to be reduced reversibly. The following formulas will help clarify these relations.



Nicotinic acid amide, a pyridine derivative



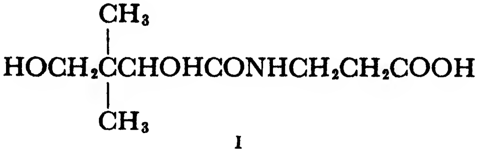
Quaternary ammonium salt, a pyridinium derivative



Dihydropyridine derivative, reduction product of the pyridinium salt

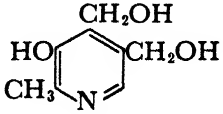
The B Vitamins. The material originally obtained from yeast and other natural sources and called the *water-soluble B* fraction, has been found to consist of a number of substances differing widely in chemical structure and complexity. Among them *p*-aminobenzoic acid (p. 305), pantothenic acid (I), pyridoxin

(II), and biotin (p. 379) have been shown to have vitamin activity, but have not been shown to be essential in human nutrition.



$$HOCH_2\overset{CH_3}{\underset{CH_3}{C}}CHOHCONHCH_2CH_2COOH$$

I



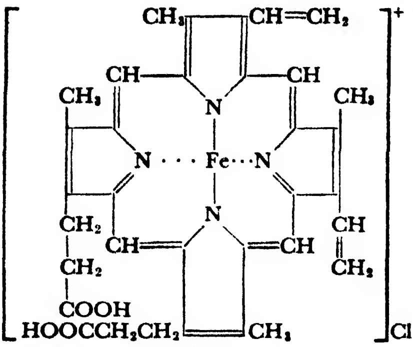
II

Three other members of the B group have been established as essential in human nutrition. They are nicotinic acid and its amide (p. 359) and vitamins B_1 (thiamin, p. 379) and B_2 (p. 377). Still another member of the B group, folic acid, is discussed on p. 377.

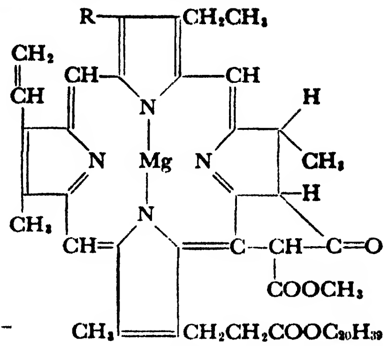
Polynuclear Pyrrole Pigments. Chlorophyll, the green material involved in the process of photosynthesis, and hemoglobin, the red coloring material of blood, both owe their color to a combination of four pyrrole nuclei joined in a complex molecule. **Chlorophyll** contains a magnesium atom, and **hemoglobin** an iron atom. Both metallic atoms are similarly joined to colored molecules as complex salts. The magnesium is readily removed from chlorophyll by the action of dilute acids; the iron is much more tightly bound in hemoglobin.

When the protein, hemoglobin (p. 235), is treated with hydrochloric acid under suitable conditions, the colored portion of the molecule is split off. In this way, the colorless globin (a protein) and the black, crystalline compound, hemin, $C_{34}H_{32}N_4O_4FeCl$, (I), are formed. Removal of the iron from hemin furnishes the purple pigment **protoporphyrin.** It is a representative of a class of pigments known as the *porphyrins*. They are highly colored, weakly basic, and have a characteristic type of absorption spectrum. Unlike most organic compounds, the absorption spectrum *in the visible* of solutions of porphyrins is composed of a number of relatively narrow bands. The pattern is the same for all porphyrins, but the exact position of the lines is somewhat affected by changes in structure; the metallic compounds such as hemin have a different type of banded spectra. Porphyrins have been found in small quantities in both the animal and plant kingdoms. In certain rare diseases, porphyrins are produced in quantity and excreted in the urine. These porphyrins differ from protoporphyrin in the nature of the groups attached to the group of pyrrole nuclei.

The two chlorophylls present in the chloroplast are known as *chlorophyll a* and *chlorophyll b*. Their basic structural skeleton (II) is the same as that in hemin. They differ from each other only in that chlorophyll b has an aldehyde group where chlorophyll a has a methyl group. Degradation of chlorophyll leads to a porphyrin.

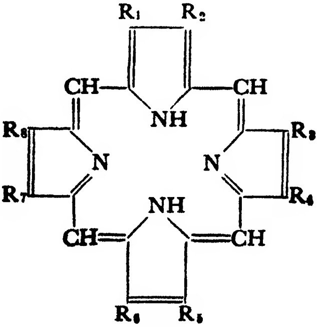


Hemin I



II
Chlorophyll (a) R=CH_3
(b) R=CHO

All the porphyrins may be considered as derivatives of a parent substance (III) in which all the R's are hydrogen. The parent substance is named *porphin*. In **protoporphyrin** R_1, R_3, R_5, R_8 are methyl groups, R_6 and R_7, CH_2CH_2COOH groups, and R_2 and R_4, vinyl groups. The porphin ring consisting as it does of four pyrrole nuclei joined together is an essentially aromatic structure. Different arrangements of double linkages can be written without shifting an atom or group. No isomers corresponding to such formulas have ever been found, however. There is undoubtedly a good deal of resonance energy which imparts to the porphin ring a marked stability.

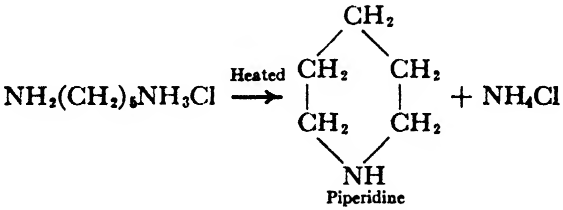


III

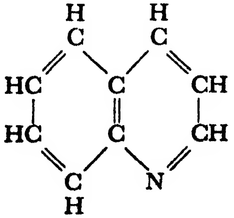
Porphyrins readily form metallic derivatives in which the two hydrogen atoms on two of the four nitrogen atoms are replaced by metal. A model of the porphin ring shows that all four pyrrole rings and connecting —CH= groups lie in a plane. The space between the four nitrogen atoms is thus like a hole in a doughnut in which various metallic atoms readily fit.

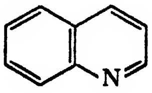
Basic Properties. Pyrrole and those derivatives in which there is the *same degree of unsaturation in the ring* show no basic properties in aqueous solutions; they are like the amides. Pyridine on the other hand is a weak base of the same strength as aniline (Fig. 8, p. 157). At first sight this difference may seem surprising; but it will seem less so when one examines the properties of open chain compounds containing the grouping $C{=}N{-}C$ and finds that they too are basic whereas those containing the group $=C-\underset{\underset{H}{|}}{N}-C=$ are not. As might be predicted, both the hydrogenated pyrrole and hydrogenated pyridine ring confer on a compound a basicity comparable to the secondary aliphatic amines; the significant structure is the same, namely, $-CH_2-NH-CH_2-$.

Completely hydrogenated pyrrole is known as *pyrrolidine;* hexahydropyridine is called *piperidine.* As a method of synthesizing heterocyclic compounds, one may mention the formation of piperidine when the hydrochloride of 1,5-diaminopentane is heated.

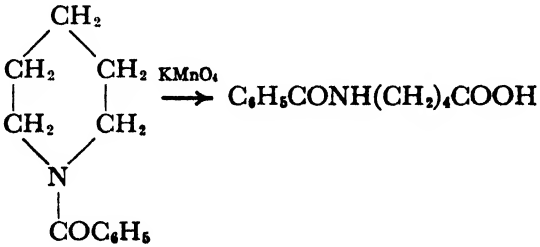


Quinoline. A number of alkaloids (p. 382) have a structure in which a benzene ring is condensed with a pyridine ring; the parent substance of this arrangement of atoms is known as **quinoline.** The formula is often written in an outline form without showing the individual carbon atoms following the convention used with naphthalene.

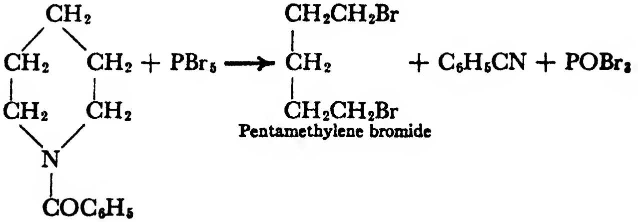




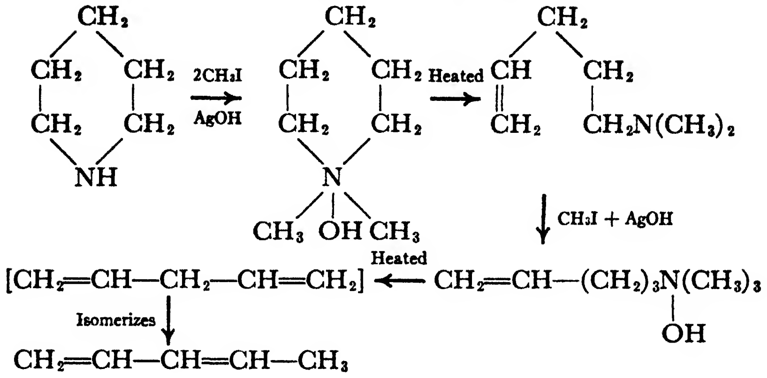
Opening Heterocyclic Rings. For the purpose of determining structure, it is important to be able to transform heterocyclic compounds into open-chain derivatives. In general, the unsaturated heterocyclic compounds and their hydrogenated products contain rings which are opened with difficulty. In certain cases, however, vigorous oxidizing agents will cleave the ring with the resulting formation of dibasic acids. For example, the N-benzoyl derivative of piperidine (prepared by treating piperidine with benzoyl chloride and sodium hydroxide) is oxidized as follows by permanganate.



Treatment of N-benzoyl piperidine with phosphorus pentabromide also results in ring cleavage.

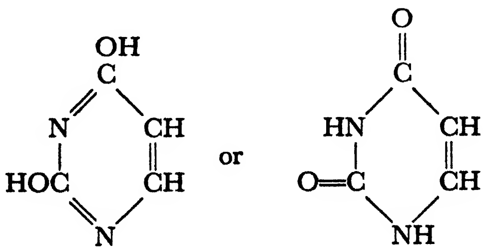


Exhaustive Methylation. A very important method of opening nitrogen-containing rings which has been much employed in determining the structure of alkaloids (p. 382) is the series of reactions known as exhaustive methylation. The heterocyclic compound is converted to the quaternary ammonium hydroxide (p. 160) by treatment with methyl iodide and silver hydroxide, and the quaternary ammonium hydroxide is subjected to thermal decomposition. The application of the process to a simple heterocyclic compound, piperidine, is shown by the following equations.



RINGS CONTAINING THE UREA RESIDUE (N—C—N)

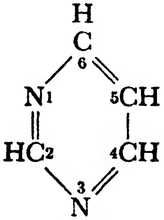
A group of heterocyclic compounds containing the grouping N—C—N are widely distributed in the products of plant and animal metabolism. The same arrangement of atoms occurs in urea, NH_2CONH_2 (p. 153); it is also present in the open-chain compounds, arginine (p. 221), creatine, and creatinine (p. 225) as $N{=}C(NH_2){-}NH{-}$. The recurrence of this arrangement of atoms suggests that in some unknown way plant and animal cells can use this unit in building complex structures; the situation is reminiscent of the recurrence of the isoprene unit in alicyclic compounds (p. 342). The simplest representative of this class of substances which is of importance to the biologist is uracil, the formula of which is often written in either of the two following ways.



No isomers corresponding to these two tautomeric formulas have ever been isolated in this or in any closely related compound.

We therefore conclude that in solution the shift in position of the hydrogen atom is too rapid to allow a separate existence of the one form or the other; the structure of the molecule in the solid state is still a matter of argument. Modern opinion tends towards the dihydroxy formulation, for it will be noted that the unsaturated ring is analogous to that of benzene and a considerable degree of resonance would be expected (p. 257).

Pyrimidines. One can imagine that uracil was formed by the condensation of a urea molecule with a triose. We have no knowledge as yet of the mechanism by which living cells build this type of structure, but this possibility will help the student remember the fundamental structure of the ring in uracil which contains a urea residue and a three-carbon system joined in a ring. This arrangement is known as the pyrimidine ring. The formula for the parent substance is as follows; it is not found in nature.

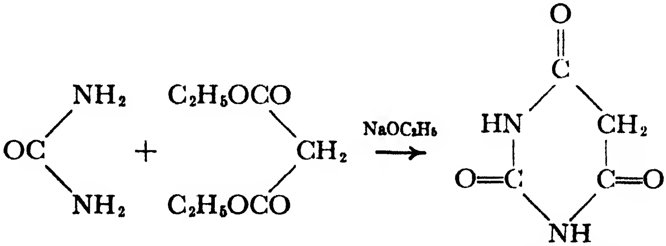


Pyrimidine

The method of naming derivatives is indicated by the numbering of the ring. Thus, uracil is 2,6-dihydroxypyrimidine; those who prefer the alternative structure often designate the compound as 2,6-diketopyrimidine.

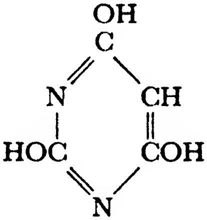
While pyrimidine is a weak base, the hydroxyl derivatives which occur in nature are weak acids; one may say that the phenolic nature of the hydroxyl group overbalances the basicity of the nitrogen in the unsaturated ring system. The significance of these substances as components of the nucleic acids will be considered shortly.

Barbituric Acid. A group of interesting drugs which have soporific powers contain a reduced pyrimidine ring. These are known as the *barbiturates*. The simplest representative of this class of compounds is barbituric acid which is readily prepared by treating the ethyl ester of malonic acid with urea in the presence of sodium ethoxide.



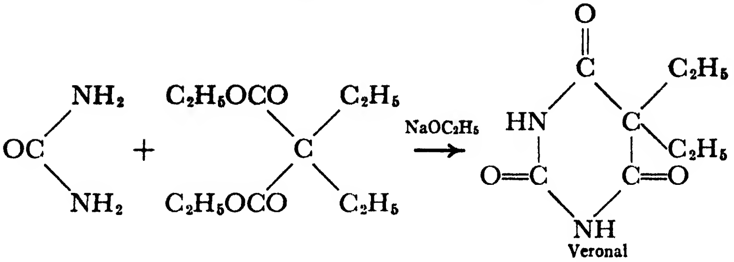
Barbituric acid

The formula of this substance may be written in the tautomeric form shown below; the name corresponding to this structure is 2,4,6-trihydroxypyrimidine.



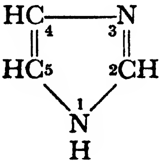
As would be predicted from the presence of three hydroxyl groups attached to an unsaturated ring system, barbituric acid shows acidic properties comparable to those of acetic acid.

Barbituric acid was first obtained as an oxidation product in the investigation of the structure of natural products (purine). It was later synthesized by the method outlined above and it was discovered that the dialkyl derivatives, which were readily prepared in a similar fashion, were very useful as drugs for producing sleep; a number of these substances are now currently employed and sold in large amounts. The synthesis of one of these, the diethyl derivative known as *veronal* or *barbital*, is outlined on the next page.



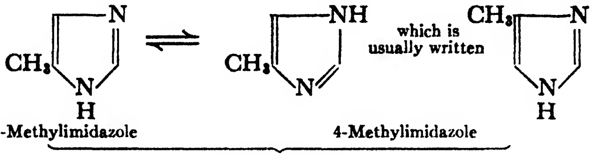
Ureides. A ureide is a derivative of urea in which one or more hydrogen atoms are replaced by acyl groups. Thus $(CH_3CONH)_2CO$ is diacetylurea, an open-chain ureide. Those pyrimidine derivatives which can be synthesized from urea and the esters of dibasic acids are often referred to as *cyclic ureides.* On this basis barbituric acid is sometimes referred to as malonylurea. Cyclic ureides are also known which contain five-membered rings; thus the condensation product of ethyl oxalate and urea is oxalyl urea.

Imidazole Derivatives. The amino acid histidine (p. 222) contains a five-membered ring which, like the pyrimidine ring, contains the urea unit; the parent substance is known as **imidazole.** The method of numbering the ring is shown below.



There are no simple derivatives of imidazole found in nature except the amino acid histidine. In this compound the 4 position is occupied by the side chain $—CH_2CH(NH_2)COOH$. The imidazole ring contains the N—C—N link characteristic of the pyrimidine ring, but joined to *two* carbon atoms. We have no inkling of how this structure is formed in nature. Imidazole is a weak base and therefore histidine has two basic groups, one the characteristic amino group of the amino acids, the other the imidazole ring.

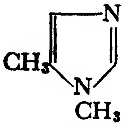
Tautomerism of Imidazole. Imidazole contains both an >NH and a =N— linkage. The interchange of hydrogen between the two nitrogen atoms is very rapid. If the ring in imidazole, for example, is made unsymmetrical by the introduction of a methyl group, two isomers might be expected according to whether the group is adjacent to the >NH or =N—. Such isomers have never been isolated.

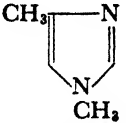


5-Methylimidazole 4-Methylimidazole

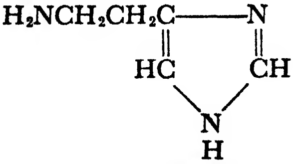
One compound

For this reason the 4 and 5 positions are identical in the imidazole ring. If, however, the hydrogen atom on nitrogen is replaced by a methyl group, a tautomeric shift is no longer possible and the following isomers, for example, can be readily obtained.

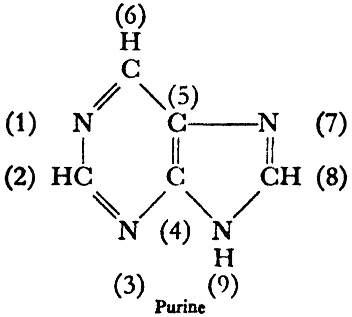

N-methyl-5-methylimidazole


N-methyl-4-methylimidazole

Histamine. The decarboxylation of histidine yields the corresponding primary amine, **histamine,** which is 4-(β-aminoethyl)imidazole. This substance is the most powerful stimulant for the production of gastric juice. It has been suggested that histamine is responsible for many allergic reactions such as hives and asthma, and a number of compounds have been prepared which will stop these allergic reactions in many individuals. The compounds are known collectively as anti-histaminics. The way in which they act is not known, but it seems fairly certain that they do not act by combining with histamine.


Histamine

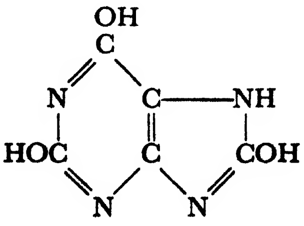
Purines. Just as the condensation of two benzene rings gives the naphthalene structure and a condensation of a benzene ring and a pyrrole ring gives the indole structure, so a fusion of a pyrimidine and an imidazole ring gives a persistent grouping of atoms known as **purine**; the hydroxyl derivatives and amino derivatives are present in all living cells. The method of numbering the ring is indicated below.

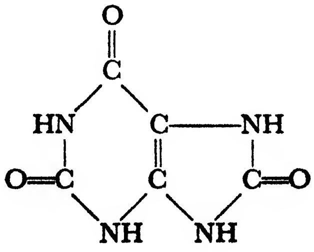


Purine

Uric Acid. The trihydroxyl derivative of purine is present in the body fluids and urine of the higher animals. It is known as uric acid or 2,6,8-trihydroxypurine; it may be written in the keto form and is then designated as 2,6,8-triketopurine or 2,6,8-trioxypurine.

Under certain pathological conditions large quantities of uric acid are produced in man and are deposited as the sparingly soluble sodium salt. Such deposits occur in the joints and produce the unpleasant symptoms characteristic of gout. Urinary calculi which may form in the bladder also contain uric acid, and the acid was isolated from such material as long ago as 1776 by Scheele. The ammonium salt of uric acid is the chief constituent of the excrement of reptiles, birds, and insects.

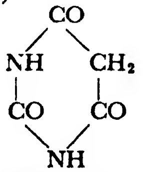




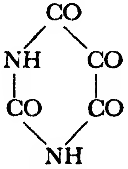
The two formulas written above for uric acid represent two tautomeric possibilities, but such tautomeric isomers have never been isolated. The situation is very similar to that encountered in the hydroxy pyrimidines (p. 365).

Uric acid is a white, crystalline solid very slightly soluble in water. It is a weak, dibasic acid; the monosodium salt is difficultly soluble in water but the disodium salt is readily soluble. Uric acid has no basic properties.

Structure of Uric Acid. On oxidation uric acid is converted into alloxan and urea, NH_2CONH_2. Alloxan may also be made by the oxidation of barbituric acid (p. 366).

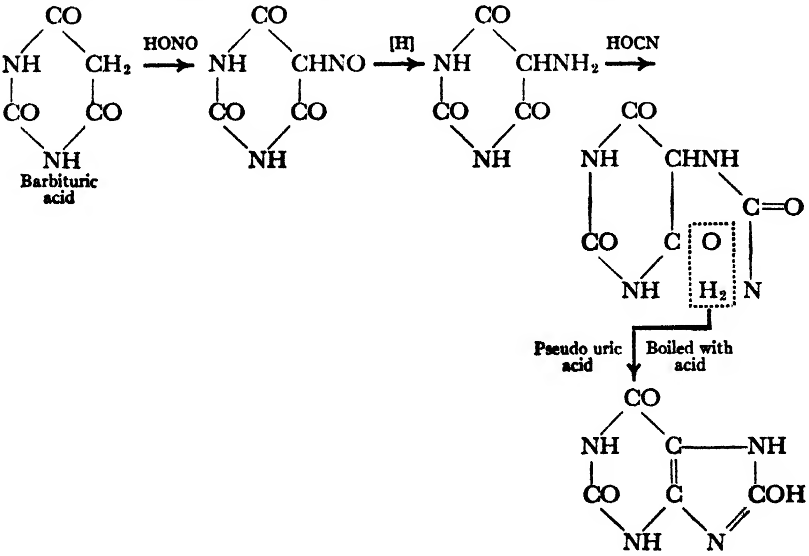


Barbituric acid



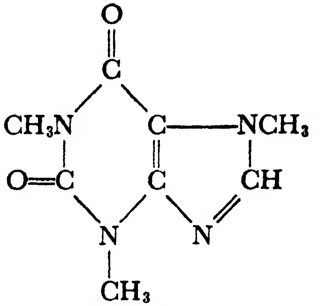
Alloxan

Since alloxan and urea are the oxidation products of uric acid, it is probable that the original molecule contained the skeleton of alloxan and, in addition, another ring containing a urea linkage. The proof of the structure of uric acid was finally accomplished by its synthesis by the following series of reactions.

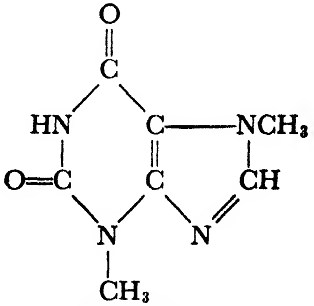


The history of the investigation of the structure of uric acid covers almost the whole classical period of organic chemistry. The greatest knowledge of the subject is due to the work of Liebig and Wöhler over a hundred years ago (1838). Baeyer in 1863 prepared pseudo uric acid (see above), but it was not till 1897 that Emil Fischer succeeded in finding the right conditions for converting this compound into uric acid itself. No other compound has had the honor of being the subject of investigation by four such masters of the science of organic chemistry.

Caffeine. This close relative of uric acid which occurs in coffee and tea to the extent of a few per cent is used in medicine as a stimulant and diuretic. It crystallizes from water in silky needles which melt at 237°. It is only slightly soluble in water. It is a very weak base but forms characteristic salts with acids. It is related to uric acid by the substitution of three hydrogen atoms on nitrogen by methyl groups and the replacement of one hydroxyl group by hydrogen. The weak basic properties in contrast to uric acid (which has no basic properties) are probably due to the fact that the imidazole ring carries no hydroxyl group. **Theobromine** is present in cocoa beans to the extent of a few per cent. Theobromine is a colorless crystalline powder which melts at 337° and which is only slightly soluble in water. It differs from caffeine in having only two methyl groups on the nitrogen atoms. Caffeine is prepared industrially from theobromine by methylation.



Caffeine



Theobromine

NUCLEIC ACIDS

Very complex acids containing phosphorus occur widely distributed in plant and animal cells; they are known as the *nucleic acids*. They often occur together with certain proteins (Chap. 14), either as salts or perhaps joined by an amide linkage. Such combinations of nucleic acid and proteins have been designated as the *nucleoproteins;* they occur in particularly large amounts in the thymus and pancreatic glands of animals. A different nucleic acid is present in plant cells and is readily prepared from yeast. The nucleoproteins are essential constituents of the nuclei of both plant and animal cells although their precise physiological function is not yet understood.

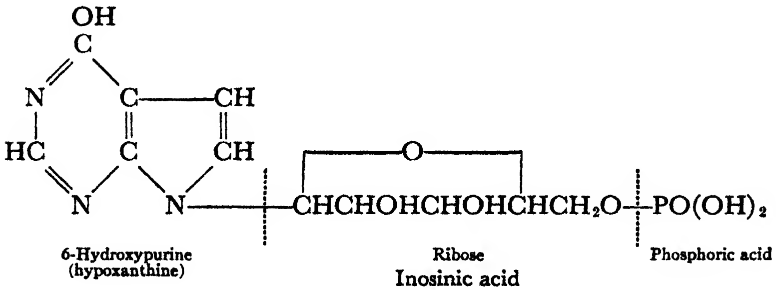
On hydrolysis, the nucleic acids yield phosphoric acid (H_3PO_4), a molecule of a pentose, and five heterocyclic nitrogen compounds: cytosine, uracil, thymine, guanine, and adenine. The first three substances are derivatives of pyrimidine, the last two are derivatives of purine.

The nature of the pentose is of great significance. The type of nucleic acid which predominates in yeast contains ribose (p. 203); the other, which was first isolated from animal cells, contains desoxyribose (p. 203). It was at one time thought that these two different nucleic acids were characteristic of plant and animal tissues, respectively; we now know this is not the case. Rather, it seems clear that they are both present in all cells, the desoxyribose compound being characteristic of the nuclei. In this connection it is interesting that studies with "tagged" atoms of heavy nitrogen (introduced into the body as a purine) show that the desoxyribose nucleic acid molecule is much less rapidly metabolized than the one containing ribose. This suggests that the nucleic acids of the nuclei are among the longest lived of the body constituents.

The nucleic acids are constituents of the viruses (p. 235). Evidence is accumulating that the units which determine heredity, the *genes,* are similar to the viruses. Both have the property of self-duplication but this takes place only within the *living* cell. Both appear to be of the same size. It seems probable that they are both nucleoproteins or contain nucleoproteins as essential parts. In duplicating themselves within the living cell genes may be assumed to be master molecules from which exact copies are made. If this is so, their actions may be thought of as directing the construction of specific protein types which are characteristics of the gene in question; whether the nucleic acid portion is essentially the same in many different genes is still a matter of debate.

Structure of Nucleic Acids. Our knowledge of the structure of the nucleic acids and nucleoproteins is still far from complete. The isolation of what is commonly called nucleic acid involves rather drastic chemical treatment which may well alter the molecule. In some way the large molecule of the nucleoprotein is composed of protein components and combinations of a pentose (either ribose or desoxyribose), a purine or pyrimidine, and phosphoric acid; a few such simple combinations of sugar-base-phosphoric acid can be isolated from animal tissue. They are known as the mono-nucleotides. Similar units are probably united in some way in the nucleic acids which are thus often spoken of as the *polynucleotides.*

Mono-nucleotides. Two mono-nucleotides which can be isolated from muscle tissue are **inosinic acid** and **adenylic acid.** On drastic hydrolysis both yield ribose, phosphoric acid, and a purine which from the former is a monohydroxy derivative, from the latter a monoamino compound. The structure of inosinic acid follows.

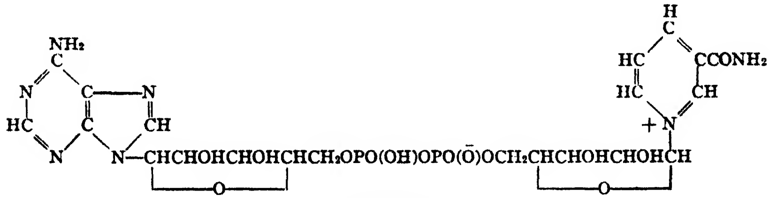


Inosinic acid

Adenylic acid has a structure identical with inosinic acid *except* the hydroxyl group in the 6 position is replaced by an amino group. A third mono-nucleotide isolated from both yeast and animal tissue (pancreas, liver, spleen) is known as **guanylic acid.** In this compound, the purine ring contains a hydroxyl group in the 6 position and an amino group in the 2 position; the phosphoric acid group is on the middle carbon atom of the ribose molecule instead of being at the end of the chain.

The terminal group, $OPO(OH)_2$, of adenylic acid can readily condense with additional molecules of phosphoric acid forming what are essentially anhydrides containing two or three phosphoric acid residues. Such anhydrides contain energy-rich bonds (p. 249), and in the presence of the proper enzymes can add or subtract phosphate groups from the products of carbohydrate metabolism (p. 250). It is convenient to name this series of polyphosphoric acid derivatives by referring to the phosphate-free compound as *adenosine*. Then, adenylic acid can be called adenosine monophosphate, and the other two *adenosine diphosphate* (abbreviated ADP) and *adenosine triphosphate* (ATP), respectively. Adenosine itself can be isolated from adenylic acid by alkaline hydrolysis which splits off the phosphoric acid group but not the sugar. It is an example of a class of compounds known as the *nucleosides*.

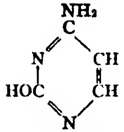
Coenzyme I. Closely related to adenylic acid is Coenzyme I, also known as codehydrogenase I or diphosphopyridine nucleotide (DPN). Half of the molecule is like adenylic acid; the other half contains the pyridinium ring which, as we have seen, can readily and reversibly pick up two hydrogen atoms.

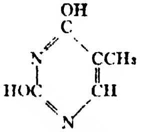


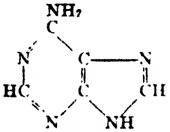
Coenzyme I

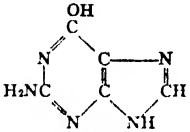
The closely related **Coenzyme II,** or triphosphopyridine nucleotide, contains a third phosphate group.

Purines and Pyrimidines from Nucleic Acids. The complete hydrolysis of the nucleic acids yields, as already stated, phosphoric acid, a pentose, and five heterocyclic compounds. Three are pyrimidines, two are purines; the structure of one, uracil, has already been considered (p. 365); the structures of the others follow.


Cytosine

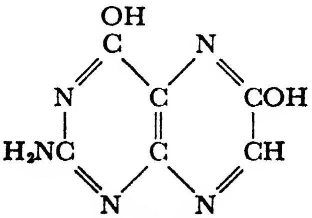

Thymine


Adenine


Guanine

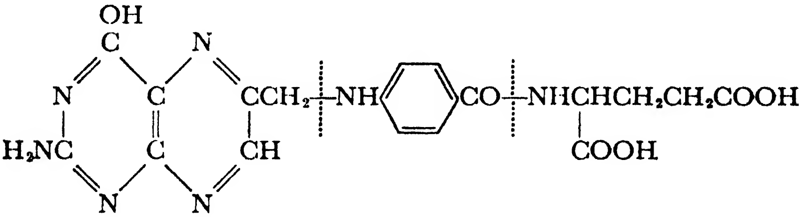
It may assist the student to remember these formulas by recalling the fact that they all have in common the recurrence of the urea linkage N—C—N in the ring; once in the pyrimidine derivatives, twice in the purines. Indeed, one could imagine the purine compounds as formed by the condensation of a triose and *two* molecules of urea under oxidizing conditions with subsequent replacement of hydroxyl groups by amino groups. There is no evidence for such a hypothesis but the recurring similar pattern in all these heterocyclic compounds indicates that such a mechanism is perhaps involved in the synthetic process in the living cell; a four-carbon keto acid (p. 179) might of course be equally well involved with subsequent decarboxylation.

Pteridine Derivatives. A bicyclic system containing four nitrogen atoms is found in some substances which have recently acquired importance in biochemistry. In this instance one may regard the structure as the result of the fusion of a pyrimidine ring with a six-membered ring containing two nitrogen atoms symmetrically disposed. The grouping may be illustrated by writing the formula of one of a group of pigments known as pterins isolated from butterfly wings. The ring system present is called the pteridine ring.


Xanthopterin

These substances are, like the quinones, rapidly reduced in solution by reagents like sodium hydrosulfite; the reduction product contains the grouping NH—C=C—NH in ring II (above). On exposure to air the process is reversed and the more unsaturated ring is reformed.

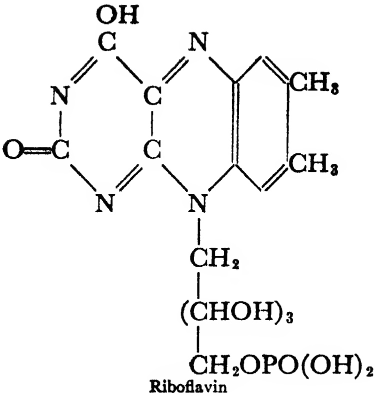
A vitamin which is one of the B complex of vitamins responsible for growth has been isolated and named **folic acid** or **pteroylglutamic acid.** It is effective as an anti-anemia agent. The structure has been shown to be that of a hydroxy amino pteridine linked through the group —$CH_2NHC_6H_4CO$— to glutamic acid. (One may imagine that it is formed in nature by the condensation of a triamino hydroxy pyrimidine, a triose, *p*-aminobenzoic acid, and glutamic acid.) The structure follows.

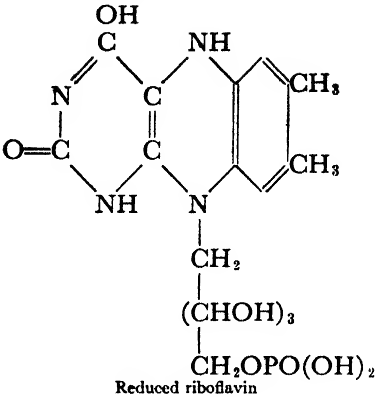


Folic acid

The substance has been synthesized industrially.

Riboflavin or vitamin B_2 is another member of the vitamin B complex. It is also a component of the respiratory enzyme known as flavoprotein which is involved in carbohydrate metabolism The enzyme picks up two hydrogen atoms from the pyridine — pyrimidine nucleotide (Coenzyme I) described on p. 375, and is in turn oxidized by another enzyme. This is the second step in a long chain of reactions by which the hydrogen atoms of the sugar molecule finally combine with atmospheric oxygen to form water. The structure of riboflavin which enables it to perform this function is similar to that in the pterins above which, it will be recalled, are easily reduced and oxidized. Indeed, the tricyclic ring in riboflavin may be regarded as the pteridine ring fused to a benzene ring. The ribose-phosphoric acid residue attached to one of the nitrogen atoms of the central ring forces a shift in the unsaturation, however, so the system N=C—C=N is to be traced through two rings, not one.

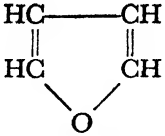

Riboflavin

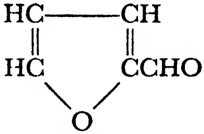

Reduced riboflavin

RINGS CONTAINING OXYGEN AND SULFUR

Persistent ring systems containing oxygen are present in the structures of a few substances of general interest. Ascorbic acid (p. 207) is one such compound. (For reasons already given lactones and cyclic anhydrides are not included in this class.)

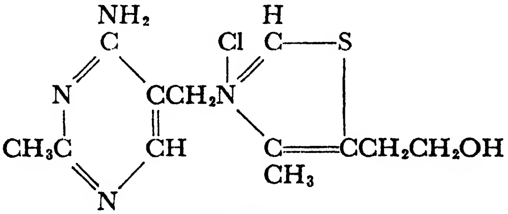
The five-membered ring containing two double bonds and one oxygen atom is known as *furan.* The aldehyde which corresponds to this parent substance as benzaldehyde does to benzene is known as *furfural.* It is formed when pentoses are heated with acid. It is prepared industrially from oat hulls and corn cobs.


Furan


Furfural

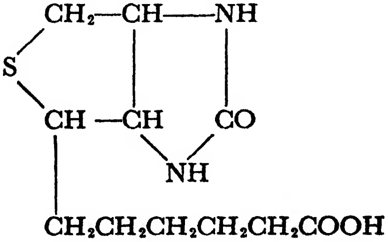
The brilliant red and blue coloring materials of flowers, fruits, and variegated leaves are glucosides of phenolic compounds whose structure includes a six-membered ring containing one oxygen atom. These glucosides are known as **anthocyans** or **anthocyanins;** after removal of the sugar by hydrolysis the brightly colored heterocyclic compounds left are known as **anthocyanidins.** They are remarkable as being salts of a base which contains *no nitrogen.* To elucidate their structure and show how the six-membered ring containing oxygen acquires basic properties lies beyond the province of this book.

Thiophene is the sulfur compound corresponding to furan. Neither the parent substance nor its derivatives warrant a discussion in an elementary treatment of organic chemistry. One heterocyclic ring containing a sulfur atom should be mentioned, however, as it is present in the structure of **vitamin B_1**, the antineuritic vitamin, also known as **thiamin.** An examination of the structural formula given below will show the presence of a pyrimidine ring and a five-membered ring containing both sulfur and nitrogen (known as thiazole). The substance is a quaternary ammonium salt, and is isolated as the hydrochloride. One mole of hydrochloric acid is bound by the aminopyrimidine ring. The material is now manufactured synthetically.



Thiamin
(Vitamin B_1)

Sulfur containing rings are rarely found in the structure of natural products. One other instance may be mentioned. **Biotin,** a substance which has been shown to have vitamin activity and to be essential for the growth of yeast but not necessary to animals, has a structure in which a hydrogenated imidazole ring and a hydrogenated thiophene ring are fused together.



Biotin

QUESTIONS AND PROBLEMS

1. Write structural formulas for pyrimidine and 2,6-dihydroxypyrimidine, pyrrole and 2,3-diethylpyrrole, caffeine, biotin, and furan.
2. Using indigo as an example write equations to show the chemistry involved in vat dyeing.
3. Write structural formulas for and indicate the usefulness of the several B vitamins.
4. What is the relationship between histidine and histamine? What are antihistaminics?
5. Show the oxidation-reduction relationship between quaternary pyridinium salts and dihydropyridines. What is the importance of this relationship to the metabolism of carbohydrates?
6. Discuss briefly the nucleic acids indicating what is known about their structure and function.
7. Write structural formulas for pyridine and 3,5-dimethylpyridine, purine, furfural, indole, and 3-methylindole.
8. Define exhaustive methylation and illustrate the process with pyrrolidine (tetrahydropyrrole).
9. What are the barbiturates? How are they prepared?
10. Compare the basicity of the following pairs of substances: (*a*) pyridine and piperidine, (*b*) quinoline and decahydroquinoline, (*c*) pyrrole and tetrahydropyrrole.
11. Show the structural similarities and differences between chlorophyll and hemoglobin.

CHAPTER 23

Natural and Synthetic Drugs

Until about the middle of the nineteenth century the *materia medica* of the medical profession was based on the accumulation of generations of experience with regard to the physiological action of inorganic chemicals and natural drugs. The latter were particularly valuable and have remained so to the present day. With the rapid growth of organic chemistry that began in the second half of the nineteenth century, however, many completely new drugs became available to supplement the natural ones.

These new drugs were the result of two distinct types of activity on the part of the organic chemist. The first was the synthesis of a multitude of new organic compounds. When these substances were tested for physiological action, some were found to be valuable. Two examples will suffice: phenacetin (p. 288) and aspirin (p. 307). The second was the study of the natural drugs themselves.

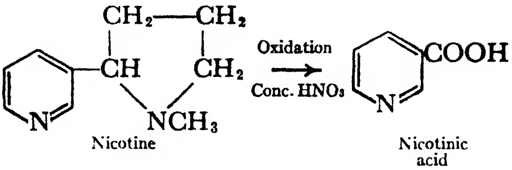
The study of naturally occurring products has always been an important part of organic chemistry. With the development of the structural theory, however, and as knowledge of the chemical behavior of different structures accumulated, the study of the naturally occurring drugs often resulted in the elucidation of their structural formulas. Once the structural formula of a drug had been established, the organic chemist undertook to synthesize the compound and then to synthesize structurally similar compounds which would be either more effective or as effective but lacking some of the undesirable properties of the natural drug. Procaine, which we shall discuss shortly, is an example of this.

Since we have already considered a number of synthetic drugs (aspirin and other salicylic acid derivatives, the barbiturates), we can consider now some of the naturally occurring drugs and related products whose synthesis was inspired by a study of the structure and action of the natural substances.

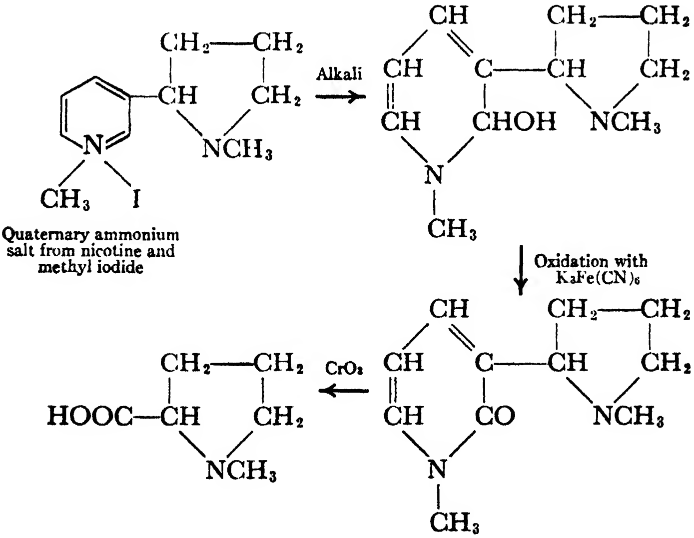
Alkaloids. The name *alkaloid* is usually restricted to a group of several hundred basic, nitrogenous plant products which have a marked physiological action. The majority of these are complex, heterocyclic compounds. In recent years, certain bases isolated from animal tissues have been sometimes included in the alkaloids. The basic properties of the alkaloids are due to the presence of amino groups or trivalent nitrogen atoms which are part of a heterocyclic system. The plant alkaloids have a bitter taste and are almost all laevorotatory. They are extracted from the plants by using dilute acids in which they dissolve because of the formation of soluble salts. Their purification is often an elaborate process. They are usually sold in the form of the water-soluble chlorides or sulfates; the free alkaloids are for the most part crystalline solids which are only very slightly soluble in water.

Nicotine, which is the principal alkaloid of tobacco, is one of the simplest of the alkaloids. It is also one of the few liquid alkaloids. Nicotine is found in the tobacco plant combined with citric and malic acids (p. 175), the amount of nicotine in the leaves varying between two and eight per cent. Nicotine is highly toxic. It is used as an insecticide on plants and animals.

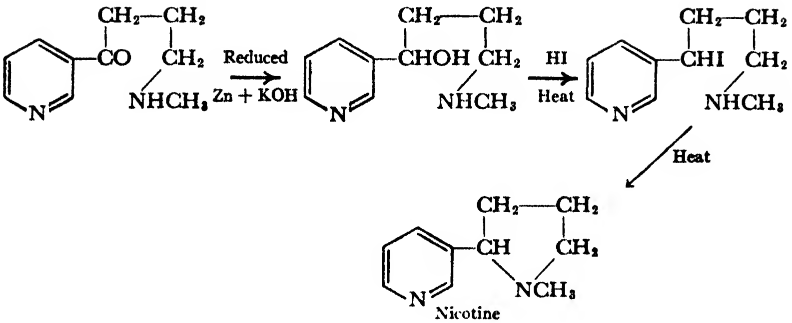
The molecular formula of nicotine is $C_{10}H_{14}N_2$. The structural formula is given below. It will be seen that the molecule contains two heterocyclic rings; one is a pyridine ring, the other a completely hydrogenated pyrrole ring (pyrrolidine ring) with a methyl group attached to the nitrogen atom. On vigorous oxidation the five-membered ring is broken and the β-carboxylic acid of pyridine, **nicotinic acid,** is formed.



The structure of nicotine follows from two oxidative cleavages of the molecule. Direct oxidation with nitric acid (as given above) shows that the compound contains the pyridine ring with an attachment on the beta carbon atom. If the quaternary ammonium salt is formed by adding methyl iodide to the pyridine ring (p. 360), the six-membered ring becomes sensitive to oxidation in alkaline solution and is destroyed by this treatment. The structure of the reduced pyrrole thus formed can be established by synthesis and the complete structure of nicotine follows.



Synthesis of Nicotine. Nicotine has been synthesized by several methods. In one, an open-chain, amino-keto derivative of pyridine is cyclized by the following reactions:

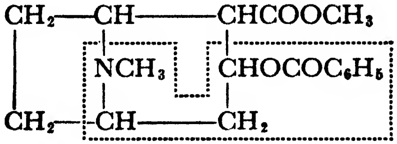


Nicotine

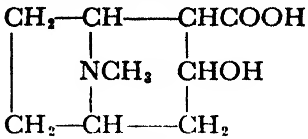
Natural nicotine is laevorotatory (the beta carbon atom of the five-membered ring through which the pyridine nucleus is attached is asymmetric). The synthetic alkaloid is, of course, the racemic mixture. This can be separated by crystallizing the salts with an optically active acid as described in Chap. 12.

Cocaine. One group of drugs is composed of those which act as *local anesthetics*. These substances when injected under the skin produce local insensibility to pain. For years the alkaloid cocaine was the only important drug of this type. It is extracted from the leaves of the *coca plant* which grows in the semitropics. (The coca plant should not be confused with the cacao bean from which cocoa and chocolate are prepared.) Cocaine, like many alkaloids, is usually marketed as one of the salts (e.g., the hydrochloride). The salts unlike the alkaloid itself are soluble in water.

Cocaine has the following structure.



On hydrolysis the two ester linkages are readily broken, the products being methyl alcohol, benzoic acid, and a hydroxy acid called *ecgonine*. The structure of ecgonine has been established both by degradation and synthesis.



Ecgonine

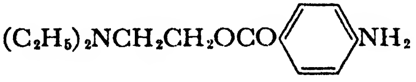
Ecgonine is not symmetrical. There are therefore a number of different stereoisomers possible (eight in all). The synthesis usually produces two racemic mixtures. On resolution by the usual methods, one of these yields a laevorotatory compound which on benzoylation and esterification with methyl alcohol produces the natural alkaloid cocaine. From the other pair of isomers **pseudo cocaine** can be prepared which is not very different in its physiological action from the natural alkaloid. This synthesis has been employed commercially. The industrial production of this rather complicated natural product is one of the striking feats of the synthetic chemist.

Procaine. A study of cocaine and other substances has led pharmacologists to the conviction that the grouping

$$>N-C-C-C-OCOC_6H_5$$

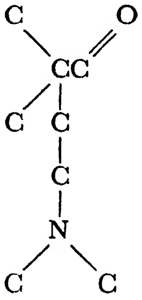
present in cocaine is largely responsible for its physiological action. (This grouping has been enclosed in dotted lines in the formula.) A number of new compounds have been synthesized which are simpler than cocaine and which contain this grouping or the similar one $>N-C-C-OCOC_6H_5$. These have been found to be local anesthetics of considerable value and several have been put on the market.

The most successful synthetic local anesthetic is **procaine** (**novocaine**). This is used as the hydrochloride which is soluble in water; the free base has the following structure.

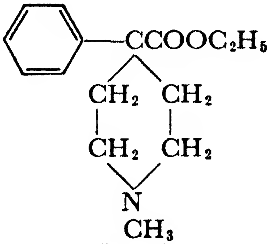


Except for the introduction of the para amino group and the shortening of the chain by one carbon atom, this compound has the same characteristic grouping that occurs in cocaine. The raw materials for the synthesis of procaine are para nitrobenzoic acid, ethylene chlorohydrin, and diethylamine.

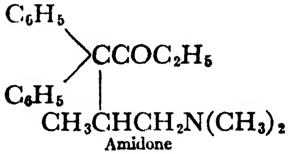
Analgesics. Drugs which relieve pain are known as analgesics. Aspirin is most commonly used for the relief of mild pain. For severe pain, the alkaloid morphine is employed. Morphine, which is remarkably effective, has several undesirable effects, the worst of which is habituation. As a consequence much effort has gone into the search for morphine substitutes. It has been found that the structure



produces analgesic effects, and a variety of new analgesics are available which contain this structural skeleton. The formulas and names of two of them follow.

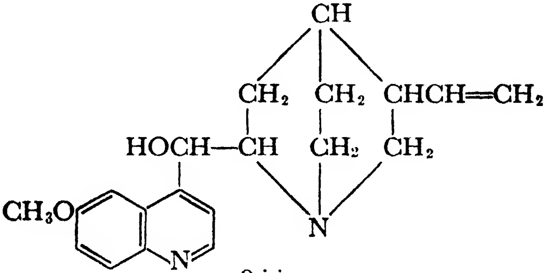


Demarol



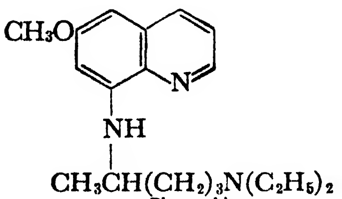
Amidone

Quinine and Synthetic Antimalarials. Quinine, together with a number of related alkaloids, is found in the bark of the cinchona tree, native to South America. It has been used for over three hundred years in the treatment of malaria. In recent years the cultivation of the cinchona tree was undertaken in the East Indies and quinine from this source displaced that from South America. (The parallel with rubber is striking.) In World War I some work was done in Germany on substitutes for quinine as that country was shut off from external sources of supply by the Allied blockade. This work was continued successfully in the period between wars. In World War II the cinchona plantations of the East Indies were seized by the Japanese, so that intensive efforts had to be made in the United States and the British Empire to replace quinine. The problem was particularly acute in World War II as so much of the war was fought in malaria-infested areas.

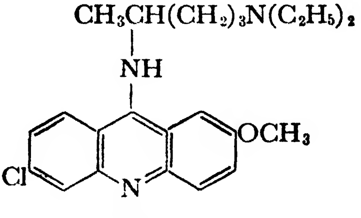


Quinine

The British-American effort did not aim at the synthesis of quinine. The synthesis has been accomplished; but, as can be seen from the complexity of the quinine molecule, it is not likely to be of practical value. Instead this effort was toward the development of synthetic materials which would be equivalent to or superior to quinine. German work had led to two antimalarials: Plasmochin and Atebrin.

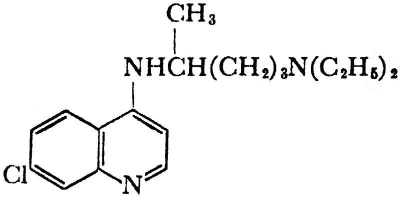


Plasmochin

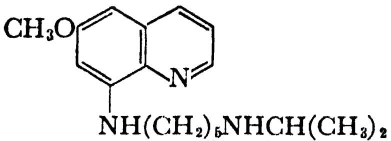


Atebrin

The work in the Allied countries involved testing for antimalarial activity a large number and variety of compounds already on hand in academic and industrial laboratories, as well as the preparation and testing of many new compounds which it was hoped would be effective. The work led to the development of a number of promising antimalarials. The structural formulas of two of these developed in the United States are shown below.

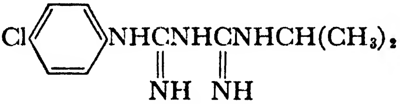


SN 7618



SN 13,276

An interesting aspect of all this work on antimalarials is that quinine, for which synthetic substitutes were being sought in the same way that novocaine was developed as a substitute for cocaine, does not prevent malaria and is curative for only certain types of malaria. A radically different approach, therefore, was the search for organic compounds which were not necessarily related to fragments of the quinine molecule and would not be expected to have quinine activity, but which might have preventive or curative action or both. One of the developments along this line is Paludrine, synthesized in England.



Paludrine

Adrenaline and Ephedrine. These two substances are relatively simple natural bases which were formerly not classified as alkaloids, although they have a powerful and very important pharmacological action. Adrenaline is one of the active principles secreted into the blood stream by the *suprarenal glands.* The production of this hormone in the animal organism has great physiological importance; its prime function appears to be to reinforce the action of the sympathetic nervous system.

The isolation of adrenaline from the suprarenal glands obtained from slaughtered animals provides the physician with one of his most valuable drugs. It is employed in very dilute solutions (0.1 to 0.01 per cent) and is administered by subcutaneous injection. It causes local contraction of the blood vessels and thus checks bleeding; for this reason it is used in surgery. It has also other uses in general medicine.

The structure of adrenaline was established in 1905 by the synthesis of the racemic mixture and its subsequent resolution into the dextro and laevo forms. The latter proved to be identical with the natural drug.

A comparison of the physiological activity of the dextro and laevo forms has shown that the latter is by far the more active. This is an illustration of the general principle mentioned in Chap. 12; although enantiomorphs are chemically identical, they usually differ in their relation to living things.

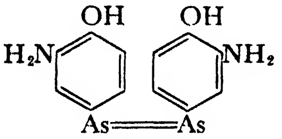
Adrenaline is now manufactured both by extraction from suprarenal glands and by synthesis. The racemic mixture obtained by synthesis must of course be separated into the optically active isomers. The substance is sold as the hydrochloride since it is more soluble in this form, and the solutions are more stable. Adrenaline itself is a white, crystalline substance which melts at 207°.

Ephedrine, $C_6H_5CHOHCH(CH_3)NHCH_3$, a very interesting plant product, finds rather wide use in medicine. This substance is closely related to adrenaline and resembles it in its pharmacological action. It is superior to adrenaline for many purposes because it can be taken by mouth. Ephedrine is the active principle of a Chinese plant which for 5000 years has been used in China as a medicinal. Synthetic ephedrine is now manufactured in this country.

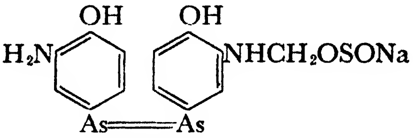
Chemotherapy. Two lines of activity which led to the discovery of useful drugs were outlined at the beginning of this chapter. A third, the science of chemotherapy, can be considered briefly now.

Once the germ theory of disease was established it was logical to think of chemical attacks on the germs. Selective staining by dyes was known and the classification of bacteria in this way as Gram-positive and Gram-negative was begun in the eighteen-eighties. Many dyes were shown to be bactericidal. Ehrlich, the founder of chemotherapy, undertook to find chemicals which would be toxic to an invading organism and harmless to the host. It was natural in view of the fact just outlined that the first substances tried were dyes. The first practical results were obtained by the use of certain complex azo dyes, trypan blue and afridol violet, for the treatment of trypanosome infections of cattle.

The first outstanding achievement of chemotherapy came in the early nineteen hundreds with the synthesis by Ehrlich of two organic arsenic derivatives — *salvarsan* and *neosalvarsan* — which proved to be extremely valuable in combating syphilis. The first compound, salvarsan, was called *606* by its discoverer because it was the 606th synthetic compound he had tried.

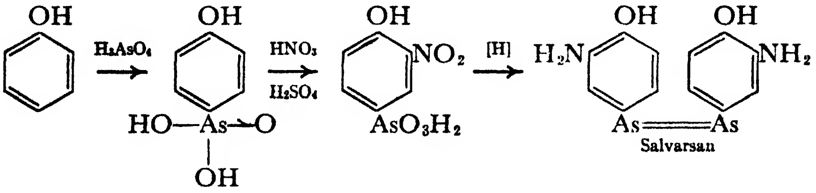


Salvarsan



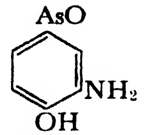
Neosalvarsan

The synthesis of salvarsan from phenol is of some interest. Arsenic acid, H_3AsO_4, is closely related to hydrated nitric acid ($HNO_3 + H_2O = H_3NO_4$), since arsenic and nitrogen occur in the same group in the periodic table. It is therefore not surprising that phenol may be arsenated by heating with arsenic acid. The product is analogous to nitrophenol but is hydrated. A nitro group is now introduced into the molecule in the usual way and the product reduced with sodium hydrosulfite. The nitro group is thus converted to an amino group and the arsenic acid group to the arsenic analog of the azo linkage.

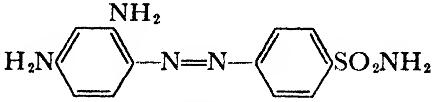


Salvarsan itself is isolated and sold as the dihydrochloride.

Ehrlich and his collaborators recognized that arsenoxide was more effective than salvarsan, but they preferred the latter material as it was apparently less toxic. More recent work has indicated that salvarsan owes its activity to oxidation to arsenoxide in the body; and that, when arsenoxide is administered in the form of derivatives which hydrolyze to form arsenoxide, it is no more toxic than salvarsan. Consequently arsenoxide is coming into extensive use in the treatment of syphilis.



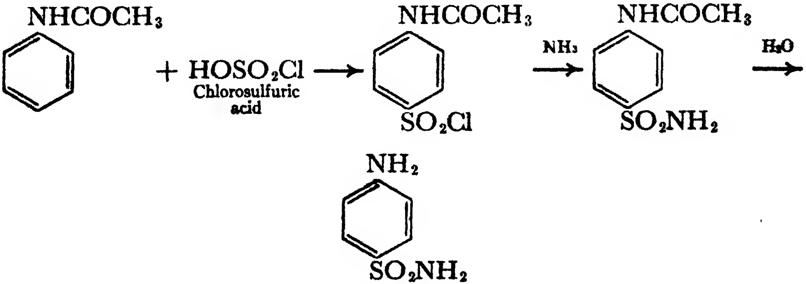
Arsenoxide



Prontosil

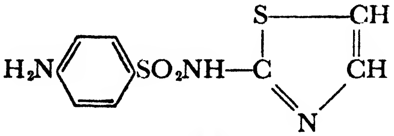
Until the nineteen thirties the successful applications of chemotherapy to disease were limited to those infectious diseases caused by spirochetes (e.g., syphilis) and by protozoa. Here the results were impressive, for many of the protozoal diseases of man (sleeping sickness, amebic dysentery, leishmaniasis) can be cured by early treatment with the appropriate drugs. The search for chemical agents for control of such bacterial infections as streptococcal, staphylococcal, pneumococcal, and others of this class was not successful, however, until some twenty-five years after the discovery of salvarsan. Then the first substance employed with striking success in treating certain coccal infections was a red dye known as *Prontosil.* Pharmacological studies showed that sulfanilamide, formed from Prontosil in the body, was responsible for the effectiveness of the dye.

Sulfanilamide is manufactured from acetanilide in the following manner.

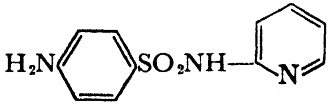


Sulfanilamide

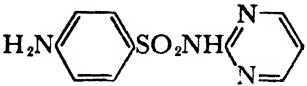
The successful use of sulfanilamide led to the preparation and study of hundreds of related compounds. Of these, **sulfathiazole, sulfapyridine,** and **sulfadiazine** are probably the most important. They have proved to be of great value against pneumococci, gonococci, and a variety of streptococcal infections.



Sulfathiazole



Sulfapyridine



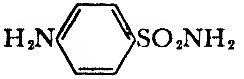
Sulfadiazine

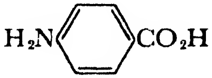
In view of the current importance of the sulfa drugs (over 6,000,000 lb were produced in the United States in 1947) it is worth noting that sulfanilamide was first prepared at almost the same time as salvarsan (1908), and was prepared then for use in a study of the behavior of various amides on hydrolysis.

Drug Antagonism. The adverse action of sulfanilamide on bacterial growth can be prevented by addition of small amounts of *p*-aminobenzoic acid (p. 305). Studies of this and other examples of drug antagonism have revealed the possibility of further and more rational development of chemotherapy.

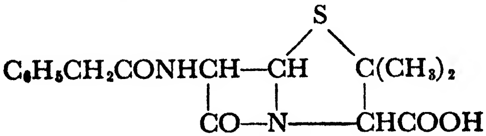
In Chap. 15 it was shown that the metabolism of carbohydrates involved a complex series of reactions between a substrate, an enzyme, and a coenzyme or prosthetic group. If the metabolic processes in bacteria or protozoa could be disrupted without serious interference with the metabolism of the cells of the host, the growth of germs could be retarded or prevented. Sulfanilamide apparently acts in this way. It is apparently able to replace *p*-aminobenzoic acid in the first steps of a chain of reactions normally leading to the synthesis of pteroylglutamic acid. (The structural similarity between sulfanilamide and *p*-aminobenzoic acid can be seen in the formulas below. The *p*-aminobenzoic acid portion of pteroylglutamic acid is indicated in the formula on p. 377.) The replacement of the *p*-aminobenzoic acid by this abnormal analog prevents the completion of the normal synthesis. If *p*-aminobenzoic acid is supplied in quantity to the medium in which the bacteria grow it can displace by mass action the foreign substance, and the bacteria can continue to synthesize the necessary pteroylglutamic acid and can grow.

Our knowledge of *p*-aminobenzoic acid-sulfanilamide antagonism is by no means complete; nor is the description just given more than a grossly oversimplified picture. It does show the possibility, however, of a new approach to chemotherapy: the study of cellular metabolism, the essential metabolites, enzymes, and enzyme reactions may enable one to select on a rational basis the specific chemicals that will interfere with metabolism by combining with the enzymes or coenzymes or by replacing the substrate.





Antibiotics. A living organism may form specific substances which interfere seriously with the metabolic processes of other organisms. These substances are known as *antibiotics* and much effort has been spent on attempts to use them in the treatment of bacterial infections. The early efforts were unsuccessful: the materials used were only weakly antibacterial and were highly toxic. The first antibiotic to be used successfully is penicillin, formed by the mold *penicillium notatum.* This material is remarkable both for its great antibacterial activity and its low toxicity. Up to the present time penicillin, actually a group of related compounds, has been prepared by cultivation of the mold and extraction of the active material. Chemical studies indicate that the structure of one of the penicillins is that shown below; synthesis has furnished a product from which small amounts of penicillin G have been isolated.

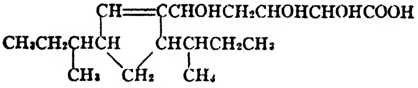


Penicillin G

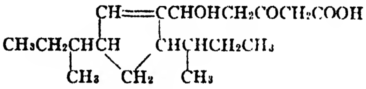
The current interest in antibiotics, stimulated by the results obtained with penicillin, is comparable to that shown in the sulfa drugs some ten years ago. Already several other antibiotics have been isolated and are being studied by the physician to determine their clinical value and by the chemist and biochemist to determine their structure and mode of action. Among these other antibiotics, *aureomycin* and *chloromycetin* are effective against certain rickettsial and virus infections, while *streptomycin* is useful in tuberculosis. Chloromycetin has been shown to have the structure written below and has been synthesized.

Chloromycetin

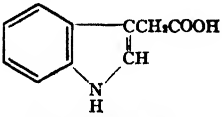
Plant Hormones. The substances selected for inclusion in this chapter and the vitamins and hormones mentioned earlier have marked physiological action on the human animal or on pathogenic organisms. Other organic compounds are known which affect the growth of plants; they are often referred to collectively as plant hormones. They vary widely in structure as their formulas below indicate. The auxins, β-indoleacetic acid (heteroauxin), α-naphthylacetic acid, and vitamin B_1 (p. 379) stimulate plant growth; the latter two in particular stimulate the growth of roots. 2,4-Dichlorophenoxyacetic acid (2,4-D)



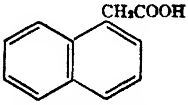
Auxin a



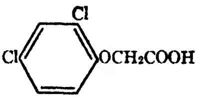
Auxin b



β-Indoleacetic acid
(Heteroauxin)



α-Naphthylacetic acid



2,4-Dichlorophenoxyacetic acid
(2,4-D)

stimulates abnormal growth of many broadleafed plants and is therefore used as a weed killer.

QUESTIONS AND PROBLEMS

1. Write structural formulas for nicotine, sulfanilamide, procaine, amidone, and sulfapyridine.
2. Discuss briefly the development of synthetic antimalarials. Write structural formulas for two such materials.
3. Describe the phenomenon of drug antagonism. What is the explanation for drug antagonism? Can you account for the fact that procaine, like *p*-aminobenzoic acid, is an antagonist to sulfanilamide?
4. Define and illustrate the following terms: *alkaloid*, *analgesic*, *chemotherapy*, *antibiotic*.
5. What is the practical importance of stereochemistry in the study and synthesis of drugs and medicants?
6. Outline the synthesis of sulfanilamide from aniline.
7. Show the probable relationship between metabolism, drug antagonism, and chemotherapy.
8. Ephedrine and adrenaline have similar pharmacological action. To what part of the molecule might this action be attributed?
9. The development of synthetic drugs has often taken the following path: isolation of the active ingredient of a naturally occurring drug; determination of the structure of the active ingredient; synthesis of the active ingredient; synthesis of materials structurally related to the active ingredient. Show the status in this scheme of each of the following materials: penicillin, novocaine, quinine, plasmochin.
10. Show the importance of the organic dyes in the development of chemotherapy.

INDEX

Numbers in **bold-face** refer to entries in tables.