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Identification of Unknowns

Along with synthesis and the examination of reaction mechanisms, an equally important part of organic chemistry has to do with the characterization and identification of compounds, which may be encountered in sources ranging from a laboratory reaction to exotic tropical plants. In any case, sufficient information must be accumulated to establish the identity of the compound in question with that of a previously described compound of known structure or else to determine, *ab initio*, the structure of the unknown.

In earlier days, organic chemists relied heavily on chemical behavior in the characterization of compounds and structure elucidation. Various reactions were applied to diagnose the presence of functional groups and structural units, and final evidence for a new structure usually involved systematic degradation to identifiable products. The development of spectroscopic methods has had a revolutionary effect on this area of organic chemistry. Today it is possible to characterize and arrive at the structure of a previously unknown compound entirely by physical and spectroscopic methods, without recourse to any "wet chemistry" at all. Very often, the structure stands revealed as soon as the ultraviolet, infrared, NMR, and mass spectra are in hand. With highly complex molecules, the entire structure can be determined by X-ray crystallography.

The approach to the problem of identifying or assigning the structure of an unknown organic substance will of course depend on the circumstances and the source of the sample. If the compound has been obtained as a component in a mixture of naturally occurring alkaloids or steroids, it will in all likelihood represent a variation of a known pattern, and the structural problem is relatively restricted, although subtle stereochemical differences, for example, may still present a challenging problem. Similarly, with an unknown arising as a by-product in a synthesis, one can generally assume some relationship to the starting materials, and after a few pieces of information are obtained, a probable structure may be inferred.

Another type of situation, sometimes mentioned in textbook problems but, hopefully, very rarely encountered in practice, is one in which the labels have come off all the bottles in the storeroom. In this case, the only premise that can be made is that most of the unknowns resulting from the disaster are to be found among the 25,000-odd entries in chemical suppliers' catalogs. Although artificial, this is essentially the context of this experiment, in which unknown samples selected from the entire range of simple organic compounds are to be identified.

In the classic approach to qualitative organic analysis, the main guidance that a student had in solving an unknown was a rather rigid classification scheme and a table of compounds for each of the principal functional groups, arranged according to increasing boiling point or melting point. This approach places a great deal of emphasis on these two physical properties and requires that most or all of the unknowns be included in relatively limited tables.

The present experiment is intended to be of a more open type, with infrared and NMR spectra as well as melting or boiling points providing orientation. With spectral data available, a broader range of unknowns is possible, and the approach in some cases assumes some of the character of a structural determination rather than simply narrowing a given list of compounds to one member.

The objective of the experiment should be to apply the methods available as efficiently as possible in arriving at a firm, well-documented identification. Spectral data can and should take the place of a number of the older chemical methods for detecting functional groups, but this identification experiment is not intended to be purely an exercise in spectral interpretation. It will often be necessary to seek information from hydrolytic or oxidative degradation of the unknown. In a particular situation, some special reaction or confirmatory test may be uniquely appropriate. Frequent reference to general textbooks and library sources will be essential. Although a thorough and complete job should be done, unnecessary or irrelevant steps should be avoided so that as many unknowns as possible can be done in the time allotted; some will require much more time and effort than others.

GENERAL APPROACH

The first step in the identification process will be to obtain physical constants, infrared and NMR spectra, and solubility properties of the unknown. These data will then be assessed, and further information as needed will be obtained to permit a tentative conclusion about structure. The identification is to be completed by locating the compounds or candidate compounds in handbook tables or other literature and by preparing derivatives for confirmation.

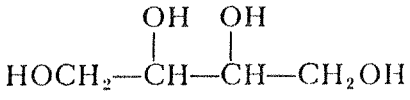
The unknowns provided in this experiment are of the purity normally encountered in commercial organic chemicals, which is usually in the range of 95 to 99%. Minor impurities will generally not interfere in the identification procedure, but preliminary recrystallization or distillation of a sample of the unknown may be desirable.

PHYSICAL PROPERTIES

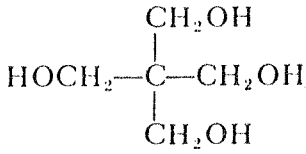
The melting point of a solid or the boiling point of a liquid is traditionally one of the first physical constants cited in characterizing an organic compound; in early work these temperatures were among the few measurements that could be made. Several other properties, such as the refractive index and density of liquids and optical rotation of chiral compounds, are often recorded for additional characterization, although these have become less important since the advent of routine spectral data, and they are not particularly useful in locating a compound in the literature.

In using the observed melting point or boiling point of an unknown or a derivative for comparison with literature values, it is necessary to allow sufficient "leeway" and to consider a range of several degrees in literature values on either side of the observed temperature. Literature values as well as the observed ones are subject to inaccuracies; frequently, more than one value can be found because of differences among individual investigators.

The melting point of a compound conveys little structural information in itself, since it depends on such diverse factors as molecular size, symmetry, rigidity, and polarity of functional groups. Although there is a regular progression of melting points within a typical aliphatic homologous series, large disparities in the melting points of closely similar compounds can arise because of differences in molecular shape, as illustrated with the polyols erythritol and pentaerythritol.



erythritol, mp 121°C



pentaerythritol, mp 254°C

The boiling point of a liquid is much more directly related to the functional group and molecular size, since forces operating in the liquid state are less affected by symmetry and rigidity than those in a crystal. Within any straight-chain aliphatic homologous series, the boiling point increases in a regular way with increasing molecular weight, with increments between successive members becoming smaller, the longer the chain. Branching, particularly in the vicinity of a functional group, markedly lowers

Table 46.1 Boiling Point Ranges of Aliphatic Alcohols (°C)

TYPE	4-CARBON	6-CARBON	8-CARBON
Primary	108–116	148–156	183–194
Secondary	99	120–139	150–180
Tertiary	83	120–125	149–165

the boiling point within a group of isomers. The presence of an alicyclic or aromatic ring causes a significant increase in boiling point over that of an aliphatic compound having the same functional groups and number of carbon atoms. Table 46.1 contains representative data on the boiling points of a few simple monofunctional aliphatic alcohols. Within each group, the lowest boiling point is that of the most highly branched isomer, and the highest boiling point corresponds to the longest chains (*n*-alkanol).

It is obvious that a relatively low boiling point for an unknown, say, below 100°C, greatly limits the number of possible compounds and may even define the structure uniquely with little other data. A boiling point in the range of 100 to 160°C, together with information on functional groups, provides a rough indication of molecular size. On the other hand, the number of possible compounds increases enormously in this range, and the boiling point cannot be used to pinpoint one or two candidates if all known compounds are admitted as possibilities. If the boiling point is above 180°C, the value as a means of narrowing possibilities is practically nil. Moreover, boiling points above this temperature are likely to be very inaccurate. Your instructor will indicate whether the boiling point should be determined or not.

PROCEDURES

MELTING POINTS. For solid unknowns, the melting point is determined in the usual way, raising the temperature of an initial sample rapidly to get an approximate range, then repeating at a rate of 2 to 3°C per minute in this region. If a sample is recrystallized, the melting point should be checked before and after recrystallization.

BOILING POINTS. If sufficient sample is available (at least 3 to 5 mL) the boiling point can be observed by distillation in a simple 10-mL distilling flask (Fig. 46.1). The flask is mounted at an angle on wire gauze so that excessive heating of the glass is avoided. A test tube fitted over the side arm and chilled in ice serves as a condenser and receiver. Be sure to add a boiling stone; heat with a microburner. Care must be taken to distill slowly enough to permit thermal equilibrium to be reached. Walls of the

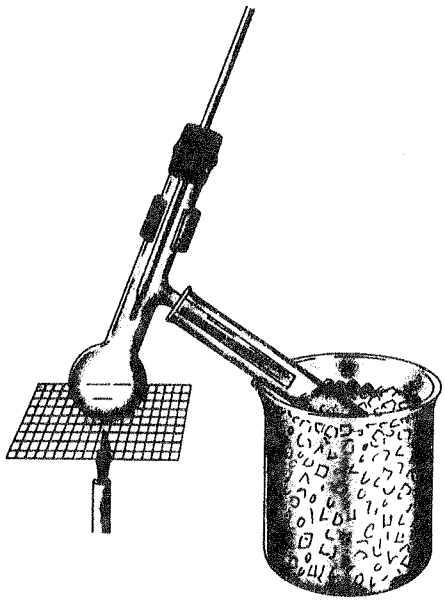


Figure 46.1 Distillation apparatus for unknowns.

flask above the thermometer should be wet with condensing vapor, and there should be a drop of condensate on the thermometer bulb. For strictly accurate results the barometric pressure should be taken into account.

An alternative procedure that is often more accurate and convenient is a **micro boiling point** determination. This method is described in Part F of the Experimental Section in Chapter 5. The determination should be repeated at least once. Remove the capillary tube and drain out the liquid before reheating.

SOLUBILITY CLASSIFICATION

A good deal can be learned about a compound from its solubility in a few media; the solubility classification complements spectral data and helps to determine the direction of further work. The solubility of the unknown is checked in water, dilute acid, dilute base, and concentrated sulfuric acid in that order, stopping when a positive result is obtained. If the compound is soluble in water, nothing is learned by testing in dilute acid or base; if it is soluble in any aqueous medium, it will also dissolve in or react with concentrated H_2SO_4.

A summary scheme of solubility classification is given in Chart 46.1.

WATER. Solubility of an organic compound in water reveals the presence of ionic or "polar" groups that can be solvated or can participate in hydrogen bonding. The extent of solubilization depends, of course, on the "ratio" of

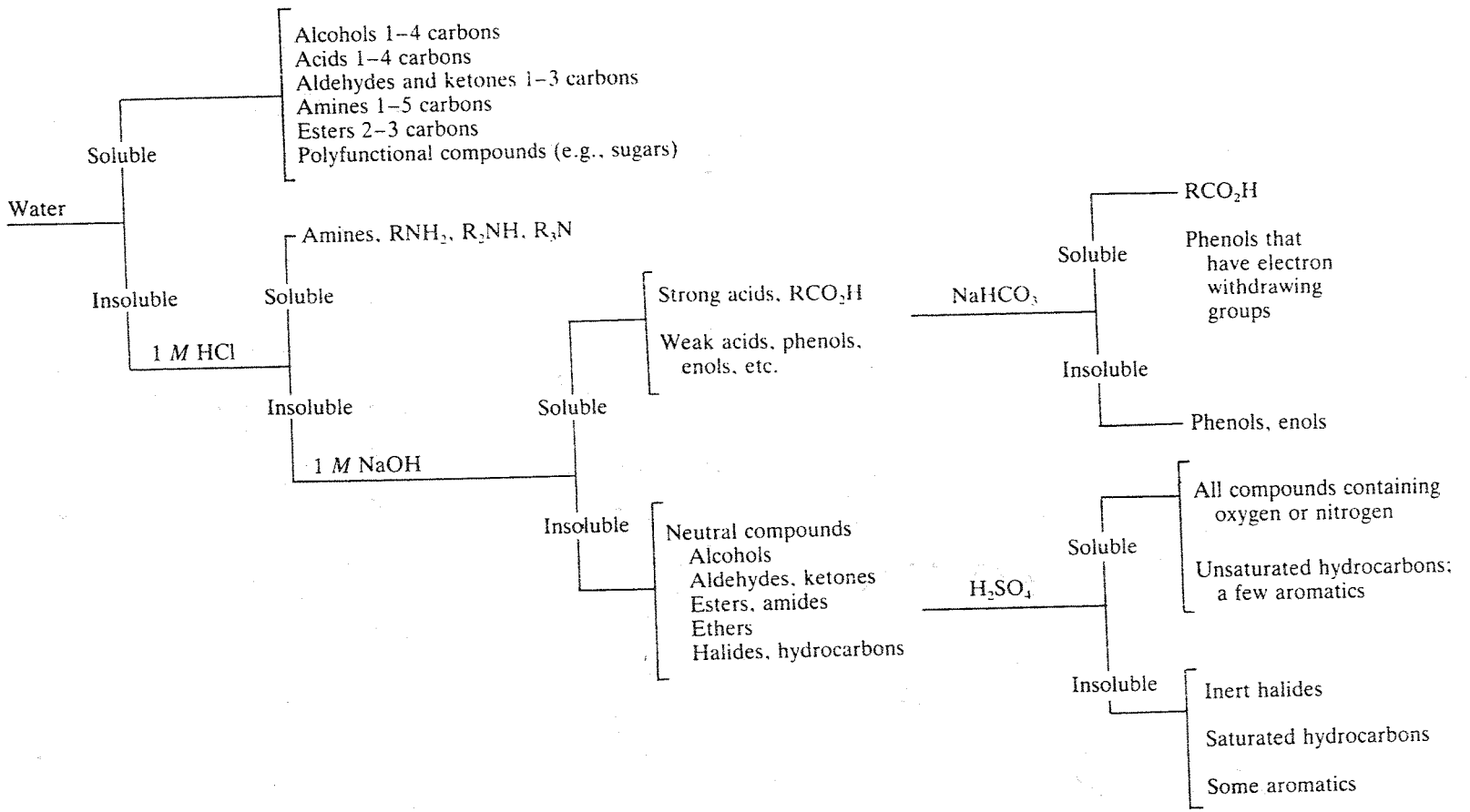


Chart 46.1 Summary scheme for solubility classification.

functional group to carbon skeleton. Liquids containing hydroxyl, carboxyl, amino, or amide groups and no more than four or five carbon atoms are miscible with water in all proportions (indicated by "∞" in solubility tables) or have appreciable solubility. With two or more of these groups, a much larger molecule will be soluble in water.

With solids, crystal structure has a major influence, and solubility in any solvent, water or organic, is related to melting point as well as to the polarity of the molecule. Thus oxamide, $NH_2COCONH_2$, which has the unusually high melting point of 410°C, is only very slightly soluble in water.

In testing for solubility in water, approximately 50 mg of solid or 0.1 mL (2 drops) of liquid is added to 1 mL of water in a 10 × 75-mm test tube. Large hard crystals of a solid may dissolve slowly and should be powdered and stirred well. If a clear solution is obtained, or a major amount of the compound dissolves with the amounts specified, the compound is considered "soluble" in water.

If the unknown is soluble in water, the pH should be estimated with indicator paper to detect the presence of acidic or basic groups in the molecule. The solubility in ether should also be checked if the unknown is readily soluble in water. A multiplicity of polar groups, as in a polyol, may render the compound insoluble in ether. With a solid, solubility in water and insolubility in ether may also suggest the possibility of an ionic salt, and this should be explored by treating the solution with acid or base, in which case the free acid or base may precipitate.

AQUEOUS ACID OR BASE. Compounds that can be converted to ionic species can be recognized by their solubility in water at certain pH values. Three major classes of compounds can be distinguished in this way: *strong acids*, *weak acids*, and *bases*. All compounds with $K_a > 10^{-12}$ ($pK_a < 12$) are converted to anions to a significant extent in 1 *M* NaOH (pH 14). Acids with pK_a in the range of 3 to 7, including all carboxylic acids and nitrophenols, are also soluble in aqueous sodium bicarbonate (pH 8). Solubility in NaOH, but not $NaHCO_3$, indicates a weak acid such as a phenol, enol, or aliphatic nitro compound. Organic bases with K_b 10^{-3} to 10^{-10} are soluble in 1 *M* HCl by virtue of the conversion to cations. The only compounds that can be protonated in dilute aqueous acid are amines.

$$RCO_2H + HCO_3^- \rightarrow RCO_2^- + CO_2 + H_2O$$
$$R_3N + H_3O^+ \rightarrow R_3NH^+ + H_2O$$

In detecting basic or acidic properties by these solubility criteria, the important point is whether the unknown is significantly more soluble in aqueous acid or base than in water. If a test is doubtful, neutralization of the test solution should cause reprecipitation of an amine or an acid that is dissolved because of salt formation. One possible complication that must

be kept in mind is the relatively low solubility of certain salts, particularly in the presence of an excess of the common ion. For example, it is possible to mistake the formation of a slightly soluble hydrochloride for insolubility of a solid amine.

CONCENTRATED SULFURIC ACID. Virtually all compounds of moderate molecular size that contain a nitrogen or oxygen atom or a double or triple bond are protonated in 96% H_2SO_4 and therefore dissolve to some extent. This test should be deferred until after the infrared spectrum is obtained. If there is no clear indication of any functional group in the spectrum, it will then be useful to check the solubility in concentrated H_2SO_4 to detect the presence of ether oxygen, reactive double bonds, and so forth. The solution may become dark in color or polymer may separate; these reactions constitute a positive test, but slight darkening without actual solution may be due to trace impurities.

ADDITIONAL DATA ON UNKNOWNS

After assessing the information obtained from physical properties, solubility, and spectra, as illustrated in the preceding pages, it frequently will be possible to draw a tentative conclusion as to the identity of the unknown and proceed to selection and preparation of a derivative. In other cases, certain features will be established, but further data will be desirable to define the environment, or even the nature of the functional group, or to decide between two possible interpretations. Additional information can usually be obtained from one or more of the approaches discussed in the following paragraphs. More complete information on these and other procedures can be obtained from the references at the end of the chapter.

DETECTION OF OTHER ELEMENTS

One important item that may be needed is information on the presence of elements other than C, H, and O. Although C—Cl bonds can sometimes be seen in the infrared spectrum (800 to 600 cm^{-1}), these bands may be obscured; C—Br and C—I stretching bands occur in the far infrared (<600 cm^{-1}). A qualitative test for halogen may therefore be indicated, particularly if the NMR spectrum suggests an odd number of protons. The common functional groups containing nitrogen are usually revealed by the basicity (amines) or the infrared spectrum (amide CO, C≡N, NO_2), but a confirmatory test for nitrogen can readily be carried out.

Detection of N, Cl, Br, and I is accomplished by the total decomposition of the compound with hot metallic sodium, followed by detection of anions in the usual way. With rare exceptions, any compound containing a C—N bond will give cyanide ion under these conditions; excess carbon is usually converted to the amorphous element.

$$[C, H, O, N, X, S] \xrightarrow{Na} \xrightarrow{H_2O} C, OH^-, CN^-, X^-, S^=$$

In this and other tests that require observation of a positive or negative result, there is one all-important rule: *always run a control.* It is quite futile to attempt a conclusion from the reaction of an unknown when the observer does not know exactly the appearance of a positive and a negative result. Run a known compound first, on the scale that will be used for the unknown, to see the behavior and to insure that you are doing it properly. It may be

equally important in some cases to run a *blank* in order to observe a negative result. If there is doubt about the result with a known, clear it up before turning to the unknown.

SAFETY NOTE METALLIC SODIUM IS EXTREMELY REACTIVE WITH WATER OR HYDROXYLIC SOLVENTS. HANDLE AND TRANSFER WITH A SPATULA; THE METAL IS SOFT, AND A SMALL PIECE CAN BE PICKED UP BY SPEARING IT WITH THE TIP OF A SPATULA. THE SODIUM FUSION SHOULD BE CARRIED OUT BEHIND A SHIELD OR HOOD WINDOW, AND ALWAYS WEAR SAFETY GOGGLES.

PROCEDURE

Obtain a small piece of sodium (a cube about 4 mm on edge) and place in a clean *dry* 10 × 75-mm test tube. Handle the test tube with a holder or clamp, not with your fingers. Have ready a sample of approximately 100 mg of a solid unknown or 0.1 mL (2 drops) of a liquid. Heat the sodium over a flame until it melts and begins to glow red. Add the sample to the tube, making sure that it falls directly on the molten sodium and not on the wall of the test tube where it may be volatilized. With a very volatile liquid, add a second 0.1-mL sample. Heat the tube briefly again and allow it to cool. Add 1 mL of ethanol dropwise and stir thoroughly with a glass rod to dissolve the excess sodium. After bubbling (hydrogen evolution) has stopped, cautiously add, dropwise, distilled water. Heat the mixture to boiling, filter through paper, and rinse with distilled water. If the solution is brown in color (indicating incomplete decomposition in the fusion), add a little charcoal and filter again.

TEST FOR N. This test, and the alternate one described below, are quite sensitive and care must be taken that a false positive is not obtained because of nitrogen containing impurities. If there is doubt, a standard should be run. In a 13 × 100-mm test tube, mix 10 drops of a 0.1 *M* solution of *p*-nitrobenzaldehyde in 2-methoxyethanol (methyl cellosolve), 10 drops of a 0.1 *M* solution of *o*-dinitrobenzene in 2-methoxyethanol, and 1 drop of 0.50 *M* aqueous sodium hydroxide, and then add 1 drop of the sodium fusion solution. The formation of a deep blue-purple color indicates the presence of nitrogen, while a yellow or tan color constitutes a negative test.

ALTERNATE TEST FOR N. To 1 mL of the solution, add 2 drops of saturated ferrous ammonium sulfate solution and 2 drops of 30% potassium fluoride solution. Boil the mixture for 30 seconds and acidify by dropwise addition of 30% sulfuric acid until the iron hydroxide just dissolves. The appearance of a brilliant blue precipitate of Prussian blue indicates the presence of cyanide ion and nitrogen in the compound.

TEST FOR S. Acidify 1 mL of the solution with acetic acid and add several drops of 0.1 *M* lead(II) acetate solution. A black precipitate of lead sulfide indicates the presence of sulfur.

TEST FOR HALOGEN. Acidify a 2-mL portion of the alkaline fusion solution in a small beaker with 3 *M* nitric acid and boil briefly to expel any HCN that may be present. The appearance of a distinct white or yellow precipitate on addition of silver nitrate indicates the presence of halogen. A yellow color suggests bromide or iodide.

To differentiate the halogens in the event of a positive silver halide precipitate, acidify another 2- to 3-mL portion of the original solution and add approximately 0.3 mL of methylene chloride. Then add a few drops of fresh chlorine water, a few mg of calcium hypochlorite, or several drops of Clorox (be sure the pH remains acidic). A yellow-orange color in the CH_2Cl_2 layer indicates bromine; a violet color, iodine.

ALTERNATE TEST FOR HALOGEN. A rapid test for chlorine, bromine, or iodine can be carried out on the original sample using the **Beilstein procedure**, based on the formation of a volatile copper halide when an organic halide is strongly heated with copper oxide. The value of the test is that it is easily carried out and is highly sensitive. To perform the test, a small loop of copper wire is heated to redness in a Bunsen burner flame until the flame is no longer colored. The wire is cooled and the now oxide-coated loop is immersed into a small amount of the solid or liquid to be tested. On reheating in the Bunsen flame, a blue-green flame indicates the presence of chlorine, bromine, or iodine (copper fluoride is nonvolatile).

Although the test is rapid, there are potential problems. Occasionally, the blue-green flame is fleeting and one must look quickly so as not to miss it. Further, highly volatile substances may vaporize before the copper halide forms, and such compounds as urea, quinoline and pyridine derivatives can give a false positive because of the formation of copper cyanide. Thus, the test should always be confirmed by other methods such as those mentioned earlier.

EQUIVALENT WEIGHTS

There are many methods for the quantitative determination of various functional groups in organic compounds; these reveal the number of such groups in the molecule if the molecular formula is known. If the formula of the compound is not known, quantitative analysis of a particular group provides the *equivalent weight*, i.e., molecular weight ÷ the number of functional groups per molecule.

The simplest of all these quantitative methods is acid–base titration, which is used to determine the *neutralization equivalent* of acids. Practically

any carboxylic acid can be titrated with standard base to a sharp end point with phenolphthalein, since the pH at complete neutralization for an acid of pK_a 3 to 6 is somewhat above 7. With care, the neutralization equivalent of a pure, dry acid can easily be determined with an accuracy of 1%, providing very useful information about an unknown acid. The neutralization equivalent of a monobasic acid is the molecular weight, whereas for dibasic or polybasic acids, it is some integral fraction of the molecular weight. The procedure given can also be used for the neutralization equivalent of amine salts, but it is generally difficult to obtain the latter sufficiently pure and dry for accurate results.

PROCEDURE

Weigh out a 150- to 200-mg sample of benzoic acid to ± 1 mg on an analytical balance. Place the acid in a 125-mL Erlenmeyer flask with 50 mL of water, add 2 to 3 drops of phenolphthalein solution, and titrate to a pink end point with ~0.1 *M* NaOH from a 25- or 50-mL buret. From the volume of titrant and weight of benzoic acid (eq wt 122) used, calculate the exact molarity of the NaOH solution. As a check of your technique and the result obtained, titrate a second sample of benzoic or another known acid.

Repeat the process using the standardized base with a similar accurately measured quantity of the unknown acid (*in duplicate*), and calculate its equivalent weight. Liquid acids should be freshly distilled and weighed in a capped vial with minimum exposure to air, since they are generally hygroscopic. Solid unknown acids should be recrystallized and thoroughly dried. Acids that are very insoluble in water can be titrated in aqueous alcohol. If this is necessary, the standardization should be carried out with the same amount of added alcohol.

Other quantitative methods, including the saponification equivalent of an ester or quantitative hydrogenation of an olefinic compound, may be desirable in certain cases. Procedures for these or other special methods should be obtained from the literature or the references at the end of the chapter, and arrangements should be made with the instructor for necessary reagents and equipment.

MISCELLANEOUS CHEMICAL TESTS

A large variety of qualitative chemical tests for organic functional groups have been developed. Their use in structural analysis has been largely replaced by spectral methods, but a few of the simpler tests may be found useful in resolving ambiguities in other data. *In each case the test should be run on known compounds similar to those suspected to be the unknown to insure that the reagent is correctly prepared and so as to be able to recognize the appearance of a positive test.*

PROCEDURES

CHROMIC ACID TEST FOR 1° AND 2° ALCOHOLS. This test, described in Chapter 15, is a reliable method for confirming the presence of a primary or secondary hydroxyl group (aliphatic aldehydes also react). A rapid color change to dark green constitutes a positive test. With amines or phenols, a brown color and a dark precipitate are usually seen.

FERRIC CHLORIDE TEST FOR PHENOLS. The presence of phenolic or enolic hydroxyl groups in a compound is usually indicated by formation of a red or violet color due to an Fe(III) complex when treated with ferric chloride solution. Some phenols give negligible or very weak tests because of interference by substituents in the ring.

The test is carried out by adding 1 drop or a few crystals of the unknown to 1 mL of freshly prepared 1% $FeCl_3$ solution.

IODOFORM TEST. Methyl ketones ($RCOCH_3$) and also methyl carbinols ($RCHOHCH_3$) react rapidly with iodine under basic conditions to give a carboxylic acid and iodoform. (Also see Chapter 20.)

$$RCHOHCH_3 \xrightarrow[OH^-]{I_2} RCOCH_3 \xrightarrow[OH^-]{3I_2} RCOCI_3 \xrightarrow{OH^-} RCO_2^- + CHI_3\downarrow$$

To carry out the test, dissolve approximately 20 mg or 1 drop of the unknown in 0.5 mL of water (if insoluble in water, dissolve in 0.5 mL of methanol) and add 0.5 mL of 10% aqueous NaOH. Add dropwise, with shaking, a solution of KI_3* until the dark iodine color persists. Warm the solution slightly, and if the color fades, add more KI_3 until the color remains for 1 to 2 minutes at 50°C. Then add a drop or two of NaOH solution to remove excess iodine, and dilute with water. Iodoform, if present, will separate as a dense, pale yellow solid, mp 119 to 121°C.

2,4-DINITROPHENYLHYDRAZINE TEST FOR ALDEHYDES AND KETONES. This reagent is commonly used for preparing dinitrophenylhydrazones of aldehydes and ketones and can also be used as a qualitative test for these functional groups to distinguish them from other carbonyl compounds, particularly esters, that do not react. The procedure used for preparing 2,4-dinitrophenylhydrazones (p. 513) is followed, and the formation of a red or orange precipitate constitutes a positive test. The test is also described in Chapter 20.

Since the reagent solution contains sulfuric acid, amines may give a heavy precipitate of the amine sulfate, which appears yellow in the solution and can be mistaken for a positive test.

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*Prepare by dissolving 5 g KI and 2.5 g I_2 in 25 mL of water.

TOLLENS TEST FOR ALDEHYDES. Tollens reagent, a solution of silver ammonia complex $Ag(NH_3)_2^+$, provides a test (also described in Chapter 20) to distinguish between aldehydes and ketones. Aldehydes react by undergoing oxidation, and silver ion is reduced to form a metallic silver mirror.

$$RCHO + Ag(NH_3)_2^+ + 2OH^- \rightarrow RCO_2^-NH_4^+ + 2Ag \downarrow + H_2O + 3NH_3$$

In a clean test tube (water should drain out without leaving beads), place 1 mL of 5% $AgNO_3$ solution and add, dropwise, a dilute solution (1 to 2%) of aqueous ammonia, shaking after each drop, until the brown precipitate of silver oxide just dissolves (avoid excess ammonia). To this solution add 2 to 3 drops or a few crystals of the unknown. Formation of a silver mirror indicates a positive test.

SAFETY NOTE THIS REAGENT MAY FORM AN EXPLOSIVE PRECIPITATE ON STANDING; DO NOT MAKE UP A LARGER AMOUNT AND STORE FOR LATER USE. EXCESS TOLLENS REAGENT CAN BE DESTROYED BY THE ADDITION OF DILUTE NITRIC ACID.

HINSBERG TEST FOR AMINES. Primary and secondary amines react with benzenesulfonyl chloride in the presence of sodium hydroxide to give solid benzenesulfonamides. The sulfonamide from a simple primary amine is usually soluble in excess hydroxide solution because of the acidity of the $—NHSO_2Ar$ group. Tertiary amines do not react under mild conditions.

$$RNH_2 + C_6H_5SO_2Cl \xrightarrow{OH^-} RNHSO_2C_6H_5 \xrightarrow{OH^-} [R\ddot{N}SO_2C_6H_5]^-Na^+$$

soluble in aq NaOH

$$R_2NH + C_6H_5SO_2Cl \xrightarrow{OH^-} R_2NSO_2C_6H_5$$

insoluble in NaOH

The test can be ambiguous if the amine is insoluble in water or is a solid, since it is necessary to distinguish between unreacted amine in excess, unreacted benzenesulfonyl chloride, and an insoluble sulfonamide.

To carry out the test (also described in Chapter 27), mix approximately 50 mg or 1 drop of the amine and 0.2 g of benzenesulfonyl chloride in 4 mL of 10% aqueous NaOH solution, stopper the test tube and shake vigorously until the oily sulfonyl chloride has reacted (5 minutes or longer may be needed). If a clear or nearly clear solution is obtained, a primary amine is indicated; acidification should give a precipitate of $RNHSO_2C_6H_5$.

Formation of a significant amount of insoluble solid from a liquid amine indicates that the unknown is a secondary amine. To distinguish from the possibility of unreacted solid amine, acidify the mixture; an amine will be soluble.

DERIVATIVES

The final point in the identification is conversion of the unknown to a solid derivative whose melting point can be compared with a literature value. The derivative may be any compound that is formed in a reaction that is characteristic for the unknown. It is obviously desirable to choose, when possible, a derivative that can be obtained in good yield and readily isolated, and that has a melting point in the most convenient region, i.e., 80 to 180°C. In many cases, the derivative will be confirmatory evidence for a tentative conclusion, but occasionally it may be necessary to choose between two possible candidates; in this case, the derivative or reaction product from both compounds must be known.

In all cases the derivative should be recrystallized from a suitable solvent before measuring its melting point, since the melting point will be the basis for identification of the derivative. The product that precipitates or crystallizes from the reaction mixture may be quite impure, and an incorrect melting point is worse than none at all in this situation.

For acids, alcohols, amines, and carbonyl compounds, a variety of simple condensation products can serve as derivatives, and a number of these are given in the Tables of Derivatives at the end of this chapter. Procedures for the more useful of these standard derivatives are given below. Solid acids obtained by hydrolysis of esters, amides, or nitriles are usually satisfactory derivatives if the acid represents the major portion of the molecule. It may, however, be much better to characterize the entire molecule by a more specific reaction. For example, hydrolysis of acetanilide gives acetic acid and aniline, both liquids. Either the acid or amine or both could be isolated and converted to solid derivatives, but a much simpler and far more effective derivative is obtained by nitration to *p*-nitroacetanilide (see p. 300) or bromination to the *p*-bromo derivative.

A number of the unknowns may lend themselves to special derivatives that will be suggested by the tentative structure deduced from spectral and other data. Cyclization products can be readily obtained from many bifunctional compounds, and occasionally rearrangement or partial degradation will provide highly characteristic derivatives. In such cases, details for carrying out the reaction and isolation of the product should be obtained from the literature for the specific compound that is under consideration.

NOTE ON DERIVATIVES. In directions for preparing derivatives of unknowns, amounts of reagents are given for a compound of "average" molecular weight, and solvents suggested are for compounds with typical solubilities. For certain unknowns, these directions may not be optimum, and it may be desirable to modify the procedure according to the properties expected for the unknown in question. For experiments on a **microscale**, the quantities given can usually be carried out at one-half to one-tenth scale.

Merely reduce the amounts of sample, reagents, and solvents by the required amounts.

SAFETY NOTE IN MANY OF THESE PROCEDURES, HIGHLY REACTIVE REAGENTS, SUCH AS ACID CHLORIDES AND ISOCYANATES, OR STRONG ACIDS AND BASES, ARE USED. MOST SOLVENTS ARE FLAMMABLE. KEEP IN MIND THE SAFETY NOTES THAT YOU HAVE SEEN THROUGHOUT THIS BOOK AND THE STANDARD PRECAUTIONS. ALWAYS WEAR SAFETY GLASSES. PIPET ONLY WITH A BULB. WASH THOROUGHLY WITH WATER IF ANY CHEMICALS COME IN CONTACT WITH THE SKIN. IF IN DOUBT, WORK IN A HOOD.

ACIDS

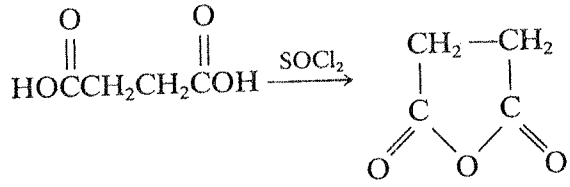
The most satisfactory general derivatives of carboxylic acids are amides, particularly the anilides and *p*-toluidides, which are prepared by the general sequence:

$$RCO_2H + SOCl_2 \rightarrow RCOCl + SO_2 + HCl$$

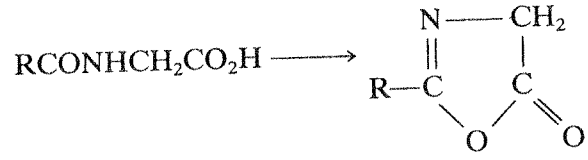
$$RCOCl + 2\,R'NH_2 \rightarrow RCONHR' + R'NH_3^+Cl^-$$

The second reaction requires the use of some base to combine with HCl. In the derivatization of an acid, an excess of the amine is usually used, but if the amine is the important component, some other base, usually aqueous NaOH, is used as the acid acceptor.

It should be noted that in the reaction with thionyl chloride, polyfunctional acids will often give cyclization or condensation products rather than an acid chloride. Thus, dibasic acids may form anhydrides, and α-acylamino acids give oxazolones (azlactones).



(an anhydride)



(an oxazolone)

PROCEDURES

ACID CHLORIDE. A very suitable procedure is that given for naphthalene-1-acetic acid in Chapter 32. Cool a mixture of 1 g or 1 mL of the acid plus 1 mL of thionyl chloride in a test tube and add 0.2 mL of dimethyl-

formamide. Allow the mixture to warm and stand 30 minutes, and then proceed with the next step.

AMIDES. For conversion to the anilide or *p*-toluidide, dilute the acid chloride with 5 to 10 mL of methylene chloride, and add it to a solution of 1.5 g of aniline or *p*-toluidine in 10 mL of methylene chloride. After mixing, allow the reaction to stand for a few minutes, add 10 mL of water and transfer the mixture to a separatory funnel. Add more solvent if necessary to dissolve all of the amide. At this point it is convenient to add sufficient ether to make the organic layer lighter than water. Wash the organic phase with dilute HCl until the aqueous layer is acidic, then with bicarbonate solution and finally water. Dry the organic phase ($MgSO_4$) and evaporate the solvent on the steam bath and recrystallize and collect the derivative.

Conversion to the amide may be preferable if the acid is a high-melting solid. In this case, add the acid chloride, without dilution, *dropwise* to a mixture of 10 mL of concentrated ammonium hydroxide and an equal volume of ice.

ALCOHOLS

The most generally useful derivatives of alcohols are esters of substituted benzoic or carbamic acids; the carbamate esters are commonly called urethanes. The *p*-nitrobenzoates or 3,5-dinitrobenzoates are obtained by treatment of the alcohol with the acid chloride and pyridine, which serves as a catalyst and acid acceptor.

$$ArCOCl + ROH + C_5H_5N \rightarrow ArCO_2R + C_5H_5NH^+Cl^-$$

Urethanes are prepared from the alcohol and an aryl isocyanate;

$$ArN{=}C{=}O + ROH \rightarrow ArNHCO_2R$$

In any reactions with isocyanates, the following sequence leading to the diarylurea will occur if water is present.

$$ArN{=}C{=}O + H_2O \rightarrow [ArNHCO_2H] \rightarrow ArNH_2 + CO_2$$

$$ArN{=}C{=}O + ArNH_2 \rightarrow ArNHCONHAr$$

The urea is a high-melting insoluble compound (diphenylurea, mp 238°C) and can seriously interfere with the isolation of the desired derivative. Alcohols should be dry, and an excess of isocyanate must be avoided.

Chromic acid at room temperature converts primary alcohols to carboxylic acids and secondary alcohols to ketones. The latter transformation is often useful in dealing with an aliphatic alcohol, since derivatives of the ketone may be more reliable. The experimental procedure in Chapter 19 for the preparation of norcamphor can be followed, adjusting the scale to the amount of unknown available.

PROCEDURES

***p*-NITRO- AND 3,5-DINITROBENZOATES.** Dissolve 1 mL of the alcohol in 3 mL of pyridine and add 0.5 g of the acid chloride corresponding to the derivative desired. Warm the solution for a few minutes and pour into 10 mL of water. If a well-crystallized ester separates, this is collected; otherwise, extract the product with ether and wash the ether solution free of pyridine with dilute HCl, dry, and evaporate.

URETHANES. To approximately 0.1 mL or 0.1 g of the anhydrous alcohol, add about 0.1 mL of phenyl isocyanate (**CAUTION**: lachrymator) and warm the solution for a few minutes in a beaker of hot water (do not expose to steam bath vapors). Cool, add about 1 mL of high boiling petroleum ether and heat to dissolve the product. If a very slightly soluble precipitate remains, it is probably the urea. This must be removed by filtration, followed by cooling the filtrate in ice, and scratching to induce crystallization.

PHENOLS

Nitrobenzoates or urethanes of phenols can be obtained by the same procedures described for alcohols. For a few phenols, only the benzoate esters are described: these should be prepared by the procedure given for eugenol benzoate (Chapter 8).

For a few phenols, derivatives can be obtained by reaction with chloroacetic acid to give the aryloxyacetic acid.

$$\mathrm{ArOH} + \mathrm{ClCH_2CO_2H} \xrightarrow{\mathrm{NaOH}} \mathrm{ArOCH_2CO_2Na} \xrightarrow{\mathrm{H_3O^+}} \mathrm{ArOCH_2CO_2H}$$

PROCEDURE

ARYLOXYACETIC ACIDS. To 1 g or 1 mL of the phenol add 5 mL of 30% NaOH solution and 1.5 g of chloroacetic acid. Stir and warm the mixture, and if solid is present, add water dropwise to obtain a clear solution. Heat the solution on the steam bath for 30 to 40 minutes, cool, and dilute with 10 mL of water. Acidify the solution (test paper) with 6 *M* HCl and extract the acid with ether. Wash the ether solution with a little water and then extract with saturated bicarbonate solution. Cautiously acidify the bicarbonate solution; stir to prevent loss from foaming. Collect the precipitate of aryloxyacetic acid and recrystallize from hot water.

ETHERS

A variety of derivatives are possible for aryl ethers; most of these involve reactions of the aromatic ring rather than the ether linkage. Examples include bromination, chlorosulfonation followed by conversion to the sul-

fonamide, and nitration. The benzene ring of simple aryl ethers is also sufficiently electron-rich that stable charge transfer complexes with picric acid can be isolated and characterized by melting points. For highly substituted aryl ethers, a more appropriate derivative may be the corresponding phenol obtained by cleavage of the ether linkage.

Enol ethers may be hydrolyzed to a carbonyl compound as described on page 514. No generally useful derivatives exist for saturated aliphatic ethers.

PROCEDURES

SAFETY NOTE BROMINE CAUSES SEVERE BURNS ON CONTACT WITH THE SKIN. AS FIRST AID FOR BROMINE BURNS, APPLY A SOLUTION OF SODIUM THIOSULFATE TO THE AFFECTED AREA. IN SEVERE CASES, SEEK MEDICAL HELP. AVOID BREATHING THE VAPORS OF THE BROMINATING REAGENT AND CARRY OUT THE REACTION IN A HOOD IF POSSIBLE.

BROMINATION. Dissolve 0.2 g or 0.2 mL of the aryl ether in 2 mL of acetic acid, and add a solution of 10% bromine in acetic acid in 0.5-mL portions until the yellow color persists for at least a minute after mixing. Add 5 mL of water, mix well, and collect the precipitate by filtration. Rinse the solid with water, and recrystallize from aqueous ethanol or hexane.

NITRATION. Aryl ethers can be nitrated under the conditions used for acetanilide in Chapter 25, adjusting the procedure to use 0.2 to 0.5 g or less.

CHLOROSULFONATION. Aryl ethers (and halides) can be converted to the sulfonyl chlorides with chlorosulfonic acid, and further to the sulfonamides (Chapter 38). The latter are generally more useful derivatives because of their higher melting points. Dissolve 0.2 g of the unknown in 1 mL of chloroform (**CAUTION:** carcinogen) in a test tube and cool the solution in an ice bath. In the hood, add 1 mL of chlorosulfonic acid dropwise, and let the mixture warm to room temperature. If the ring is deactivated by one or more halogen substituents, warm the solution in a beaker of warm (50 to 70°C) water for 10 to 15 minutes. Add 5 mL of ice water and mix well by stirring or shaking, pipet off the aqueous layer, and pour the chloroform solution into 5 mL of concentrated ammonium hydroxide. Mix well and evaporate the chloroform by heating on a steam bath in the hood. Add 2 mL of 10% NaOH to dissolve the sulfonamide, filter out any undissolved impurities, and reacidify with dilute hydrochloric acid. Collect the sulfonamide and recrystallize it from ethanol or aqueous ethanol.

PICRIC ACID COMPLEXES. Dissolve 0.2 g of the aryl ether in a minimum volume of warm chloroform and add a solution of 0.25 g of picric acid in 1 mL of boiling chloroform (**CAUTION:** Chloroform is carcino-

genic—carry out this procedure in a hood). Mix well, let the solution cool, and collect the crystals. Determine the melting point of the complex as soon as possible since some picrates decompose on standing.

CLEAVAGE OF ETHERS. Place 0.2 g or 0.2 mL of the alkyl aryl ether, 2 mL of acetic acid, and 2 mL of concentrated hydriodic acid in a test tube. Add a boiling stone and heat in a steam bath *in the hood* for 1 hour. Cool the solution, and pour into 25 mL of water. Add, in small portions, sufficient solid $NaHCO_3$ to neutralize the solution (pH ~8), mixing well between additions. Transfer the mixture to a separatory funnel and extract the phenol with two 5-mL portions of methylene chloride or ether. Wash with water, dry, and evaporate the solvent to obtain the phenol.

AMINES

A variety of amides and ureas are available as derivatives of 1° and 2° amines. Amides derived from secondary amines are often much more difficult to isolate because the R_2NCOAr structures are not hydrogen-bonded, and the compounds are therefore lower-melting and more soluble. The ureas are generally better derivatives. Picrate salts are useful derivatives for certain tertiary amines.

PROCEDURES

ACETAMIDES. Acetamides of aromatic amines are readily prepared by dissolving approximately 0.5 g of the amine in 1 to 2 mL of acetic anhydride and heating for a few minutes. Then add a few mL of water and warm the mixture until the excess acetic anhydride is destroyed (second liquid layer disappears). If the amide does not crystallize directly, extract with ether, wash the ether solution with bicarbonate solution, dry, and evaporate.

BENZAMIDES. Mix the amine (1 g) with 10 to 15 mL of 10% sodium hydroxide solution and add 2 mL of benzoyl chloride. Shake or stir the mixture for 10 minutes and isolate the amide by collecting the solid and washing with water. In some cases it may be desirable to add a solvent such as methylene chloride and recover the amide from solution.

SUBSTITUTED UREAS AND THIOUREAS. The reaction of an amine with an isocyanate or isothiocyanate leads to the corresponding urea; the precautions about water mentioned under alcohols must be kept in mind with isocyanates. Isothiocyanates are much less reactive and the reaction with amines occurs on warming, but hydrolysis with water is negligible and an excess of the reagent can be removed by recrystallization.

$$ArN{=}C{=}O + RNH_2 \rightarrow ArNHCONHR$$

$$ArN{=}C{=}S + RNH_2 \rightarrow ArNHCSNHR$$

To 1 g of the amine, add 0.5 mL or less of the isocyanate or isothiocyanate; a few mL of methylene chloride or toluene can be used as diluent. Warm the solution if an isothiocyanate was used. Excess amine should be removed by washing the solution with dilute acid before isolating the urea.

PICRATES. Dissolve 0.2 g of the tertiary amine in 5 mL of 95% ethanol and add the solution to 5 mL of a saturated solution of picric acid in ethanol. Heat the mixture to boiling; let it cool to room temperature. Collect the crystals by filtration and recrystallize the product from methanol or ethanol.

AMIDES AND NITRILES

Alkaline hydrolysis of these compounds leads to the acid salt and ammonia or the free amine.

$$RCONHR' + H_2O \xrightarrow{NaOH} RCO_2Na + R'NH_2$$

$$RC{\equiv}N + H_2O \xrightarrow{NaOH} RCO_2Na + NH_3$$

Amides or esters of carbamic acids give amines, alcohols, and CO_2.

$$CH_3NHCONH_2 + H_2O \xrightarrow{NaOH} CH_3NH_2 + NH_3 + CO_3^{=}$$

$$C_6H_5NHCO_2C_2H_5 + H_2O \xrightarrow{NaOH} C_6H_5NH_2 + C_2H_5OH + CO_3^{=}$$

With high-melting amides or nitriles of aromatic acids, the rate of hydrolysis and the solubility are low, and alcoholic alkali or hydrolysis in acid is recommended. Most nitrogen-containing compounds are quite soluble in 40 to 60% sulfuric acid and fairly high temperatures can be obtained by refluxing such solutions.

$$ArCONHR' + H_2O \xrightarrow{H_2SO_4} ArCO_2H + R'NH_3^{+}\ HSO_4^{-}$$

An additional possibility for the characterization of *aromatic* nitriles is conversion to the amide. This reaction, which strictly speaking is not a hydrolysis but a hydration, is carried out by treatment of the nitrile with alkaline hydrogen peroxide; hydroperoxide ion (O_2H^-) is the specific reagent involved:

$$RC{\equiv}N + 2\ H_2O_2 \xrightarrow{OH^-} RCONH_2 + H_2O + O_2$$

The hydrolysis and hydration procedures given are generally useful only for amides or nitriles of aromatic acids or amides of aromatic amines. Low molecular weight aliphatic amides or nitriles cannot easily be converted to useful derivatives by hydrolysis, since isolation of the product is usually impractical. Reduction of these compounds to amines with sodium boro-

hydride in the presence of cobalt(II) chloride is one alternative that can generally be used to obtain a derivative:

$$R'CONHR \xrightarrow[CoCl_2]{NaBH_4} R'CH_2NHR$$

$$RC{\equiv}N \xrightarrow[CoCl_2]{NaBH_4} RCH_2NH_2$$

PROCEDURES

ALKALINE HYDROLYSIS. Add 1 mL of a liquid or 1 g of a solid amide or nitrile to 30 mL of 10% NaOH or KOH solution and reflux the solution for 30 minutes. Test for the presence of a volatile amine or ammonia by holding a piece of moist indicator paper at the top of the condenser. Cool the solution to room temperature. If an insoluble amine is present, or if the presence of an aliphatic amine of intermediate solubility is suspected from the odor, extract the solution with several 10- to 15-mL portions of ether, wash the ether solution, dry with $MgSO_4$ or K_2CO_3, and evaporate the solvent to obtain the amine. A low molecular weight aliphatic amine will probably be lost in this procedure because of its solubility in water and its volatility during removal of ether.

After removing the amine, if any, acidify the aqueous solution and collect the acid if it is a solid. A low molecular weight aliphatic acid can be isolated by thorough extraction, but will usually be of little value as a derivative.

ACID HYDROLYSIS. Slowly add 5 mL of concentrated sulfuric acid to 10 mL of water. To this solution add 1 g of the amide or nitrile (this procedure will generally be used with high-melting solids). Reflux the solution for 30 to 60 minutes, then cool in ice and dilute with an equal volume of water. If a solid acid separates, this is collected, washed with water, and characterized.

The amine is recovered by making the aqueous solution basic by the addition of 10% NaOH. A heavy precipitate of inorganic salts usually separates, and more water must be added. The amine is then recovered as described in the section on alkaline hydrolysis.

CONVERSION OF NITRILE TO AMIDE. In a 100-mL round-bottom flask, place 1 mL or 1 g of the nitrile, 5 mL of 20% hydrogen peroxide, and 1 mL of 6 *M* (20%) NaOH solution. If the nitrile is insoluble, add 5 to 10 mL of ethanol. The reaction should occur exothermically, and cooling may be necessary at first. Keep the temperature at 40 to 50°C by cooling or gentle warming for 2 hours. Neutralize the solution and concentrate it by distillation to remove most of the alcohol. The amide will usually separate

from the aqueous solution on chilling; if it does not, extract with methylene chloride, and isolate the amide by evaporating the solvent from the dried extract.

REDUCTION TO AMINES. In a 125-mL Erlenmeyer flask, dissolve 0.5 g of the nitrile or amide and 2 g of $CoCl_2 \cdot 6H_2O$ in 25 mL of methanol. In the hood, add 2 g of $NaBH_4$, in small portions, shaking vigorously after each addition. Hydrogen is evolved and a black precipitate usually separates. When the addition is completed, add 3 *M* HCl until the solution is acidic (5 to 10 mL) and heat the solution on the steam bath to evaporate the methanol. Make the residual aqueous solution basic with NaOH, extract the amine with ether, and prepare a derivative of the amine.

ALDEHYDES AND KETONES

Semicarbazones and 2,4-dinitrophenylhydrazones are the most generally satisfactory derivatives of simple aldehydes and ketones:

$$RCOR' + NH_2NHCONH_2 \rightarrow \begin{matrix} R' \\ \diagdown \\ \quad C{=}NNHCONH_2 \\ \diagup \\ R \end{matrix}$$

$$RCOR' + NH_2NHC_6H_3(NO_2)_2 \rightarrow \begin{matrix} R' \\ \diagdown \\ \quad C{=}NNHC_6H_3(NO_2)_2 \\ \diagup \\ R \end{matrix}$$

PROCEDURES

(These derivatives are also described in Chapter 20.)

SEMICARBAZONES. Prepare a solution of 0.5 g of semicarbazide hydrochloride and 1 g of sodium acetate in 2 mL of methanol; the large crystals are ground together with a glass rod, and finely divided sodium chloride separates. Add approximately 0.5 mL of the carbonyl compound and allow the solution to stand for 15 to 30 minutes. Add 1 mL of water to dissolve the NaCl, chill the solution, and collect and recrystallize the derivative.

2,4-DINITROPHENYLHYDRAZONES. Dissolve approximately 0.2 g of the solid or liquid ketone or aldehyde in 1 mL of ethanol and add dropwise 3 mL of the 2,4-dinitrophenylhydrazine solution (1 g of 2,4-dinitrophenyl-

hydrazine, 5 mL of concentrated sulfuric acid, 8 mL of water, and 25 mL of ethanol). The dinitrophenylhydrazone should precipitate from the solution. If a product does not precipitate, warm the solution briefly on the steam bath; this is necessary for sterically hindered carbonyl compounds. Isolate the derivative by filtration and recrystallize it from ethanol or aqueous ethanol.

ACETALS, KETALS, AND ENOL ETHERS

Acetals, ketals, and related carbonyl derivatives such as enol ethers, imines, and enamines may be hydrolyzed in warm dilute aqueous or alcoholic acid. The aldehyde or ketone that is liberated can be isolated by extraction and converted to a derivative as described in the preceding section. If the 2,4-dinitrophenylhydrazone is desired, generally it is sufficient to warm the unknown directly with the acidic 2,4-dinitrophenylhydrazine reagent; the hydrolysis takes place and the hydrozone is formed and can be isolated by filtration.

ESTERS

Hydrolysis (saponification) of an ester to the acid and alcohol is a very general reaction, but the choice of a procedure depends on the type of ester and the product that is to be isolated. For esters of aromatic acids the acid is nearly always the most practical derivative, and hydrolysis should be carried out in aqueous alcohol by the first procedure given; this procedure, of course, does not permit characterization of the alcohol portion.

With an ester of an aliphatic acid, isolation of the acid is usually impractical. In order to isolate the alcohol, the hydrolysis can be carried out in the high-boiling sovent diethylene glycol ($HOCH_2CH_2OCH_2CH_2OH$, bp 244°C); the alcohol from the ester is isolated by distillation.

Another approach for the derivatization of an aliphatic ester is the direct conversion to a substituted amide. An aromatic amine is converted to the more reactive amide anion by treatment with ethylmagnesium bromide, and the ester is then refluxed with this reagent.

$$ArNH_2 + C_2H_5MgBr \rightarrow ArNH^- MgBr^+ + C_2H_6$$

$$ArNH^- MgBr^+ + RCO_2R' \rightarrow RCONHAr + R'OMgBr$$

PROCEDURES

HYDROLYSIS—ETHANOLIC BASE. In a 50-mL round-bottom flask, place 5 mL of ethanol, 5 mL of water, 1 mL or 1 g of the ester, and 1 g of KOH. Add a boiling stone and heat the solution under reflux for 30 to 40 minutes. Cool, add 5 mL additional water, and arrange the condenser for distillation. Distill the solution until 5 to 6 mL is collected to remove alcohol,

cool the solution, and acidify with 2 *M* HCl. Collect the acid or, if it is a liquid, extract with ether, dry, evaporate, and convert it to a derivative.

HYDROLYSIS—DIETHYLENE GLYCOL. In a 10-mL distilling flask (Fig. 46.1), place 3 mL of diethylene glycol (bp 244°C), 0.5 g of KOH pellets, and 0.5 mL of water. Heat the mixture until the alkali has dissolved and then cool and add 1 to 2 mL of the ester. Heat again until the ester dissolves and then more strongly, distilling the alcohol into a cooled test tube. The potassium salt of the acid may separate as a solid during the reaction.

CONVERSION OF ESTER TO SUBSTITUTED AMIDE. In a 50-mL round-bottom flask, prepare a solution of ethylmagnesium bromide from 10 mL of anhydrous ether, 1 mL of ethyl bromide, and 0.2 g of magnesium (see Chapter 17). After the formation of the Grignard compound and brief refluxing to ensure completion of the reaction, add a solution of 1.5 mL of aniline or 1.5 g of *p*-toluidine in a small amount of dry ether. After reaction of the Grignard reagent is complete, add 1 mL of the ester and reflux the mixture for 10 minutes. Cool, add 10 mL of 2 *M* HCl and shake to extract unreacted amine, adding more ether if needed. Isolate the derivative by the usual procedure from the ether solution.

ALKYL HALIDES

Alkyl halides that contain no reactive functional groups can be derivatized by conversion to the Grignard compound and treatment of the latter with an aryl isocyanate to give a substituted amide of the homologous acid. This method is quite general for halides that can form Grignard compounds.

$$\mathrm{R{-}X \xrightarrow{Mg} RMgX \xrightarrow{ArNCO} R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}NHAr}$$

PROCEDURE

Convert 1 to 2 mL of the halide (the sample must be anhydrous) to the Grignard compound in the usual way (see Chapter 17) with approximately 0.2 g of magnesium and 10 mL of anhydrous ether; a crystal of iodine can be added if needed. To this solution add, in small portions, a solution of 0.3 to 0.5 mL of the isocyanate (an excess must be avoided, **CAUTION:** lachrymator) in 5 mL of ether or methylene chloride. After hydrolysis with 2 *M* HCl, isolate the amide from the ether solution in the usual way.

NITRO COMPOUNDS

For aromatic nitro compounds, the oxidation of alkyl side chains or further nitration often provides satisfactory derivatives (see following section). An-

other general approach is the reduction to the amine, which can then be converted to an amide.

PROCEDURE

In a 100-mL round-bottom flask with reflux condenser, place 2 g of tin (granulated or mossy) and 1 g of the nitro compound. Then add 20 mL of 2 *M* HCl through the condenser, in small portions with constant shaking. After warmimg the solution on the steam bath for 10 minutes, allow it to cool and slowly add 40% NaOH solution to liberate the amine, which can then be steam distilled or extracted with ether and further characterized by a derivative.

ARYL HALIDES AND AROMATIC HYDROCARBONS

As noted in the discussions of phenol and aryl ether derivatives, the benzene ring can often serve as a satisfactory functional group for derivative preparation. For aryl halides and aromatic hydrocarbons, ring substitution may be the most practical reaction available. Nitration (Chapter 25) and chlorosulfonation (pages 415 and 509) are the two most generally useful reactions. In addition, aryl bromides can be converted to Grignard reagents and converted with CO_2 to benzoic acids (Chapter 17) or with phenyl isocyanate to the corresponding anilide as described for alkyl halides (page 515).

Alkylbenzenes can be degraded oxidatively to the corresponding benzoic acids. Other aliphatic side chains can also be oxidized, e.g., 2-phenylethyl chloride or phenylacetic acid to benzoic acid. The reaction is not generally useful for dialkylated or polyalkylated benzenes because of the inconveniently high melting points of the acids produced.

PROCEDURE

SIDE CHAIN OXIDATION. In a 50-mL round-bottom flask place 2 g of $KMnO_4$, 25 mL of water, 5 mL of 10% NaOH, 0.5 g or 0.5 mL of the unknown, and a boiling stone. Reflux gently over a flame for 1 hour or until the purple color has disappeared. Cool and acidify with dilute sulfuric acid. Reheat the mixture to boiling and add a few grains of sodium bisulfite to dissolve any tan manganese dioxide present. Cool the solution and collect the acid by filtration. Recrystallize from ethanol or aqueous ethanol.

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Table 46.2 Acids

COMPOUND	Mp, °C	Bp, °C	DERIVATIVE, Mp, °C		
			Amide	*Anilide*	p-*Toluidide*
Acetic		118	82	114	147
Acetylanthranilic	185		171	167	
o-Anisic (methoxybenzoic)	100		128	131	
p-Anisic	184		162	169	186
Benzoic	122		128	163	158
o-Bromobenzoic	150		155	141	
Butanoic		163	115	95	72
Chloroacetic	63		118	134	120
o-Chlorobenzoic	140		139	118	131
m-Chlorobenzoic	158		134	122	
p-Chlorobenzoic	242		179	194	
4-Chloro-3-nitrobenzoic	182		156	131	
Cinnamic	133		147	153	168
Dichloroacetic		189	98	118	153
2,4-Dichlorobenzoic	158				
3,4-Dichlorobenzoic	208		133		
Diglycolic (oxydiacetic)	148		135 (mono)	118 (mono)	
3,4-Dimethoxybenzoic	182		164	154	
2,2-Dimethylsuccinic	140				
Diphenylacetic	146		167	180	
p-Ethoxybenzoic	198		202	169	
Glutaric	97		174	224	
Hippuric (benzoylglycine)	187		183	208	
p-Hydroxybenzoic	215		162	202	204
Itaconic	165 (*d*)		192 (di)		
p-Methoxyphenylacetic	85		189		
Methylpropanoic (isobutyric)		155	129	105	109
Methylsuccinic	115		165 (mono)		
Naphthalene-1-acetic	133		181	155	
1-Naphthoic	162		205	161	
m-Nitrobenzoic	140		142	155	162
p-Nitrobenzoic	241		201	217	
Phenylacetic	76		154	117	
2-Phenylbutanoic	42		86		
3-Phenylpropanoic	48		82	92	
5-Phenylpentanoic	60		109	90	
Phthalic	208 (*d*)		149		
Propionic		140	81	106	126
Salicylic (*o*-hydroxybenzoic)	158		139	136	156
Succinic	188		242 (mono)		
o-Toluic	102		142	125	144
m-Toluic	111		97	126	118
p-Toluic	177		158	140	160
3,4,5-Trimethoxybenzoic	170		176		

Table 46.3 Alcohols

COMPOUND	Bp, °C	Mp, °C	DERIVATIVE, Mp, °C	
			3,5-Dinitrobenzoate	*Phenylurethane*
Benzyl alcohol	206		113	78
1-Butanol	117		64	57
2-Butanol	99		75	65
2-Buten-1-ol	122			
Cinnamyl alcohol	257	33	121	90
2-Chloroethanol	130			51
1-Chloro-2-propanol	127		83	
Cholesterol		148		168
Cyclohexanol	161		112	82
Cyclopentanol	141		115	132
Diphenylmethanol		69	141	140
Ethanol	78		93	52
2-Ethyl-1-butanol	149		52	
1-Heptanol	177		47	68
2-Heptanol	160		49	
1-Hexanol	156		58	42
Methanol	65		108	47
4-Methoxybenzyl alcohol	260	25		92
1-Methoxy-2-propanol	119		85	
4-Methylbenzyl alcohol		60	118	79
2-Methyl-1-butanol	129		70	31
3-Methyl-1-butanol	132		61	57
3-Methyl-2-butanol	113		76	68
2-Methyl-3-buten-2-ol	98			
2-Methyl-1-pentanol	148		51	
3-Methyl-2-pentanol	134		43	
4-Methyl-2-pentanol	132		65	143
2-Methyl-1-propanol	108		87	86
1-Octanol	192		61	74
2-Octanol	179		32	114
1-Pentanol	138		46	46
2-Pentanol	119		61	
3-Pentanol	116		101	48
2-Phenoxyethanol	237			
1-Phenylethanol	203		95	94
2-Phenylethanol	219		108	80
1-Phenyl-1-propanol	219			
2-Phenyl-2-propanol	202	34		
1-Propanol	97		74	51
2-Propanol	82		123	88
2-Propen-1-ol	97		48	70
2-Propyn-1-ol	115			

Table 46.4 Aldehydes

COMPOUND	Bp, °C	Mp, °C	DERIVATIVE, Mp, °C	
			Semicarbazone	*2,4-Dinitro-phenylhydrazone*
o-Anisaldehyde (*o*-methoxybenzaldehyde)	246	38	215	254
p-Anisaldehyde	247		210	254
Benzaldehyde	179		222	237
Butanal	75		106	123
2-Butenal	103		199	190
o-Chlorobenzaldehyde	208		225	207
p-Chlorbenzaldehyde	214	47	230	270 (*d*)
Cinnamaldehyde	252		215	255
Citral	228		164	116
Citronellal	206		82	77
2,5-Dimethoxybenzaldehyde		52	—	—
3,4-Dimethoxybenzaldehyde		44	177	263
p-Dimethylaminobenzaldehyde		74	222	325
o-Ethoxybenzaldehyde	248		219	
2-Ethylbutanal	116		99	134
Furfural	161		202	230
Heptanal	156		109	108
Hexanal	131		106	104
o-Hydroxybenzaldehyde (salicylaldehyde)	197		231	248
p-Hydroxybenzaldehyde		115	224	280 (*d*)
2-Methylbutanal	93		103	120
3-Methylbutanal	92		107	123
a-Methylcinnamaldehyde	270		208	
5-Methylfurfural	187		211	212
1-Naphthaldehyde	292	34	221	
p-Nitrobenzaldehyde		106	221	
o-Nitrobenzaldehyde		44	256	250
Phenylacetaldehyde	194		156	121
Piperonal (3,4-methylenedioxybenzaldehyde)	264	36	230	266
o-Tolualdehyde	200		212	195
p-Tolualdehyde	204		215	234

Table 46.5 Amides

COMPOUND	Mp, °C
Acetamide	82
Acetanilide	114
Acetoacetanilide	85
o-Acetoacetanisidide	84
p-Acetoacetanisidide	115
o-Acetoacetotoluide	104
o-Acetotoluide	112
m-Acetotoluide	66
p-Acetotoluide	153
Benzamide	130
p-Bromoacetanilide	167
p-Bromobenzamide	155
o-Bromobenzanilide	141
m-Bromobenzanilide	136
p-Chloroacetanilide	179
p-Chloroacetoacetanilide	134
m-Chlorobenzamide	134
p-Chlorobenzanilide	194
Cinnamanilide	153
o-Ethoxybenzamide	133
m-Ethoxybenzamide	139
o-Methoxybenzamide	129
N-Methylacetanilide	102
o-Toluamide	142
m-Toluamide	97
p-Toluamide	158

Table 46.6 Amines

COMPOUND	Bp, °C	Mp, °C	DERIVATIVE, Mp, °C		
			Acetamide	*Benzamide*	*Phenylthiourea*
Aniline	183		114	160	154
Benzylamine	184		60	105	156
N-Benzylaniline		37			
o-Bromoaniline	229		99	116	146
p-Bromoaniline		66	167	204	148
n-Butylamine	77			42	65
iso-Butylamine	69			57	82
sec-Butylamine	63			76	101
tert-Butylamine	46			134	120
o-Chloroaniline	207		87	99	156
m-Chloroaniline	230		72	120	124
p-Chloroaniline		70	179	192	152
Cyclohexylamine	134		104	149	148
Di-*n*-butylamine	160				86
2,4-Dichloroaniline		63	145	117	
2,5-Dichloroaniline		50	132	120	
Diethylamine	55			42	34
Di-*n*-propylamine	110				69
Di-*iso*-propylamine	86		[picrate, 140]		
p-Ethoxyaniline	250		137	173	136
Ethyl *p*-aminobenzoate		89	110	148	
N-Ethylaniline	205		54	60	
o-Ethylaniline	216		111	147	
n-Hexylamine	128			40	77
o-Methoxyaniline	225		87	84	
p-Methoxyaniline		58	128	155	154
2-Methoxy-5-methylaniline		50	110		
4-Methoxy-2-methylaniline		30	134		
N-Methylaniline	196		102	63	87
o-Nitroaniline		71	92	94	142
m-Nitroaniline		114	155	155	160
p-Nitroaniline		147	210	199	
α-Phenylethylamine	185		57	120	
β-Phenylethylamine	198		114	116	135
Piperidine	105			48	101
o-Toluidine	199		112	143	136
m-Toluidine	203		65	125	94
p-Toluidine		45	153	158	141

Table 46.7 Aromatic Halides and Hydrocarbons

			DERIVATIVE		
			Nitration Product		*Carboxylic Acid*
COMPOUND	Bp, °C	Mp, °C	*Positions*	*MP, °C*	*Mp, °C*
Anthracene		216			
Biphenyl		70	4,4′	233	
Bromobenzene	157		2,4	75	
4-Bromobiphenyl		89			
p-Bromochlorobenzene		67	2	72	
o-Bromotoluene	181				147
p-Bromotoluene	185	28	2	47	251
Chlorobenzene	132				
o-Chlorotoluene	159				140
m-Chlorotoluene	162		4,6	91	158
p-Chlorotoluene	162		2	38	242
p-Cymene (isopropyltoluene)	175		2,6	54	
o-Dibromobenzene	224		4,5	114	
p-Dibromobenzene		89	2	84	
2,5-Dibromotoluene					157
o-Dichlorobenzene	179		4,5	110	
p-Dichlorobenzene		53	2	54	
2,4-Dichlorotoluene	195				160
2,6-Dichlorotoluene	199				130
Diphenylmethane		26			
Ethylbenzene	135				122
Fluorene		115			
Mesitylene	164		2,4	86	
1-Methylnaphthalene	240				162
2-Methylnaphthalene		32	1	81	
α-Methylstyrene	169				122
2-Phenylethyl chloride	190				122
Toluene	111		2,4	70	122
o-Xylene	142		4,5	71	
m-Xylene	139		2,4	83	
p-Xylene	137		2,3,5	137	

Table 46.8 Esters

COMPOUND	Bp, °C	Mp, °C
Diethyl ethylmalonate	75 (5 mm)	
Diethyl glutarate	237	
Diethyl maleate	225	
Diethyl malonate	198	
Diethyl oxalate	185	
Diethyl phthalate	296	
Diethyl phenylmalonate	170 (14 mm)	16
Diethyl succinate	216	
Diethyl suberate	268	
Ethyl acetate	77	
Ethyl acetoacetate	181	
Ethyl *p*-anisate	270	
Ethyl benzoate	213	
Ethyl benzoylacetate	270	
Ethyl cinnamate	271	
Ethyl cyanoacetate	208	
Ethyl *p*-hydroxybenzoate		116
Ethyl 2-methylacetoacetate	187	
Ethyl *p*-nitrobenzoate		57
Ethyl phenylacetate	229	
Ethyl propionate	98	
Ethyl salicylate	234	
Ethyl *p*-toluate	241	
Isopropenyl acetate	96	
Isopropyl acetate	91	
Isopropyl formate	68	
Isopropyl benzoate	218	
Isopropyl salicylate	255	
Methyl acetate	57	
Methyl acetoacetate	169	
Methyl *p*-anisate		49
Methyl benzoate	198	
Methyl *n*-butyrate	102	
Methyl *iso*-butyrate	92	
Methyl *o*-chlorobenzoate	230	
Methyl *m*-chlorobenzoate	231	
Methyl cinnamate		35
Methyl heptanoate	173	
Methyl hexanoate	150	
Methyl *p*-hydroxybenzoate		130
Methyl mandelate		57
Methyl *p*-nitrobenzoate		95
Methyl pentanoate	130	
Methyl phenylacetate	218	
Methyl propionate	79	
Methyl *o*-toluate	213	
Methyl *p*-toluate		30
Phenyl acetate	197	
Phenyl benzoate		69
Phenyl salicylate		42

Table 46.9 Ethers (Aryl)

COMPOUND	Bp, °C	Mp, °C	DERIVATIVE, Mp, °C	
			Nitro	*Picrate*
Anisole	154		87 (di)	81
o-Bromoanisole	218		106	
p-Bromoanisole	223		88	
o-Chloroanisole	195		95	
p-Chloroanisole	200		98	
o-Dimethoxybenzene	206		92 (dibromo)	57
m-Dimethoxybenzene	214		140 (dibromo)	58
p-Dimethoxybenzene		55	142 (dibromo)	119
o-Methylanisole	171		63 (bromo)	119
m-Methylanisole	177		91 (tri)	114
p-Methylanisole	176			89
Phenetole (ethoxybenzene)	172		58	92

Table 46.10 Ketones

COMPOUND	Bp, °C	Mp, °C	DERIVATIVE, Mp, °C	
			Semicarbazone	*2,4-Dinitro-phenylhydrazone*
Acetone	56		187	126
2-Acetonaphthone		54	234	262
Acetophenone	200		198	250
Benzophenone		48	167	239
p-Bromoacetophenone		51	208	235
Butanone	80		146	117
Butyrophenone	230		187	190
Chloroacetone	119		164	125
p-Chloroacetophenone	232		201	231
p-Chloropropiophenone		36	176	
Cyclohexanone	156		167	162
Cyclopentanone	131		203	146
3,3-Dimethyl-2-butanone	106		158	125
2,4-Dimethyl-3-pentanone	125		160	95
Fluorenone		83		283
2-Heptanone	151		127	89
3-Heptanone	148		103	
4-Heptanone	145		133	75
Hexane-2,5-dione	188		220 (di)	255 (di)
2-Hexanone	129		122	110
5-Hexen-3-one	129		102	108
4-Hexen-3-one	139		157	
p-Hydroxypropiophenone		148		229
Isobutyrophenone	222		181	163
p-Methoxyacetophenone		38	197	220
p-Methoxypropiophenone		28		
p-Methylacetophenone	226	28	205	258
3-Methyl-2-butanone	94		113	120
2-Methylcyclohexanone	163		195	137
4-Methylcyclohexanone	169		199	130
5-Methyl-3-heptanone	160		102	
6-Methyl-3-heptanone	160		132	
5-Methyl-2-hexanone	145		147	95
Methylcyclohexyl ketone	180		177	140
4-Methyl-2-pentanone	119		135	95
4-Methyl-3-penten-2-one	130		164	203
m-Nitroacetophenone		81	257	228
p-Nitroacetophenone		80		
2-Octanone	173		123	58
2,4-Pentandione	139		122 (mono)	209
2-Pentanone	102		112	144
3-Pentanone	102		139	156
Phenylacetone	216		198	156
4-Phenyl-2-butanone	235		142	
4-Phenyl-3-buten-2-one		41	187	
Propiophenone	218		174	191

Table 46.11 Nitriles

COMPOUND	Bp, °C	Mp, °C
Acetonitrile	81	
Acrylonitrile	78	
Adiponitrile	295	
Benzonitrile	191	
p-Bromobenzonitrile		112
Butyronitrile	118	
Chloroacetonitrile	127	
o-Chlorobenzonitrile	232	47
m-Chlorobenzonitrile		41
p-Chlorobenzonitrile		92
o-Chlorophenylacetonitrile	242	24
p-Chlorophenylacetonitrile	265	30
Glutaronitrile	286	
Isobutyronitrile	108	
Malononitrile	219	
p-Methoxybenzonitrile		62
1-Naphthaleneacetonitrile		35
1-Naphthonitrile	299	35
2-Naphthonitrile	306	66
o-Nitrobenzonitrile		110
m-Nitrobenzonitrile		118
p-Nitrobenzonitrile		147
p-Nitrophenylacetonitrile		116
Phenylacetonitrile	234	
o-Tolunitrile	205	
m-Tolunitrile	212	
p-Tolunitrile	217	27

Table 46.12 Nitro Compounds

COMPOUND	Bp, °C	Mp, °C
o-Bromonitrobenzene	261	43
m-Bromonitrobenzene	256	54
p-Bromonitrobenzene		126
4-Bromo-3-nitrotoluene		33
o-Chloronitrobenzene	246	32
m-Chloronitrobenzene	235	44
p-Chloronitrobenzene		83
2,5-Dibromonitrobenzene		85
2,4-Dichloronitrobenzene		52
2,4-Dimethylnitrobenzene	238	
2,5-Dimethylnitrobenzene	234	
2,6-Dimethylnitrobenzene	226	15
2,4-Dinitroanisole		89
1,3-Dinitrobenzene		90
1,4-Dinitrobenzene		172
2,4-Dinitrobromobenzene		72
2,4-Dinitrochlorobenzene		52
2,4-Dinitrotoluene		70
2,6-Dinitrotoluene		66
o-Nitroanisole	265	
p-Nitroanisole		54
Nitrobenzene	210	
4-Nitrobiphenyl		114
o-Nitrotoluene	224	
m-Nitrotoluene	231	16

Table 46.13 Phenols

COMPOUND	Mp, °C	Bp, °C	DERIVATIVE, Mp, °C		
			Benzoate	*3,5-Dinitro-Benzoate*	*Phenyl-urethane*
4-*t*-Butylphenol	100		81		
4-Chloro-3,5-dimethylphenol	115		[acetate, 48]		
o-Chlorophenol		176			121
p-Chlorophenol	43		88	186	148
o-Cresol (methylphenol)		190		138	142
m-Cresol		202	55	165	128
p-Cresol	36		70	189	146
2,4-Dichlorophenol	45		97	142	
3,5-Dichlorophenol	68		55		
2,4-Dimethylphenol	27	212	38	165	103
2,5-Dimethylphenol	75		61	137	161
2,6-Dimethylphenol	49			159	133
3,4-Dimethylphenol	62		59	182	120
3,5-Dimethylphenol	68			195	151
4-Ethylphenol	47		60	132	120
o-Hydroxyphenol (catechol)	104		84 (di)	152 (di)	169 (di)
m-Hydroxyphenol (resorcinol)	110		117 (di)	201 (di)	164 (di)
p-Hydroxyphenol (hydroquinone)	169		199 (di)	317 (di)	
2-Isopropyl-5-methylphenol (thymol)	51		33	103	107
2-Isopropylphenol		212	[aryloxyacetic acid, 133]		
4-Isopropylphenol	61		71		
2-Methoxyphenol	30	205	58	141	148
4-Methoxyphenol	56		87		137
4-Methyl-2-nitrophenol	34				
5-Methyl-2-nitrophenol	53				
1-Naphthol	94		56	217	177
2-Naphthol	122		107	210	155
o-Nitrophenol	45			155	
p-Nitrophenol	114		143	186	
Phenol	42	180	68	146	126