CHAPTER III

PREPARATION AND REACTIONS OF ALIPHATIC COMPOUNDS

PRELIMINARY LABORATORY OPERATIONS

III,1. DETERMINATION OF MELTING POINTS

THE student should read Sections **I,10** to **I,16** carefully before commencing any experimental work. A supply of melting point capillaries is prepared as described in Section **II,10** (compare Fig. *II*, *10*, 1). The apparatus illustrated in Fig. *II*, *10*, 2, *a* is assembled with concentrated sulphuric acid as the bath liquid; the thermometer selected should have a small bulb. The melting points of pure samples of the following compounds are determined in the manner detailed in Section **II,10**:—

(*a*) α-Naphthylamine, A.R. (50°) *or* diphenylamine, A.R. (53·5°).
(*b*) α-Naphthol, A.R. (96°) *or* catechol (104°) *or* benzil (95°).
(*c*) Benzoic acid, A.R. (122°) *or* β-naphthol, A.R. (123°) *or* urea (133°).
(*d*) Salicylic acid, A.R. (159°) *or* phenylurea (mono) (148°).
(*e*) Succinic acid, A.R. (185°) *or* *p*-tolylurea (mono) (180°).
(*f*) *p*-Nitrobenzoic acid (239°) *or* *s*-diphenylurea (242°).

By working in the above order, it will not be necessary to wait for the apparatus to cool between consecutive determinations. The correct melting points of the pure substances are given in parentheses; these should be compared with the values observed with the thermometer. By plotting the *differences* between the observed and the correct values for the various compounds as ordinates against temperatures as abscissae, the calibration curve for the particular thermometer used is obtained. This calibration curve should be carefully preserved so as to enable the correction to be applied for any subsequent melting point determination. It must be emphasised that the calibration curve refers only to the thermometer originally employed for the determination of the melting points of the standard substances listed above (or in Section **II,9**).

III,2. MIXED MELTING POINTS

The application of mixed melting point determinations to the identification of organic compounds has been described in Section **I,17**. In order to gain experience the student should carry out the following simple experiment.

Determine the melting point of pure cinnamic acid (133°) and pure urea (133°). Intimately mix approximately equal weights (*ca.* 0·1 g.) of the two finely-powdered compounds and determine the melting point; a considerable depression of melting point will be observed. Obtain an unknown substance from the demonstrator and, by means of a mixed melting point determination, discover whether it is identical with urea or cinnamic acid.

If time permits, carry out similar experiments with benzoic acid (122°) and β-naphthol (123°).

It is instructive for the student to construct a rough melting point diagram (compare Section **I,13** and Fig. *I*, *12*, 1) for mixtures of cinnamic acid and urea. Weigh out 1·00 g. each of the two finely powdered components, and divide each into ten approximately equal portions on a sheet of clean, smooth paper. Mix 4 portions of cinnamic acid (*A*) with 1 portion of urea (*B*) intimately with the aid of a spatula on a glass slide, and determine the melting point (the temperature at which the mixture just becomes completely fluid is noted). Repeat the procedure for 3 parts of *A* and 2 parts of *B*; 2 parts of *A* and 3 parts of *B*; and 1 part of *A* and 4 parts of *B*. Tabulate your results as follows :—

CINNAMIC ACID	UREA	M.P.
100 %	0 %	133°
80 %	20 %	—
60 %	40 %	—
50 %	50 %	—
40 %	60 %	—
20 %	80 %	—
0 %	100 %	133°

Plot temperatures as ordinates, and, as abscissae, the percentage of urea from left to right (0–100 per cent.) and of cinnamic acid from right to left (0–100 per cent.).

Alternatively, the experiment may be conducted with acetanilide (113°) and antipyrin (113°).

III,3. DETERMINATION OF BOILING POINTS

The student should first read Sections **I,1–I,3** which deal with the theory of the subject, and Section **II,12** in which the experimental details are given.

Fit up the apparatus illustrated in Fig. *II*, *12*, 1. The distilling flask should be of 50 ml. capacity and about half to three-fifths full of liquid : the thermometer should be so arranged that the top of the small bulb is just level with the side arm of the distilling flask. The flask may be heated on a wire gauze (preferably with an asbestos centre), but the most satisfactory method is to employ the air bath depicted in Fig. *II*, *5*, 3. Determine first the boiling point of distilled water (100°); immediately after the liquid is poured into the flask and before inserting the thermometer, add two or three small fragments of unglazed porcelain (" porous pot " or " boiling chips ") in order to promote regular ebullition. Read the barometric pressure and if this differs appreciably from 760 mm., correct the boiling point with the aid of Table **II**, 9, *B*. After the boiling point of water has been determined, rinse the inside of the apparatus with a little acetone (2–3 ml.) and discard the wet solvent; rinse again with a somewhat larger volume (about 5 ml.) of acetone, and pour this back into the " ACETONE FOR WASHING " bottle, and drain thoroughly. Pass a stream of dry air through the apparatus (it is best to use warm air from the " drier " shown in Fig, *II*, *2*, 1) until it is dry.

Repeat the boiling point determination with the following pure liquids: (*a*) carbon tetrachloride, A.R. (77°); (*b*) ethylene dibromide (132°) *or* chlorobenzene (132°); (*c*) aniline, A.R. (184·5°); and (*d*) nitrobenzene, A.R. (211°). An air condenser should be used for (*c*) and (*d*). Correct the observed boiling points for any appreciable deviation from the normal pressure of 760 mm. Compare the observed boiling points with the values given in parentheses and construct a calibration curve for the thermometer. Compare the latter with the curve obtained from melting point determinations (Section **III,1**).

In addition to the orthodox method, just described, for the determination of the boiling points of liquids, the student should determine the boiling points of small volumes (*ca.* 0·5 ml.) by Siwoloboff's method. Full details are given in Section **II,12**. Determine the boiling points of the pure liquids listed in the previous paragraph.* Observe the atmospheric pressure and if this differs by more than 5 mm. from 760 mm., correct the boiling point with the aid of Table II,9,B. Compare the observed boiling points with the accepted values, and draw a calibration curve for the thermometer.

III,4. FRACTIONAL DISTILLATION

The student should first study the elementary theory of fractional distillation given in Sections **I,4–I,5**. The experimental technique for simple fractional distillation is described in Section **II,15**.

To gain experience, the student should separate a mixture of pure benzene (b.p. 80°) and pure toluene (b.p. 110·5°). Prepare a mixture of 50 ml. of pure (*e.g.*, A.R.) benzene and 50 ml. of pure toluene, place it in a 200 ml. round-bottomed flask, and add 2–3 small chips of porous porcelain. Fit up the assembly shown in Fig. *II, 15*, 4; the apparatus must be dry. The Hempel column should be filled with hollow glass rings ($\frac{1}{4} \times \frac{1}{4}''$) or with porcelain plain rings ($\frac{1}{8} \times \frac{1}{8}''$ or $\frac{3}{16} \times \frac{3}{16}''$); in the latter case, a few large ($\frac{1}{4} \times \frac{1}{4}''$) glass or porcelain rings should first be placed at the lower end in order to prevent the smaller rings from falling through. The column (20–22 mm. diameter) should be filled to within 5 cm. of the side arm and the length of the packing should be about 30 cm. It is an advantage to wrap the fractionating column with asbestos paper or cloth or with linen cloth. Heat the flask in an air bath (Fig. *II, 5*, 3) and shield the apparatus carefully from draughts: make sure that a rapid stream of water is passing through the condenser (the components of the mixture are volatile and inflammable) and that no flame approaches the receiver. Distil the mixture very slowly (1–2 drops per second) at first, and collect the fractions with the following boiling points: (i) 80–83° †; (ii) 83–107°; and (iii) 108–111°. When fraction (iii) is reached, the rate of distillation may be increased. A good separation s easily obtained; the fractions should have volumes of 47, 6 and 47 ml. respectively (the last figure includes the " hold-up " of the column ‡).

* If time is limited, the boiling point determinations by the " distilling flask method " for these liquids may be omitted.

† The first few drops of this fraction are usually cloudy because of the thin film of water adsorbed on the surface of the column and packing.

‡ The packing may be conveniently dried by washing it with a little acetone and blowing warm air through the column.

Other mixtures which may be employed are : carbon tetrachloride (b.p. 77°) and toluene (b.p. 110–111°); chloroform (b.p. 61°) and toluene; methyl alcohol (b.p. 65°) and water (b.p. 100°). The last example is of interest because almost pure methyl alcohol may be isolated ; no constant boiling point mixture (or azeotropic mixture) is formed (compare ethyl alcohol and water, Sections I,4 and I,5). Attention is directed to the poisonous character of methyl alcohol; the vapour should therefore not be inhaled.

Alternatively, a modified Hempel column (Fig. *II*, *15*, 5) or an all-glass Dufton column with 30 cm. spiral (Fig. *II*, *15*, 2) may be used for the fractionation. The latter has the advantage that it is more easily cleaned.

III,5. PURIFICATION OF SOLID ORGANIC COMPOUNDS BY RECRYSTALLISATION

The student should read Sections **II,27–II,31** where the technique of the recrystallisation of solids and cognate processes is described. To gain experience, he should carry out the following experiments.

Choice of solvent for recrystallisation. Obtain small samples (about 0·5 g.) of the following compounds from the storeroom : (i) salicylic acid, (ii) acetanilide, (iii) *m*-dinitrobenzene, (iv) naphthalene, and (v) *p*-toluenesulphonamide. Use the following solvents : distilled water, methylated spirit, rectified spirit, acetone, benzene and glacial acetic acid.

Place 0·1 g. of the substance in a semicro test-tube (75 × 10 mm. or 100 × 12 mm.) and proceed systematically with the various solvents as detailed in Section **II,27**. Finally, summarise your results, and indicate the most suitable solvent or solvents for the recrystallisation of each of the above compounds.

Typical Recrystallisations

1. **Acetanilide from water.** Weigh out 4·0 g. of commercial acetanilide into a 250 ml. beaker. Add 80 ml. of water and heat nearly to the boiling point. The acetanilide will appear to melt and form an " oil " in the solution (for theory, see Section **I,18**). Add small portions of hot water, whilst stirring the mixture and boiling gently, until all the solid has dissolved (or almost completely dissolved). [If the solution is not colourless, allow to cool slightly, add about 0·5 g. of decolourising carbon, and continue the boiling for a few minutes in order to remove the coloured impurities.] Filter the boiling solution through a fluted filter paper (for preparation, see Section **II,29**) supported in a short-necked funnel ; if the solution cannot be filtered in a single operation, keep the unfiltered portion hot by heating with a small flame over a wire gauze. Alternatively, the solution may be filtered through a hot water funnel (Fig. *II*, *1*, 6, *a*). Collect the filtrate in a 250 ml. beaker. When all the solution has been filtered, cover the beaker containing the hot filtrate with a clock glass and cool rapidly with stirring. Allow to stand for about 30 minutes to complete the separation of the solid. Filter with suction through a small Buchner funnel (see Figs. *II*, *1*, 7, *a* and *c*), wash the crystals twice with 5 ml. portions of cold water (to remove the adhering mother liquor), and press them in the funnel with the back of a large, flat glass stopper. Remove the funnel from the filter flask, invert it on two thicknesses of filter or absorbent paper resting upon a pad of newspaper, and allow the crystals to dry in the air. It is advisable in air drying to

cover the crystals with a large clock glass resting upon corks, or the crystals may be covered with a large filter paper perforated with a number of holes in order to allow the solvent to evaporate. For more rapid drying, the crystals may be placed on a clock glass or in an evaporating basin in the steam oven (this process can only be used for substances which melt above 100°). Weigh the yield of recrystallised material and determine the melting point. If the recrystallised product is not sufficiently pure (melting point low or melting over a range of several degrees), repeat the recrystallisation. Pure acetanilide has m.p. 114°.

If a m.p. determination is required soon after recrystallisation, a small quantity may be rapidly dried by pressing it several times upon a pad of several thicknesses of filter or absorbent paper and placing it upon a watch glass in a warm place. A piece of unglazed porous plate may also be used.

Optional or alternative experiments are the recrystallisation of 3·0 g. of crude benzoic or salicylic acid from water.

2. **Naphthalene from alcohol (crystallisation from an inflammable solvent).** Weigh out 5·0 g. of commercial naphthalene into a 150 ml. conical or bolt-head flask. Add 25 ml. of rectified spirit (or of methylated spirit),* 2–3 fragments of porous porcelain, and fit a reflux condenser into the mouth of the flask by means of a sound cork (compare Fig. *II, 13,* 7 ; the guard tube is not required here). Heat the mixture on a water or steam bath or in an air bath until the solvent boils. Add successive small volumes (each of 2–3 ml.) of the solvent, and boil gently after each addition, until the naphthalene has dissolved (apart from insoluble impurities). [If the solution is coloured, remove it from the bath, and when it has cooled somewhat, add 0·2–0·3 g. of decolourising charcoal and shake thoroughly. Boil the mixture for several minutes.] Filter the hot solution through a fluted filter paper or through a hot water funnel (*CAUTION !* all flames in the vicinity must be extinguished), and collect the filtrate in a conical flask or in a lipped beaker. Cover the receiver with a watch or clock glass, and cool it in cold water. Stir or shake the solution as cooling proceeds. After 30 minutes, filter off the crystals through a small Buchner funnel at the pump ; wash all the crystals into the funnel by rinsing the flask or beaker with some of the filtrate. Discontinue the suction and wash the crystals with two 5 ml. portions of rectified or methylated spirit. Continue the suction and press the crystals down firmly with a flat glass stopper. Dry the crystals on filter paper as in *1.* When dry, determine the weight and also the m.p. of the purified naphthalene. Pure naphthalene has m.p. 80°.

Alternative experiments : (*a*) Recrystallisation of crude benzoic acid (5·0 g.) from methyl alcohol (30 ml.) ; the wash liquid should be 50 per cent. methyl alcohol. (*b*) Recrystallisation of acetanilide (5 g.) from toluene (100 ml.) ; filter through a preheated funnel.

3. **Sulphanilic acid from water.** Use 5·0 g. of crude (grey) sulphanilic acid and proceed as in *1.* Add 1 g. of decolourising carbon to the solution at 70–80°, and continue the boiling for several minutes. If the filtered solution is not colourless, it must be boiled with a further 1 g. of decolourising carbon. Filter the cold solution at the pump, wash with a little cold water, dry and weigh the yield of recrystallised product.

* Benzene is an alternative solvent.

SATURATED ALIPHATIC HYDROCARBONS

III,6. REACTIONS AND CHARACTERISATION OF SATURATED ALIPHATIC HYDROCARBONS

Use a sample of "purified *n*-heptane fraction from petroleum" (1), b.p. 90–100°; this consists of a mixture of hydrocarbons in which the heptanes predominate. Carry out the following tests.

(i) **Action of bromine water.** Place 1 ml. of heptane in each of two test-tubes, and add 3–4 ml. of bromine water. Shake the tubes well, and keep one of them in your locker and out of the light. Expose the other tube to bright sunlight {or hold it close to a bright (150–200 watts) electric bulb}. Compare the tubes after about 15 minutes.

(ii) **Action of bromine dissolved in a non-aqueous solvent.** Repeat experiment (i), but add 0·5 ml. of a solution of bromine in carbon tetrachloride (2) to each of the tubes. After 10–15 minutes (or as soon as a change has occurred), examine each of the tubes. Breathe across the mouth of the tube in which a change has taken place and test the vapour with blue litmus paper.

(iii) **Action of potassium permanganate solution.** Treat 1 ml. of the hydrocarbon with 2 ml. of 0·5 per cent. potassium permanganate solution and 1 ml. of dilute sulphuric acid. Shake gently for a short time, and observe if the permanganate solution is decolourised.

(iv) **Action of concentrated sulphuric acid.** Add 1 ml. of the hydrocarbon to 2 ml. of concentrated sulphuric acid and shake gently. Observe whether the acid layer is affected in any way.

(v) **Action of concentrated nitric acid.** Add 1 ml. of heptane cautiously to 2 ml. of concentrated nitric acid. Note whether any reaction occurs.

Notes.

(1) The commercial "*n*-heptane from petroleum" should be shaken with one quarter of its volume of concentrated sulphuric acid for several minutes, and the process repeated until the lower acid layer remains colourless or only very slightly coloured. If fuming sulphuric acid (containing 10–20 per cent. SO_3) is employed, only 10 per cent. of the volume of the hydrocarbon need be used in each washing: great care must, of course, be taken in the disposal of the coloured acid layer by pouring it very slowly into a large excess of water. The hydrocarbon is then washed twice with water, dried over anhydrous calcium or magnesium sulphate, and distilled.

"*n*-Hexane from petroleum," b.p. 67–69°, or "petroleum ether, free from aromatic hydrocarbons," b.p. 60–80°, are also suitable for the above tests. They must, however, be first purified as described under "*n*-heptane."

(2) A solution prepared by dissolving 2 g. of bromine in 100 g. of carbon tetrachloride is satisfactory. Carbon tetrachloride is employed because it is an excellent solvent for bromine as well as for hydrocarbons; it possesses the additional advantage of low solubility for hydrogen bromide, the evolution of which renders possible the distinction between decolourisation of bromine due to substitution or due to addition.

Characterisation of Saturated Aliphatic Hydrocarbons

Because of the chemical inertness of the paraffin hydrocarbons and of the closely related *cyclo*paraffins, no satisfactory crystalline derivatives can be prepared. Reliance is therefore placed upon the physical properties (boiling point, density, and refractive index) of the redistilled samples. These are collected together in Table **III,6**.

TABLE III,6. SATURATED ALIPHATIC HYDROCARBONS

PARAFFINS AND CYCLOPARAFFINS

Hydrocarbon	B.P.	$d_{4^\circ}^{20^\circ}$	$n_{D}^{20^\circ}$
2-Methylbutane (*iso*-pentane)	28°	0·620	1·354
n-Pentane	36	0·627	1·358
n-Hexane	68·5	0·659	1·374
n-Heptane	98	0·683	1·388
n-Octane	125	0·703	1·397
n-Nonane	150·5	0·717	1·405
n-Decane	173	0·730	1·412
n-Undecane	196 (87°/20)	0·740	1·417
n-Dodecane	216 (94°/14)	0·750	1·422
n-Tridecane	92·5°/4·5	0·756	1·425
n-Tetradecane	252 (123°/12)	0·762	1·429
n-Pentadecane	270 (120°/4·5)	0·769	1·432
n-Hexadecane	143·5°/9 (m.p. 18°)	0·774	1·435
n-Octadecane	308 (m.p. 28°)	—	—
2-Methylpentane	60	0·653	1·372
2 : 2 : 4-Trimethylpentane	99	0·688	1·389
2 : 7-Dimethyl-*n*-octane (Di-*iso*-amyl)	160	0·725	1·409
*cyclo*Pentane	49	0·745	1·406
*cyclo*Hexane	81	0·779	1·426
*cyclo*Heptane	118	0·811	1·445
Methyl*cyclo*hexane	101	0·769	1·423
Ethyl*cyclo*hexane	130	0·784	1·432
n-Propyl*cyclo*hexane	155	0·790	1·436
iso-Propyl*cyclo*hexane	154·5	0·802	1·441
n-Butyl*cyclo*hexane	177	0·800	1·440
n-Amyl*cyclo*hexane	200	0·804	1·444
iso-Amyl*cyclo*hexane	193	0·802	1·442
Di*cyclo*hexyl	237 (m.p. 3°)	0·889	1·480
trans-Decahydronaphthalene (Decalin)	185	0·870	1·470
cis-Decahydronaphthalene (Decalin)	194	0·895	1·481
1 : 2 : 3 : 4-Tetrahydronaphthalene (Tetralin)	207	0·971	1·543
trans-*p*-Menthane	161	0·792	1·439
cis-*p*-Menthane	169	0·816	1·451

III,7. *n*-OCTANE (*Wurtz Reaction*)

When an alkyl halide is treated with sodium, the main product is the paraffin hydrocarbon. The final result may be represented by the equation:

$$2R.X + 2Na = R.R + 2NaX$$

Weigh out 23 g. of clean sodium under sodium-dried ether (1), cut it up rapidly into small pieces, and introduce the sodium quickly into a dry 750 or 1000 ml. round-bottomed flask. Fit a dry 30 cm. double surface condenser (*e.g.*, of the Davies type) into the flask by means of a sound cork. Clamp the apparatus so that the flask can be heated on a wire gauze. Weigh out 67·5 g. (53 ml.) of *n*-butyl bromide (Sections **III,35** and **III,37**), previously dried over anhydrous sodium or magnesium sulphate. Introduce about 5 ml. of the bromide through the condenser into the flask. If no reaction sets in, warm the flask gently with a small luminous flame; remove the flame immediately reaction commences (the sodium will acquire a blue colour). When the reaction subsides, shake the contents of the flask well; this will generally produce further reaction and some of the sodium may melt. Add a further 5 ml. of *n*-butyl bromide, and shake the flask. When the reaction has slowed down, repeat the above process until all the alkyl bromide has been transferred to the flask (about 1·5 hours). Allow the mixture to stand for 1–2 hours. Then add, by means of a tap funnel fitted with a grooved cork into the top of the condenser, 50 ml. of rectified spirit dropwise over 1·5 hours, followed by 50 ml. of 50 per cent. alcohol during 30 minutes, and 50 ml. of distilled water over 15 minutes; shake the flask from time to time. Add 2–3 small pieces of porous porcelain and reflux the mixture for 3 hours; any unchanged *n*-butyl bromide will be hydrolysed. Add a large excess (500–750 ml.) of water, and separate the upper layer of crude *n*-octane (17–18 g.). Wash it once with an equal volume of water, and dry it with anhydrous magnesium sulphate. Distil from a Claisen flask with fractionating side arm or from a Widmer flask (Figs. *II*, *24*. 2–3) and collect the fraction, b.p. 123–126° (15 g.) (2).

Notes.

(1) Remove about 30 g. of sodium from the stock-bottle, in which it is preserved under solvent naphtha or toluene or xylene. Wipe the surface free from solvent with filter paper. By means of a large knife with a heavy wooden handle (frequently termed a "sodium knife") cut off a thin surface layer, thus exposing a clean silver-coloured surface. Place the sodium cuttings from the large pieces of sodium into the "Scrap Sodium" bottle. Weigh out rapidly the necessary quantity of clean sodium on filter paper; cut it up into small pieces, place the sodium in a beaker containing sodium-dried ether, and cover the beaker with a clock-glass. It need hardly be emphasised that all flames in the vicinity must be extinguished. The sodium may be transferred to the flask when required. The ether is returned to the "Sodium Dried Ether" bottle.

(2) All hydrocarbons prepared by the Wurtz reaction contain small quantities of unsaturated hydrocarbons. These may be removed by shaking repeatedly with 10 per cent. of the volume of concentrated sulphuric acid until the acid is no longer coloured (or is at most extremely pale yellow); each shaking should be of about 5 minutes duration. The hydrocarbon is washed with water, 10 per cent sodium carbonate solution, water (twice), and dried with anhydrous magnesium or calcium sulphate. It is then distilled from sodium; two distillations are usually necessary

to obtain a perfectly pure product. The residual sodium is destroyed by treatment with methylated spirit.

COGNATE PREPARATIONS

***n*-Hexane.** Use 23 g. of sodium and 61·5 g. (45·5 ml.) of *n*-propyl bromide (Section **III,34**). It is advisable to employ two efficient double surface condensers in series. Collect the fraction, b.p. 68–70° (10 g.).

***n*-Decane.** Use 23 g. of sodium and 75·5 g. (62 ml.) of *n*-amyl bromide (Section **III,35**) or 99 g. (65·5 ml.) of *n*-amyl iodide (Section **III,40**). Collect the fraction, b.p. 171–174° (28 g.).

***n*-Dodecane.** Use 23 g. of sodium and 82·5 g. (70·5 ml.) of *n*-hexyl bromide (Section **III,37**). Collect the fraction, b.p. 94°/13 mm. (37 g.).

III,8. *n*-HEXANE (*Hydrocarbon from Grignard Reagent*)

This preparation illustrates the preparation of a liquid hydrocarbon from a Grignard reagent. The Grignard reagent from *n*-hexyl bromide may be decomposed either with dilute sulphuric acid or with solid ammonium chloride; the latter gives a somewhat better yield.

$$CH_3(CH_2)_4CH_2Br + Mg = CH_3(CH_2)_4CH_2MgBr$$
$$2CH_3(CH_2)_4CH_2MgBr + H_2SO_4 = 2CH_3(CH_2)_4CH_3 + MgBr_2 + MgSO_4$$
$$2CH_3(CH_2)_4CH_2MgBr + NH_4Cl = 2CH_3(CH_2)_4CH_3 + NH_2MgBr + MgClBr$$

Fit a 500 or 750 ml. three-necked flask with a mercury-sealed stirrer, a 100 ml. dropping funnel and an efficient double surface condenser (Fig. *II*, 7, 11, *a*); place calcium chloride or cotton wool guard tubes on the funnel and condenser respectively. Arrange the flask so that it can be heated in a bath of hot water. Place 12·0 g. of magnesium turnings (1), 100 ml. of sodium-dried ether and a crystal of iodine in the flask. Weigh out 82·5 g. (70·5 ml.) of dry *n*-hexyl bromide (Section **III,37**) and introduce it into the separatory funnel. Run in about 10 g. of the *n*-hexyl bromide into the magnesium and ether. Set the stirrer in action. Warm the flask by surrounding it with hot water; remove the hot water immediately reaction sets in. Add the remainder of the bromide slowly and at such a rate that the reaction is under control. Continue the stirring until most of the magnesium has passed into solution (about 4 hours). Add 27 g. of A.R. ammonium chloride, and leave the reaction mixture overnight. Cool the flask in ice and add slowly a large excess of dilute hydrochloric acid; the precipitate will dissolve completely. Separate the upper ethereal layer, and wash it successively with dilute hydrochloric acid and water; dry with anhydrous magnesium or calcium sulphate. Distil the ethereal solution through an efficient fractionating column (*e.g.*, a Hempel column filled with $\frac{1}{4}''$ glass rings or $\frac{1}{8}''$ porcelain rings; a modified Hempel column; a 30 cm. all-glass Dufton column; or a Widmer column—see Sections **II,15** and **II,17**). After the ether has passed over, *n*-hexane will distil at 67–70° (13–14 g.).

Note.

(1) Commercial magnesium turnings for the Grignard reaction should be washed with sodium-dried ether to remove any surface grease which may be present, dried at 100°, and allowed to cool in a desiccator.

III,9. *n*-OCTANE (*Clemmensen Reduction of a Ketone*)

Aliphatic hydrocarbons can be prepared by the reduction of the readily accessible ketones with amalgamated zinc and concentrated hydrochloric acid (**Clemmensen method of reduction**). This procedure is particularly valuable for the preparation of hydrocarbons with an odd number of carbon atoms where the Wurtz reaction cannot be applied; with the higher hydrocarbons some secondary alcohol is produced, which must be removed by repeated distillation from sodium.

$$\underset{\text{Methyl } n\text{-hexyl ketone}}{CH_3CO(CH_2)_5CH_3} \xrightarrow[HCl]{Zn—Hg,} \underset{n\text{-Octane}}{CH_3CH_2(CH_2)_5CH_3}$$

$$\underset{\text{Di-}n\text{-propyl ketone}}{(CH_3CH_2CH_2)_2CO} \xrightarrow[HCl]{Zn—Hg,} \underset{n\text{-Heptane}}{CH_3(CH_2)_5CH_3}$$

Place 125 g. of zinc wool in a 1-litre three-necked flask and amalgamate it in accordance with *Method 1* in Section **II,50,13**. Fit the flask with a mercury-sealed stirrer, an efficient double surface condenser, and a lead-in tube dipping almost to the bottom of the flask for the introduction of hydrogen chloride gas (compare Figs. *II*, 7, 11 and 12); insert an empty wash bottle between the hydrogen chloride generator and the flask. Introduce through the condenser 300 ml. of concentrated hydrochloric acid and 60 ml. of water, set the stirrer in motion, and then add 60 g. of methyl *n*-hexyl ketone (Section **III,71**). Pass a slow current of hydrogen chloride through the mixture; if the reaction becomes too vigorous, the passage of hydrogen chloride is temporarily stopped. After 2–3 hours most of the amalgamated zinc will have reacted. Leave the reaction mixture overnight, but disconnect the hydrogen chloride gas supply first. Remove the stirrer and the condenser from the flask. Arrange for direct steam distillation from the flask by fitting a cork into one neck, a bent tube connected to a downward condenser in the central aperture, and connect the lead-in tube to a source of steam. Stop the steam distillation when the distillate passes over as a clear liquid. Separate the upper layer, wash it twice with distilled water, dry with anhydrous magnesium or calcium sulphate, and distil from a Claisen flask with fractionating side arm. Collect the fraction, b.p. 124–126° (1). The yield of *n*-octane is 31 g.

Note.

(1) All the products of Clemmensen reductions contain small amounts of unsaturated hydrocarbons. These can be removed by repeated shaking with 10 per cent. of the volume of concentrated sulphuric acid until the acid is colourless or nearly so; each shaking should be of about 5 minutes duration. The hydrocarbon is washed with water, 10 per cent. sodium carbonate solution, water (twice), dried with anhydrous magnesium or calcium sulphate, and finally distilled twice from a Claisen flask with fractionating side arm (or a Widmer flask) over sodium.

Cognate Preparation

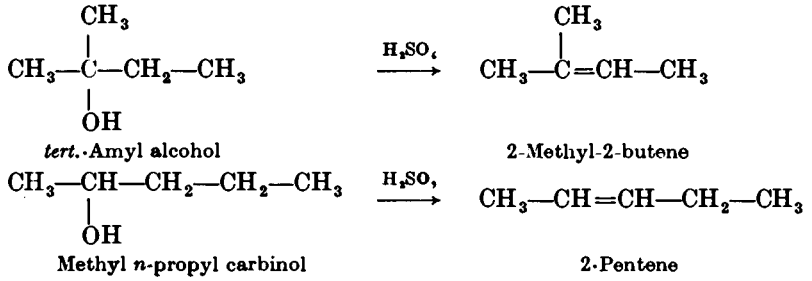
***n*-Heptane**, C_7H_{16}. Use 40 g. of di-*n*-propyl ketone * (Section **III,72**) and 100 g. of amalgamated zinc. Collect the fraction, b.p. 97–99° (26 g.).

* Satisfactory results may also be obtained with redistilled methyl *n*-amyl ketone—an inexpensive commercial product.

ETHYLENIC HYDROCARBONS (ALKENES)

III,10. AMYLENE

Amylene is a general name for the ethylenic hydrocarbons of the molecular formula C_5H_{10}. Two of these hydrocarbons are the main products of the dehydration of the appropriate amyl alcohols:



tert.-Amyl alcohol — 2-Methyl-2-butene

Methyl *n*-propyl carbinol — 2-Pentene

Tertiary alcohols are more readily dehydrated than secondary alcohols, whilst primary alcohols are dehydrated with comparative difficulty. Thus the reaction proceeds easily with 33 per cent. sulphuric acid (1 acid : 2 water, by volume) for *tert.*-amyl alcohol, but 50 per cent. (by volume) is required for *sec.*-amyl alcohol. Higher concentrations of acid tend to lead to increasing polymerisation of the olefine and are therefore usually avoided.

A. **2-Methyl-2-butene.** Assemble an apparatus consisting of a 500 ml. round-bottomed flask, a Hempel fractionating column (filled, say, with $\frac{1}{4}''$ glass rings or with $\frac{3}{16}''$ or $\frac{1}{4}''$ porcelain rings) (1), a Liebig condenser, and a bent adapter fitted by means of a cork into a filter flask as receiver (compare Fig. *II*, *16*, 1). Fit a thermometer (preferably 0–110° range) to the top of the column. The amylene is a highly volatile and inflammable liquid, and the necessary precautions against fire must be taken (*e.g.*, absence of flames in the vicinity, lead-off tube from the filter flask, *etc.*). Disconnect the flask. Cautiously add 25 ml. of concentrated sulphuric acid slowly and with constant stirring to 50 ml. of water contained in a small beaker (2). Cool the dilute acid, transfer it to the flask, add 40 ml. of tertiary amyl alcohol and a few fragments of porous porcelain. Reassemble the apparatus completely, making sure that all the corks are secure, and arrange for the flask to be heated on a water bath or steam bath. Heat gently and when distillation commences, regulate the temperature of the bath so that the temperature on the thermometer does not exceed 40–41° (1–2 drops per second). Stop the distillation when the temperature can no longer be maintained below 41°. The product is practically pure, but contains a little water (3). Transfer the distillate to a small conical flask and dry it over 1·5–2 g. of anhydrous magnesium sulphate or calcium chloride. The flask must be well stoppered owing to the volatility of the hydrocarbon. The yield is 15–16 g. Pure 2-methyl-2-butene boils at 38·5°.

B. **2-Pentene.** Proceed as in *A*, but use the following quantities: 50 ml. of water and 50 ml. of concentrated sulphuric acid; 40 g. of methyl *n*-propyl carbinol (4). Collect the distillate passing over below 40°. Pure 2-pentene boils at 36·5°.

Notes.

(1) Any other efficient fractionating column may be used, *e.g.*, an all-glass Dufton column—see Sections **II,15** and **II,17**.

(2) The addition of siliceous material (*e.g.*, kieselguhr, Fuller's earth, diatomaceous earth, or powdered pumice) promotes the acid-catalysed dehydration of the alcohol; 2–3 g. of siliceous material for each mole of alcohol is recommended.

(3) A little sulphurous acid may be present. This may be removed by transferring the product to a separatory funnel, shaking gently with 5 ml. of 10 per cent. sodium hydroxide solution (the pressure should be released from time to time by inverting the funnel and turning the stopcock), followed by water. This purification is unnecessary if the amylene is only to be used for the experiments in Section III,11.

(4) This secondary amyl alcohol (2-pentanol) is a commercial product (Sharples Solvent Corporation, etc.).

1-HEPTENE

A general method for the synthesis of 1-alkenes is provided by the action of a Grignard reagent upon allyl bromide, for example:

$$\underset{n\text{-Butyl magnesium bromide}}{CH_3(CH_2)_3MgBr} + \underset{\text{Allyl bromide}}{BrCH_2CH{=}CH_2} \longrightarrow \underset{\text{1-Heptene}}{CH_3(CH_2)_4CH{=}CH_2} + MgBr_2$$

Prepare the Grignard reagent, *n*-butyl magnesium bromide, from 12·2 g. of dry magnesium turnings, a small crystal of iodine, 69 g. (54 ml.) of *n*-butyl bromide and 260 ml. of anhydrous ether, following the experimental details given in Section III,23 (compare Section III,17). Equip a 500 ml. three-necked flask with a mercury-sealed stirrer, a 100 ml. separatory funnel and a double surface condenser. Force the solution of the Grignard reagent with the aid of pure, dry nitrogen and a tube containing a plug of purified glass wool (1) into the 500 ml. flask through the top of the double surface condenser. Charge the separatory funnel with a solution of 50 g. (35 ml.) of allyl bromide (Section III,35) in 25 ml. of anhydrous ether; place calcium chloride drying tubes into the top of the double surface condenser and of the dropping funnel. Immerse the flask containing the Grignard reagent in cold water, stir vigorously, and add the allyl bromide at such a rate that the ether boils gently; cool momentarily in ice if the reaction becomes too vigorous. It is important that the allyl bromide reacts when added, as indicated by gentle boiling of the solution (2). When all the allyl bromide has been introduced, continue stirring for 45 minutes whilst refluxing gently by immersion of the flask in a bath of warm water. Allow to cool (3). Pour the reaction mixture cautiously on to excess of crushed ice contained in a large beaker. Break up the solid magnesium complex and decompose it with ice and dilute sulphuric acid or concentrated ammonium sulphate solution. Separate the ether layer, wash it with ammoniacal ammonium sulphate solution to remove any dissolved magnesium salts, and dry over anhydrous magnesium sulphate. Distil the dry ethereal solution through an all-glass Dufton or a Widmer column: after the ether has passed over, collect the 1-heptene at 93–95°. The yield is 29 g.

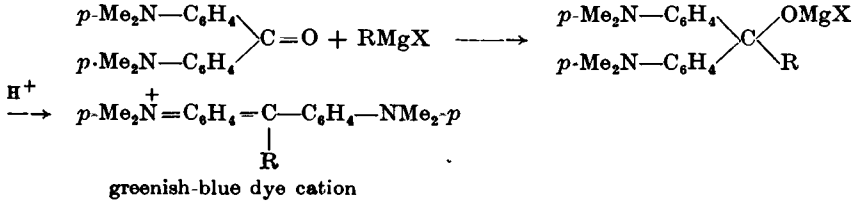
Notes.

(1) Solid magnesium must be absent to avoid the formation of diallyl via allyl magnesium bromide; the insertion of a short plug of glass wool effectively removes any finely divided magnesium.

(2) If reaction does not occur when a little allyl bromide is first introduced, further addition must be discontinued until the reaction has commenced. Remove 2–3 ml. of the Grignard solution with a dropper pipette, add about 0·5 ml. of allyl bromide and warm gently to start the reaction; after this has reacted well, add the solution to the main portion of the Grignard reagent.

(3) A slight excess of Grignard reagent should be present at this stage. The test for the presence of a Grignard reagent is as follows. Remove 0·5 ml. of the clear liquid with a dropper pipette and add 0·5 ml. of a 1 per cent. solution of Michler's ketone (4 : 4′-tetramethyldiaminobenzophenone) in benzene, followed by 1 ml. of water and 3–4 drops of 0·01*M* iodine in glacial acetic acid; shake. A greenish-blue colour results if a Grignard reagent is present. In the absence of iodine, the colour fades.

A dye of the diphenylmethane type is produced:



greenish-blue dye cation

III,11. REACTIONS AND CHARACTERISATION OF ETHYLENIC HYDROCARBONS

Carry out the following tests with the sample of amylene prepared in Section **III,10** (compare Section **III,6**).

(i) **Action of bromine water.** Shake 1 ml. of amylene with 2 ml. of bromine water, and note the result.

(ii) **Action of bromine in carbon tetrachloride solution.** To 1 ml. of amylene add 1–2 ml. of the reagent. Observe that no hydrogen bromide is evolved.

(iii) **Action of potassium permanganate solution.** Add 1 ml. of amylene to 2 ml. of 0·5 per cent. potassium permanganate solution and 1 ml. of dilute sulphuric acid, and shake. If the reagent is decolourised, add further small quantities.

(iv) **Action of concentrated sulphuric acid.** Add cautiously 1 ml. of amylene to 2 ml. of concentrated sulphuric acid. Shake very gently. Note whether any change in colour and in temperature takes place.

Cool 1 ml. of amylene in ice and add 1 ml. of cold, dilute sulphuric acid (2 acid : 1 water), and shake gently until the mixture is homogeneous. Dilute with 2 ml. of water; if an upper layer of the alcohol does not separate immediately, introduce a little sodium chloride into the mixture in order to decrease the solubility of the alcohol. Observe the odour. The unsaturated hydrocarbon is thus largely reconverted into the alcohol from which it may be prepared.

Finally, try to formulate the chemical reactions which occur in the above experiments and submit them to the instructor for comment.

Characterisation of Unsaturated Aliphatic Hydrocarbons

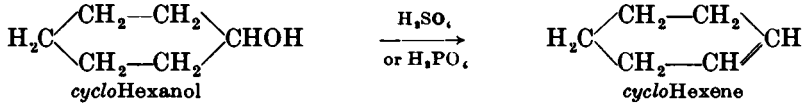
Unlike the saturated hydrocarbons, unsaturated aliphatic hydrocarbons are soluble in concentrated sulphuric acid and exhibit characteristic reactions with dilute potassium permanganate solution and with bromine. Nevertheless, no satisfactory derivatives have yet been developed for these hydrocarbons, and their characterisation must therefore be based upon a determination of their physical properties (boiling point, density and refractive index). The physical properties of a number of selected unsaturated hydrocarbons are collected in Table **III,11**.

TABLE III,11. UNSATURATED ALIPHATIC HYDROCARBONS

Hydrocarbon	B.P.	$d_{4°}^{20°}$	$n_{D}^{20°}$
1-Pentene	30°	0·641	1·371
2-Pentene	36	0·651	1·380
2-Methyl-1-butene	31	0·650	1·378
Trimethylethylene	38	0·662	1·388
1-Hexene	64	0·674	1·388
1-Heptene	93	0·697	1·400
1-Octene	121	0·716	1·409
1-Decene	169	0·742	1·422
1-Dodecene	80°/5	0·760	1·430
1-Tetradecene	125°/15	0·773	1·437
1-Hexadecene	153°/14 (m.p. 15°)	0·782	1·441
1-Octadecene	180°/18 (m.p. 18°)	0·789	1·445
Isoprene (2-methyl-1:3-butadiene)	34	0·681	1·419
Piperylene (1:3-pentadiene)	42	0·680	1·431
2 : 3-Dimethylbutadiene	69	0·726	1·439
1 : 5-Hexadiene (diallyl)	59	0·690	1·402
*cyclo*Pentene	45	0·772	1·420
*cyclo*Hexene	83	0·810	1·445
1 : 3-*cyclo*Pentadiene	42	0·803	1·443
Di*cyclo*pentadiene	170 (m.p. 32°)	—	—
1 : 3-*cyclo*Hexadiene	81	0·841	1·474
α-Pinene	156	0·860	1·456
Dipentene (*dl*-limonene)	178	0·840	1·473
Sylvestrene	176	0·847	1·475
Camphene	160 (m.p. 51°)	—	—
1-Pentyne (*n*-Propylacetylene)	39	0·695	1·385
2-Pentyne (Ethylmethylacetylene)	56	0·712	1·404
1-Hexyne (*n*-Butylacetylene)	71	0·717	1·399
1-Heptyne (*n*-Amylacetylene)	98	0·734	1·409
1-Octyne (*n*-Hexylacetylene)	126	0·748 (25°)	1·423 (25°)
1-Nonyne (*n*-Heptylacetylene)	151	0·760	1·423
Phenylacetylene	142	0·925	1·552
Furan	31	0·937	1·422
2 : 5-Dimethylfuran	94	0·888	1·436

III,12. *cyclo*HEXENE

The alicyclic secondary alcohol, *cyclo*hexanol, may be dehydrated by concentrated sulphuric acid or by 85 per cent. phosphoric acid to *cyclo*hexene. It has a higher boiling point (82–83°) than amylene and therefore possesses some advantage over the latter in the study of the reactions of unsaturated hydrocarbons.



*cyclo*Hexanol — *cyclo*Hexene

Sulphuric acid method. Place 20 g. of commercial *cyclo*hexanol and 0·6 ml. of concentrated sulphuric acid in a 150 or 200 ml. round-bottomed or bolt-head flask, add 2–3 chips of porous porcelain, and mix well. Fit the flask with a fractionating column, a Liebig condenser, adapter and filter flask receiver as in Section **III,10** (1). Heat the flask in an air bath (Fig. *II*, *5*, 3) at such a rate that the temperature at the top of the column does not rise above 90° ; alternatively, an oil bath, heated to a temperature of 130–140°, may be used. Stop the distillation when only a small residue remains and the odour of sulphur dioxide is apparent. Transfer the distillate to a small separatory funnel.

Saturate the distillate with sodium chloride, add 2 ml. of 5 per cent. sodium carbonate solution (to neutralise traces of free acid), and shake gently. Allow the two layers to separate, and run off the lower aqueous layer. Pour the crude *cyclo*hexene through the mouth of the funnel into a small dry conical flask, add 3–4 g. of anhydrous calcium chloride or anhydrous magnesium sulphate, shake for 2–3 minutes, and allow to stand for 15 minutes with occasional shaking. Decant the dried product through a small funnel supporting a small fluted filter paper into a 25 or 50 ml. distilling flask (2), add 2–3 fragments of porous porcelain, and distil. Collect the fraction, b.p. 81–83°, in a weighed flask. If appreciable high and low boiling point fractions are obtained, combine these, dry, and redistil. The yield is 12–13 g.

Phosphoric acid method. The advantages of phosphoric acid as a dehydrating agent in this preparation are the absence of carbonisation and the freedom of the product from sulphur dioxide.

Fit a 500 ml. three-necked flask with a fractionating column (*e.g.*, a Hempel column filled with $\frac{1}{4}''$ glass rings or $\frac{3}{16}''$ porcelain rings) carrying a thermometer at its upper end, and a separatory funnel ; close the third neck with a good cork. Attach an efficient double surface condenser to the column : use a filter flask, cooled in ice, as receiver. Place 50 g. of 85 per cent. orthophosphoric acid in the flask and heat it in an oil bath at 160–170°. Add, through the funnel, 250 g. of *cyclo*hexanol over a period of 1·5–2 hours. When all the *cyclo*hexanol has been introduced, raise the temperature of the bath to about 200° and maintain it at this temperature for 20–30 minutes. The temperature at the top of the column should not rise above 90°. Saturate the distillate with salt (3), separate the upper layer, and dry it with anhydrous magnesium sulphate. Distil the crude *cyclo*hexene through an efficient column and collect the fraction

boiling at 81–83°; the residue is largely *cyclo*hexanol. The yield of *cyclo*hexene is 165 g.

Notes.

(1) Alternatively, a 150 ml. Claisen flask with fractionating side arm (see Fig. *II*, *24*, 2–5) may replace the flask and fractionating column.

(2) It is preferable to use a 25 ml. Claisen flask with fractionating side arm.

(3) The phosphoric acid may be recovered by diluting the residue in the three-necked flask with water, filtering, and then evaporating with a little nitric acid to a concentration of about 85 per cent.

The student is recommended to carry out the reactions of ethylenic hydrocarbons (Section **III,11**) with part of the sample of *cyclo*hexene.

ACETYLENIC HYDROCARBONS (ALKYNES)

III,13. ACETYLENE

There are no liquid alkynes which can be conveniently prepared by the elementary student. Some of the properties of acetylenic hydrocarbons may be studied with the gas, acetylene. Although the latter may be prepared in moderate yield by the addition of ethylene dibromide to a boiling alcoholic solution of potassium hydroxide or of sodium ethoxide,

$$CH_2Br—CH_2Br \xrightarrow[\text{Alcoholic}]{KOH} CH{\equiv}CH,$$

it is most conveniently prepared in the laboratory by the action of water upon calcium carbide :

$$CaC_2 + 2H_2O \longrightarrow Ca(OH)_2 + C_2H_2$$

The only reaction which calls for comment here is the formation of red cuprous acetylide with an ammoniacal solution of cuprous chloride :

$$2[Cu(NH_3)_2]OH + HC{\equiv}CH \longrightarrow CuC{\equiv}CCu + 4NH_3 + 2H_2O$$

Fit a cork carrying a small dropping funnel into a dry 100 ml. distilling flask and clamp this gas generator at a convenient height in a retort stand ; make sure that the stopcock is properly lubricated. Connect the side arm of the distilling flask to an empty wash bottle or boiling tube (to act as a safety vessel) and attach a gas delivery tube to the latter. Place about 4 g. of calcium carbide lumps into the flask ; allow water to fall dropwise from the funnel upon the carbide, thus generating acetylene which will issue from the delivery tube (after displacement of the air) (1). Pass the gas through test-tubes containing 3–4 ml. of the following reagents :

(i) **Bromine water.** Observe any colour change and the odour of the product.

(ii) **Potassium permanganate solution** (2). Observe the colour change.

(iii) **Ammoniacal silver nitrate solution** (3). Note the formation of a white precipitate of silver acetylide, Ag_2C_2. *This is dangerously explosive when dry*, and must be destroyed in the following manner immediately after its formation. Allow the precipitate to settle, wash it once with water by decantation, add 5 ml. of dilute nitric acid (1 vol. of conc. acid : 1 vol. of water), and warm gently until the solid is *completely* decomposed.

(iv) **Ammoniacal cuprous chloride solution** (4). Observe the formation of red cuprous acetylide. *Cuprous acetylide is extremely explosive when dry*, and must be destroyed immediately after its formation with dilute nitric acid in the manner detailed under (iii).

Optional experiment. When all the air has been displaced, collect a test-tube of the gas over water (by appropriate inclination of the end of the delivery tube beneath the mouth of a test-tube filled with water and supported in a beaker of water). Observe the colour and odour of the gas. Ignite the test-tube of gas, and note the luminosity of the flame and the amount of carbon deposited. Pure acetylene is almost odourless ; the characteristic odour observed is due to traces of hydrides of phosphorus, arsenic and sulphur.

Formulate the chemical reactions which occur in the above experiments and show these to the instructor for comment.

Notes.

(1) Certain mixtures of acetylene and air are explosive. All free flames in the vicinity must therefore be extinguished.

(2) Use a mixture of 4–5 drops of 0·5 per cent. potassium permanganate solution and 4 ml. of dilute sulphuric acid.

(3) Add dilute ammonia solution dropwise to 1 ml. of 0·1*N* silver nitrate solution until the precipitate which forms *just* redissolves, and then dilute with 3 ml. of water.

(4) Dissolve 3 g. of copper sulphate pentahydrate and 1 g. of sodium chloride in 12 ml. of hot water, and add a solution of 1 g. of sodium bisulphite in 10 ml. of 5 per cent. sodium hydroxide solution. Shake, cool under the tap, and wash the precipitated white cuprous chloride with water by decantation. Dissolve the cuprous chloride in a few ml. of concentrated ammonia solution and dilute with water to 10 ml.

ALIPHATIC ALCOHOLS

Primary alcohols, $R.CH_2OH$, may be synthesised by :—

1. Reduction of esters of monobasic acids with sodium and absolute ethyl alcohol (**method of Bouveault and Blanc**), for example :

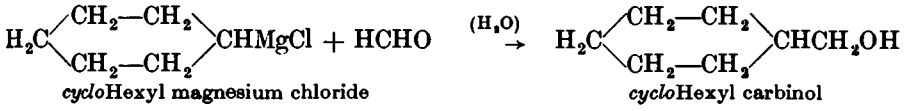
$$\underset{\text{Ethyl } n\text{-valerate}}{CH_3CH_2CH_2CH_2COOC_2H_5} \xrightarrow{4H} \underset{n\text{-Amyl alcohol}}{CH_3CH_2CH_2CH_2CH_2OH} + C_2H_5OH$$

For reduction with lithium aluminium hydride, see Section VI,10.

2. Reduction of aldehydes with iron and glacial acetic acid, for example:

$$\underset{n\text{-Heptaldehyde}}{CH_3(CH_2)_5CHO} \xrightarrow{2H} \underset{n\text{-Heptyl alcohol}}{CH_3(CH_2)_5CH_2OH}$$

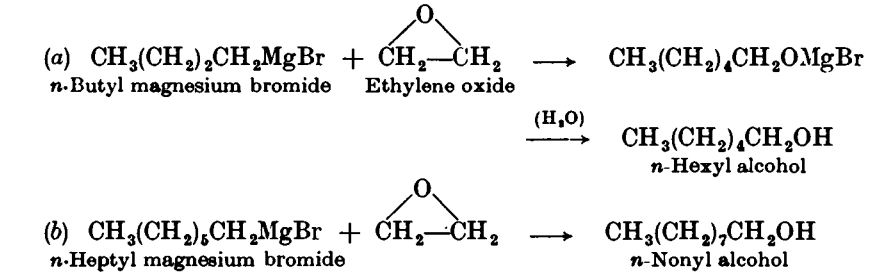
3. Action of the Grignard reagent upon formaldehyde, for example :



*cyclo*Hexyl magnesium chloride — *cyclo*Hexyl carbinol

It will be observed that the length of the carbon chain is increased by one carbon atom.

4. Action of the Grignard reagent upon ethylene oxide, for example :



Secondary alcohols, $R_1R_2.CHOH$, may be synthesised by :—

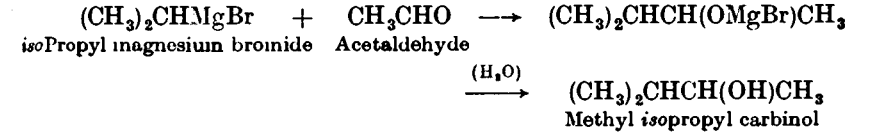
1. Reduction of ketones either with sodium and absolute alcohol,* for example :

$$\underset{\text{Methyl } n\text{-amyl ketone}}{CH_3CO(CH_2)_4CH_3} \xrightarrow{2H} \underset{\text{Methyl } n\text{-amyl carbinol (2-heptanol)}}{CH_3CH(OH)(CH_2)_4CH_3}$$

or with sodium and moist ether, for example :

$$\underset{\text{Methyl } n\text{-butyl ketone}}{CH_3CO(CH_2)_3CH_3} \xrightarrow{2H} \underset{\text{Methyl } n\text{-butyl carbinol}}{CH_3CH(OH)(CH_2)_3CH_3}$$

2. Action of the Grignard reagent upon an aldehyde, for example :



* Absolute alcohol is not essential for this reduction: 70–75 per cent. alcohol gives satisfactory results.

3. Action of the Grignard reagent upon ethyl formate, for example :

$$\underset{n\text{-Butyl magnesium bromide}}{2C_4H_9^{\alpha}MgBr} + \underset{\text{Ethyl formate}}{HCOOC_2H_5} \longrightarrow (C_4H_9^{\alpha})_2CHOMgBr + C_2H_5OMgBr$$

$$2(C_4H_9^{\alpha})_2CHOMgBr + H_2SO_4 \longrightarrow \underset{\text{Di-}n\text{-butyl carbinol (5-nonanol)}}{2(C_4H_9^{\alpha})_2CHOH} + MgBr_2 + MgSO_4$$

Tertiary alcohols, $R_1R_2R_3.COH$, may be synthesised by :—

1. Action of the Grignard reagent upon a ketone, for example :

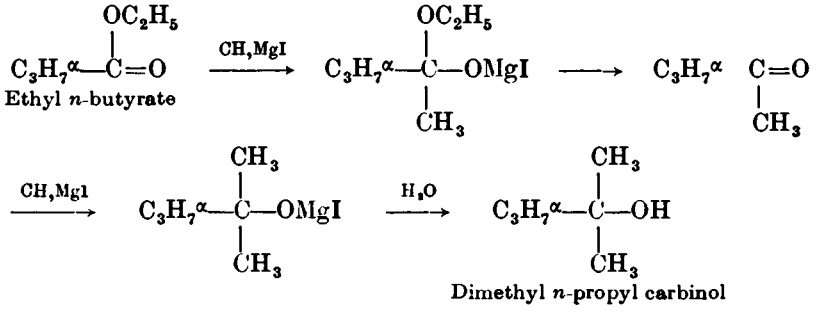
$$\underset{n\text{-Butyl magnesium bromide}}{CH_3(CH_2)_2CH_2MgBr} + \underset{\text{Acetone}}{(CH_3)_2CO} \longrightarrow \underset{\text{Dimethyl-}n\text{-butyl carbinol}}{CH_3(CH_2)_3C(OH)(CH_3)_2}$$

2. Action of the Grignard reagent upon diethyl carbonate, for example :

$$\underset{\text{Ethyl magnesium bromide}}{3C_2H_5MgBr} + \underset{\text{Diethyl carbonate}}{(C_2H_5O)_2CO} \longrightarrow (C_2H_5)_3COMgBr + 2C_2H_5OMgBr$$

$$(C_2H_5)_3COMgBr + H_2O \longrightarrow \underset{\text{Triethyl carbinol}}{(C_2H_5)_3COH} + Mg(OH)Br$$

3. Action of the Grignard reagent upon esters, for example :



Note on the mechanism of some syntheses with the Grignard reagent

A careful study of the nature of the Grignard reagent RMgX (X = halogen) has revealed the fact that under suitable experimental conditions the following equilibria may be present in solution :

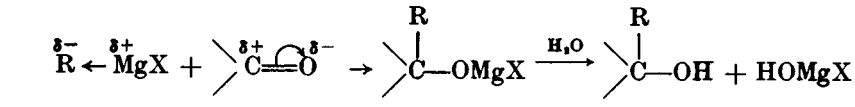
$$R^- + \overset{+}{M}gX \overset{(1)}{\rightleftharpoons} R—MgX \overset{(2)}{\rightleftharpoons} \tfrac{1}{2}R_2Mg + \tfrac{1}{2}MgX_2$$

$$\Downarrow (3)$$

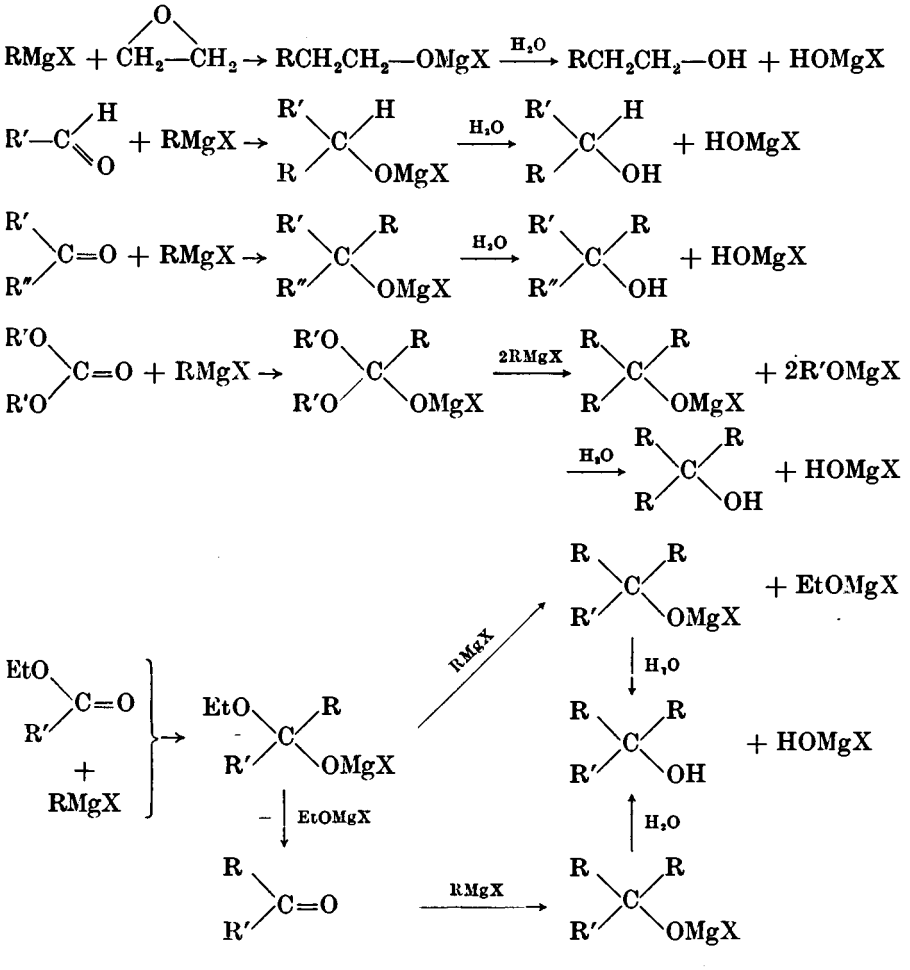
$$R\cdot + \cdot MgX$$

i.e., carbanions R^-, dialkyl magnesium compounds R_2Mg and free radicals $\cdot MgX$ may be present in solution. Under the usual reaction conditions, equilibria (1) and (2) are the most important ; upon addition of dioxan to an ethereal solution of a Grignard reagent the halogen-containing species R—MgX and MgX_2 are precipitated and only R_2Mg remains in solution. Since R—MgX and R_2Mg are similar in chemical behaviour, it is convenient to write the Grignard reagent as RMgX and remembering that any R_2Mg present in the system would exhibit similar reactivity.

The Grignard reagent RMgX is nucleophilic by virtue of the potential carbanion (alkyl anion) R^-. It will react with the electrophilic carbonyl group as follows :



Some of the applications of the Grignard reagent described above may be expressed in general terms thus :



III,14. *n*-AMYL ALCOHOL (*from Ethyl* n-*valerate*)

Fit the central neck of a 1-litre three-necked flask with an efficient double surface condenser and close the two side necks with corks (1). Place 52 g. (59·5 ml.) of ethyl *n*-valerate (Section **III,104**) and 800 ml. of "super-dry" ethyl alcohol (Section **II,47, 5**) (2) in the flask. Add 95 g. of clean sodium in small pieces through one of the apertures at such

a rate that the vigorous refluxing is continuous (20–30 minutes). Reflux the mixture in an oil bath for 1 hour in order to be certain that all the sodium has dissolved. Replace the reflux condenser by an efficient fractionating column (*e.g.*, Hempel or modified Widmer column, all-glass Dufton column, etc.) and set the condenser for downward distillation. Fractionate the mixture from an oil bath ; about 250 ml. of absolute alcohol are thus recovered. Treat the residue, consisting of *n*-amyl alcohol and sodium ethoxide, with 330 ml. of water and continue the distillation (oil bath at 110–120°) until the temperature at the top of the column reaches 83°, indicating that practically all the alcohol has been removed ; about 600 ml. of approximately 90 per cent. alcohol are recovered. Remove the fractionating column and steam distil the mixture (Fig. *II*, *41*, 1) ; about 200 ml. must be collected before all the alcohol is removed. Separate the crude amyl alcohol, dry it over anhydrous potassium carbonate or anhydrous calcium sulphate, and distil through a short column. Collect the fraction boiling at 137–139°. The yield of *n*-amyl alcohol is 35 g.

Notes.

(1) Alternatively, a round-bottomed flask and a Y-tube (compare Fig. *II*, *13*, 9) may be used. The apparatus must be perfectly dry.

(2) The alcohol used must be absolute ; a lower grade gives a poor yield.

III,15. TETRAMETHYLENE GLYCOL (1 : 4-BUTANEDIOL)

This is an example of the reduction of an ester of a dibasic acid to the corresponding glycol (**Bouveault-Blanc reduction**) :

$$(CH_2)_2(COOC_2H_5)_2 + 8H \xrightarrow{(Na + C_2H_5OH)} (CH_2)_2(CH_2OH)_2 + 2C_2H_5OH$$

Introduce a two-way adapter (Fig. *II*, *13*, 9) into the neck of a 3-litre round-bottomed flask ; fit a separatory funnel into one neck and two efficient double surface condensers in series into the other. Place 60 g. of clean dry sodium (the surface layer must be completely removed—see *Note 1* to Section **III,7**) in the flask, and add from the separatory funnel (protected by a drying tube) a solution of 35 g. of diethyl succinate (1) in 700 ml. of " super-dry " ethyl alcohol (Section **II,47,5**) as rapidly as possible consistent with the reaction being under control ; it may be necessary to immerse the flask momentarily in a freezing mixture. When the vigorous action has subsided, warm the mixture on a water bath or in an oil bath at 130° until all the sodium has reacted (30–60 minutes). Allow to cool and cautiously add 25 ml. of water (2) ; reflux for a further 30 minutes to bring all the solid into solution and to hydrolyse any remaining ester. Add 270 ml. of concentrated hydrochloric acid to the cold reaction mixture, cool in ice, filter off the precipitated sodium chloride and treat the filtrate with 300 g. of anhydrous potassium carbonate to free it from water and acid. Filter the alcoholic solution through a large sintered glass funnel, and extract the solid twice with boiling alcohol. Distil off the alcohol from the combined solutions ; towards the end of the distillation solid salts will separate. Add dry acetone, filter, and distil off the acetone. Distil the residue under diminished pressure, and collect the tetramethylene glycol at 133–135°/18 mm. The yield is 13 g.

Notes.

(1) The preparation may be adapted from the experimental details given for *Diethyl Adipate* (Section **III,99**). Another method is described in Section **III,100**.

(2) Alternatively, the following procedure for isolating the glycol may be used. Dilute the partly cooled mixture with 250 ml. of water, transfer to a distilling flask, and distil from an oil bath until the temperature reaches 95°. Transfer the hot residue to an apparatus for continuous extraction with ether (*e.g.*, Fig. *II*, *44*, 2). The extraction is a slow process (36–48 hours) as the glycol is not very soluble in ether. (Benzene may also be employed as the extraction solvent.) Distil off the ether and, after removal of the water and alcohol, distil the glycol under reduced pressure from a Claisen flask.

COGNATE PREPARATION

Hexamethylene glycol, $HO(CH_2)_6OH$. Use 60 g. of sodium, 81 g. of diethyl adipate (Sections **III,99** and **III,100**) and 600 ml. of "super-dry" ethyl alcohol. All other experimental details, including amounts of water, hydrochloric acid and potassium carbonate, are identical with those for *Tetramethylene Glycol*. The yield of hexamethylene glycol, b.p. 146–149°/17 mm., is 30 g. The glycol may also be isolated by continuous extraction with ether or benzene.

Note. Both tetramethylene glycol (1 : 4-butanediol) and hexamethylene glycol (1 : 6-hexanediol) may be prepared more conveniently by copper-chromium oxide reduction (Section **VI,6**) or, for small quantities, by reduction with lithium aluminium hydride (see Section **VI,10**).

III,16. *n*-HEPTYL ALCOHOL (*from* n-*Heptaldehyde*)

Place into a 3-litre round-bottomed flask, fitted with a mechanical stirrer (1) and a short reflux condenser, 450 g. of grease-free iron filings, 750 ml. of glacial acetic acid, 750 ml. of water, and 112·5 g. (137·5 ml.) of freshly distilled *n*-heptaldehyde, b.p. 154–156°. Heat the mixture on a water bath, with stirring (1), for 2–4 hours; if the frothing is considerable, remove the mixture momentarily from the water bath. Steam distil the reaction product directly from the flask until no more oily drops pass over (*ca.* 2 litres of distillate). Separate the oil; a further small quantity may be obtained by saturating the aqueous layer with salt. Heat the crude *n*-heptyl alcohol with 250 ml. of 20 per cent. sodium hydroxide solution with stirring or vigorous hand shaking on the water bath for 2 hours; this will hydrolyse the small proportion of *n*-heptyl acetate which is present. Allow to cool and separate the oil (2). Dry it with a little anhydrous potassium carbonate or anhydrous calcium sulphate, and distil. Collect the fraction, b.p. 173–176°, as pure *n*-heptyl alcohol. The yield is 90 g.

Notes.

(1) Stirring is not essential, but is advantageous since it reduces considerably the danger of frothing or foaming over. If mechanical stirring is not employed, the mixture must be shaken by hand from time to time, and the period of heating on the water bath increased to 6–8 hours.

(2) A further small quantity of *n*-heptyl alcohol may be obtained from the alkaline solution by mixing it with 50 ml. of water and distilling: the distillate is saturated with salt, the oil separated, dried and distilled from a small flask.

III,17. *cyclo*HEXYLCARBINOL (*from* cyclo*Hexyl Chloride*)

Set up a 1-litre three-necked flask with a mercury-sealed stirrer, a 500 ml. separatory funnel, and a double surface condenser to the upper end of which a drying tube (containing cotton wool or anhydrous calcium chloride) is attached (compare Fig. *II*, 7, 11). All parts of the apparatus must be dry. Partially immerse the flask in a bath of water. Place 26·7 g. of magnesium turnings " for Grignard reaction " and a crystal of iodine in the flask. (The turnings should have been washed with a little sodium-dried ether to remove surface grease, dried at 100–120°, and allowed to cool in a desiccator.) Measure out in separate dry vessels 121 ml. (118·5 g.) of *cyclo*hexyl chloride (Section **III,32**) and 450 ml. of sodium-dried ether. Introduce about 100 ml. of the ether and 15 ml. of the chloride into the flask. Heat the water bath so that the ether refluxes gently in order to start the reaction. When the reaction has commenced remove the water bath (cool, if necessary), set the stirrer in motion and add sufficient ether to cover the magnesium ; then introduce the remainder of the *cyclo*hexyl chloride dissolved in the residual ether during 30–45 minutes. If the reaction becomes too vigorous, cool the flask in ice-water. Continue the refluxing and stirring for 15–20 minutes to complete the formation of the Grignard reagent.

Replace the separatory funnel by a wide rubber tube fitted over the neck of the flask, and attach to this a small conical flask (Fig. *II*, 7, 12, *c*) charged with 50 g. of paraformaldehyde, which has been previously dried in a vacuum desiccator over phosphorus pentoxide (1). Stir the mixture vigorously and gradually add the paraformaldehyde by suitably inclining the conical flask. After 2 hours transfer the reaction mixture to a 2-litre bolt-head flask ; provide for mechanical stirring of its contents. Add 300 g. of finely crushed ice all at once and vigorously agitate the mixture until the decomposition is complete. Add twice the theoretical quantity of 30 per cent. sulphuric acid to dissolve the magnesium hydroxide, and then steam distil the mixture until no more oil passes over (2000–2500 ml.). Saturate the distillate with sodium chloride and separate the upper ether-alcohol layer. Dry with anhydrous potassium carbonate and distil off the ether on a water bath. Add 5 g. of freshly dehydrated lime and heat on a water bath for 30 minutes ; this will remove the last traces of water and give a halogen-free product. Filter into a Claisen flask with fractionating side arm, wash with a little anhydrous ether, remove the ether, and distil the residual alcohol under diminished pressure. Collect the fraction of b.p. 88–93°/18 mm. : most distils at 91°/18 mm. The yield is 50 g. The boiling point of *cyclo*hexylcarbinol at atmospheric pressure is 182°.

Notes.

(1) An improved yield (*ca.* 75 g.) may be obtained by substituting gaseous formaldehyde for paraformaldehyde. The former is obtained by placing 50 g. of paraformaldehyde, previously dried for 2 days over phosphorus pentoxide, in a 500 ml. round-bottomed flask provided with an inlet tube for admitting dry nitrogen. The flask is heated in an oil bath at 180–200°, and the formaldehyde vapour (produced by depolymerisation) is carried into the Grignard reagent by a slow stream of nitrogen through a wide glass tube (12 mm. in diameter) fitted into the neck of the flask. The entry tube should terminate about 1 cm. above the surface of the solution ; clogging, due to repolymerised formaldehyde, is thus largely avoided.

By using di-*n*-butyl ether (see Section **III,19**) as solvent, paraformaldehyde may be employed instead of gaseous formaldehyde without appreciable influence upon the yield. The high boiling point (141°) of *n*-butyl ether obviates the necessity of depolymerising the paraformaldehyde as a separate operation. The Grignard reagent is prepared (Section **III,19**, *Note 1*) with *n*-butyl ether as solvent using the proportions of reagents given above. The solution is heated to 100–110° in an oil bath, and 100 g. of dry paraformaldehyde is added in small portions (compare Fig. *II*, 7, 12, *c* or *d*) to the well-stirred solution over 2 hours. The product is isolated as above; 70 g. of *cyclo*hexylcarbinol, b.p. 88–93°/18 mm., are obtained.

III,18. *n*-HEXYL ALCOHOL (*from* n-*Butyl Bromide*)

The apparatus required is identical with that described in Section **III,17**. Place 37·5 g. of magnesium turnings and a small crystal of iodine in the flask. Prepare a solution of 205·5 g. (161 ml.) of *n*-butyl bromide (Sections **III,35–III,37**) in 500 ml. of sodium-dried ether. Introduce about 50 ml. of the solution into the flask; if the reaction does not commence immediately, heat the flask on a water bath so that the ether just refluxes. As soon as the reaction commences, cover the magnesium with 100 ml. of anhydrous ether; set the stirrer in motion and run in the remainder of the *n*-butyl bromide solution at such a rate that the mixture boils steadily (about 30 minutes). Cool the flask in a freezing mixture of ice and salt. Remove the separatory funnel and replace it by a tube, 4 mm. in diameter, the end of which is about 2 cm. above the surface of the liquid. Attach this delivery tube to a flask fitted with "wash bottle" tubes, the long tube being nearer the three-necked flask and the other end being connected to a supply of dry nitrogen. Cool this flask in a mixture of ice and salt and introduce rapidly 90 g. of ethylene oxide from a 100 g. sealed bulb of the reagent; the latter must, of course, be cooled in an ice and salt mixture before opening (1). Gradually introduce the ethylene oxide into the reaction flask over a period of 1·5–2 hours; the temperature should not rise above 10°. When all has been added, remove the freezing mixture surrounding the three-necked flask. The temperature of the mixture will gradually rise and the reaction mixture will boil gently. When boiling ceases, reflux on a water bath for 30 minutes. Allow to cool, insert a thermometer into a neck of the flask, arrange the condenser for downward distillation and collect 250 ml. of ether in a measuring cylinder; do not collect a larger volume of ether as a violent reaction may set in, apparently due to a rearrangement of the initial reaction product, and considerable loss may ensue. Change the receiver, and introduce 250 ml. of sodium-dried benzene into the reaction mixture. Continue the distillation with stirring until the temperature of the distilling vapour reaches 65°. Then boil the mixture under reflux for 30 minutes; generally by this time the mixture has become so viscous that stirring is no longer very effective. Allow to cool. Decompose the reaction mixture with 500 ml. of an ice-water mixture, and dissolve the precipitated magnesium hydroxide with 30 per cent. sulphuric acid; add sufficient finely-crushed ice to keep the mixture cold. Steam distil and collect about 2 litres of distillate. Separate the oily layer (*A*), and distil the aqueous layer until free of *n*-hexyl alcohol; add the oil so obtained to (*A*). Stir the crude *n*-hexyl alcohol on a water bath with 250 ml. of 20 per cent. sodium hydroxide

solution, and steam distil again as before. Dry the oil with a little anhydrous calcium sulphate, distil through an efficient fractionating column, and collect the fraction, b.p. 154–157°. The yield of *n*-hexyl alcohol is 90 g.

Note.

(1) Instead of adding the liquid ethylene oxide (b.p. 10·5°), the latter may be dissolved in 100 ml. of ice-cold anhydrous ether; this solution is added during 15–30 minutes. The yield, however, is somewhat lower.

III,19. *n*-NONYL ALCOHOL (*from* n-*Heptyl Bromide*)

This preparation is an example of **the use of di-*n*-butyl ether as a solvent in the Grignard reaction.** The advantages are: it is comparatively inexpensive, it can be handled without excessive loss due to evaporation, simple distillation gives an ether free from moisture and alcohol, and the vapour does not form explosive mixtures with air. *n*-Butyl ether cannot, of course, be employed when the boiling point of the neutral reaction product is close to 140°.

Prepare a Grignard reagent from 24·5 g. of magnesium turnings, 179 g. (157 ml.) of *n*-heptyl bromide (Section **III,37**), and 300 ml. of di-*n*-butyl ether (1). Cool the solution to 0° and, with vigorous stirring, add an excess of ethylene oxide. Maintain the temperature at 0° for 1 hour after the ethylene oxide has been introduced, then allow the temperature to rise to 40° and maintain the mixture at this temperature for 1 hour. Finally heat the mixture on a water bath for 2 hours. Decompose the addition product and isolate the alcohol according to the procedure for *n*-hexyl alcohol (Section **III,18**); the addition of benzene is unnecessary. Collect the *n*-nonyl alcohol at 95–100°/12 mm. The yield is 95 g.

Note.

(1) Commercial *n*-butyl ether is purified by washing with sodium hydroxide solution, water, drying with anhydrous calcium chloride, and then fractionating. The fraction, b.p. 140–142°, is collected.

The general procedure for the preparation of Grignard reagents in *n*-butyl ether solution may be adapted from the following description of a small scale experiment. A 200 ml. three-necked flask is fitted with a mechanical stirrer, separatory funnel, reflux condenser and thermometer. A mixture of 40 ml. of *n*-butyl ether, 1·5 g. of magnesium turnings and a small crystal of iodine is placed in the flask. The theoretical amount of the halogen compound, dissolved in sufficient *n*-butyl ether to make a total volume of 30 ml., is placed in the funnel. A small amount of the solution of the halogen compound is added and the flask is heated until the reaction commences—the exact temperature varies according to the nature of the halogen compound. Once the reaction has started, stirring is begun, and the remainder of the solution is added at a rate which permits the reaction to proceed smoothly. After the addition of the halogen compound, stirring is continued until the mixture cools to the temperature of the laboratory.

III,20. METHYL *n*-AMYL CARBINOL
(*from Methyl* n-*Amyl Ketone*)

Place a mixture of 114 g. (140 ml.) of methyl *n*-amyl ketone (2-heptanone) (1), 300 ml. of rectified spirit (95 per cent. ethyl alcohol) and 100 ml. of water (2) in a 1500 ml. three-necked flask or in a 1500 ml. round-bottomed flask provided with a two-way addition tube (Fig. *II*, *13*, 9). Attach an efficient double surface condenser to the flask and close the

other opening with a cork ; with a three-necked flask, the third neck should carry a thermometer dipping into the liquid. Add 65 g. of clean sodium, preferably in the form of wire (Section **II,47,*1***) although small pieces may be used with somewhat inferior results, gradually and at such a rate that the reaction is under control ; cool the flask in running water or in ice during the addition. The temperature should not rise above 30°. When the sodium has *completely* reacted, add 1 litre of water and cool the mixture to about 15°. Separate the upper layer, wash it with 25 ml. of dilute hydrochloric acid (1 : 1), then with 25 ml. of water, and dry with anhydrous potassium carbonate or anhydrous calcium sulphate. Distil through an efficient fractionating column and collect the methyl *n*-amyl carbinol (2-heptanol) at 156–158°. The yield is 75 g.

Notes.

(1) The ketone may be synthesised as in Section **III,152** ; it is also available commercially. The latter should first be dried, redistilled, and the fraction, b.p. 150–152°, collected.

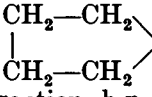
(2) Absolute alcohol may be used, but this is not essential.

III,21. METHYL *n*-BUTYL CARBINOL

(from Methyl n*-Butyl Ketone)*

Use the apparatus detailed in Section **III,20.** Dissolve 100 g. (123 ml.) of methyl *n*-butyl ketone (2-hexanone) (Section **III,152**) in 750 ml. of ether and add 150 ml. of water. Introduce 69 g. of clean sodium in the form of wire (or small pieces) as rapidly as possible ; the reaction must be kept under control and, if necessary, the flask must be cooled in ice or in running water. When all the sodium has reacted, separate the ethereal layer, wash it with 25 ml. of dilute hydrochloric acid (1 : 1), then with water, dry with anhydrous potassium carbonate or with anhydrous calcium sulphate, and distil through a fractionating column. Collect the fraction of b.p. 136–138°. The yield of methyl *n*-butyl carbinol (2-hexanol) is 97 g.

COGNATE PREPARATION

cycloPentanol,  . Use *cyclo*pentanone (Section **III,** 73) ; collect the fraction, b.p. 139–142°.

III,22. METHYL *iso*-PROPYL CARBINOL

The broad experimental details, including the apparatus, are similar to those given in Section **III,17.** The apparatus and reagents must be perfectly dry. Place 49 g. of dry magnesium turnings and 90 ml. of sodium-dried ether in the flask. Prepare a solution of 200 g. (154 ml.) of *iso*-propyl bromide (Section **III,34**) in 100 ml. of anhydrous ether and place it in the dropping funnel ; insert a cotton wool or calcium chloride guard tube in the mouth of the latter. Run in about 15 ml. of the bromide solution into the flask. The reaction should start almost immediately ; if it does not, warm gently on a water bath. Once the reaction has commenced, add the bromide solution at such a rate that the reaction mixture refluxes gently (60–90 minutes). If the refluxing becomes too

vigorous, cool the flask with running water. Finally reflux the reaction mixture on a water bath for 30 minutes. Cool the flask to $-10°$ to $-5°$ in a freezing mixture of crushed ice and salt or of crushed ice and anhydrous calcium chloride, and add a solution of 67 g. (83·5 ml.) of acetaldehyde (1) in 90 ml. of anhydrous ether over a period of 30 minutes. Do not allow the temperature to rise above $-5°$. When all the acetaldehyde has been added, pour the reaction product upon 700 g. of crushed ice; the excess of magnesium should remain in the flask. Dissolve the basic magnesium bromide by the addition of 350 ml. of 15 per cent. sulphuric acid. Separate the ethereal solution and extract the aqueous layer with four 50 ml. portions of ether. Dry the combined ethereal solutions over 8 g. of anhydrous potassium carbonate (or the equivalent quantity of anhydrous calcium sulphate), and fractionally distil through an all-glass Dufton (or other efficient fractionating) column. Collect the methyl *iso*-propyl carbinol at 110–111·5°. The yield is 70 g.

Note.

(1) The acetaldehyde should be freshly distilled (b.p. 20·5–21°). It can be conveniently prepared by depolymerising pure dry paraldehyde (see Section III,65).

III,23. DI-*n*-BUTYL CARBINOL (*from* n-*Butyl Bromide*)

The broad experimental details, including the apparatus, are similar to those given in Section **III,17**. All the reagents and the apparatus must be perfectly dry. Place 12·2 g. of dry magnesium turnings, a small crystal of iodine, and 170 ml. of sodium-dried ether in the flask. Prepare a solution of 69 g. (54 ml.) of *n*-butyl bromide (Sections **III,35** and **III,37**) in 90 ml. of anhydrous ether, place it in the separatory funnel and protect it by a calcium chloride (or cotton wool) guard tube. Set the stirrer in motion and run 10–15 ml. of the bromide solution into the flask. The reaction soon commences and, within a few minutes, the refluxing is vigorous. When this occurs, surround the flask by an ice-water mixture, and add the bromide solution at such a rate that moderate refluxing occurs. Remove the cooling bath after the solution has been added (15–20 minutes) and continue the stirring for a further 15 minutes; only a small residue of magnesium should remain. Cool the flask in ice. Place a solution of 18·5 g. (20 ml.) of pure ethyl formate (1) in 40 ml. of anhydrous ether in the separatory funnel. Stir the solution of the Grignard reagent and run in the ethyl formate solution at such a rate that the ether refluxes gently (10–15 minutes). Remove the ice bath and continue the stirring for 10 minutes.

Place 35 ml. of water in the separatory funnel and run it into the *vigorously stirred* reaction mixture at such a rate that rapid refluxing occurs. Follow this by a cold solution of 15·5 ml. of concentrated sulphuric acid in 135 ml. of water. Two practically clear layers will now be present in the flask. Decant as much as possible of the ethereal layer (*A*) into a 500 ml. round-bottomed flask. Transfer the remainder, including the aqueous layer, into a separatory funnel: wash the residual solid with two 10 ml. portions of ether and combine these washings with the liquid in the separatory funnel. Separate the ethereal portion and combine it with (*A*). Distil off the ether through an efficient fraction-

ating column until the temperature of the vapour rises to about 50°. The residual crude di-*n*-butyl carbinol contains a little of the formic ester of the carbinol. Remove the latter by refluxing for 3 hours with 25 ml. of 15 per cent. aqueous potassium hydroxide, and then isolate the purified carbinol by steam distillation (volume of distillate about 500 ml.). Separate the upper layer of the secondary alcohol, dry it over anhydrous potassium carbonate or anhydrous calcium sulphate, and distil from a Claisen flask under reduced pressure. Collect the pure di-*n*-butyl carbinol at 97–98°/20 mm.; the yield is 30 g. The boiling point under atmospheric pressure is 195°.

Note.

(1) Freshly distilled ethyl formate must be used. Commercial ethyl formate may be purified as follows. Allow the ethyl formate to stand for 1 hour with 15 per cent. of its weight of anhydrous potassium carbonate with occasional shaking. Decant the ester into a dry flask containing a little fresh anhydrous potassium carbonate and allow to stand for a further hour. Filter into a dry flask and distil through an efficient fractionating column, and collect the fraction, b.p. 53–54°; protect the receiver from atmospheric moisture.

III,24. DIMETHYL *n*-BUTYL CARBINOL

Experimental details devised for elementary students (*Method A*) and for advanced students (*Method B*) will be given for this preparation.

Method A. All the apparatus and reagents must be thoroughly dry. The *n*-butyl bromide should be dried over anhydrous sodium, magnesium or calcium sulphate and the A.R. acetone over a similar desiccant or over anhydrous potassium carbonate. Fit a 500 ml. round-bottomed flask with a two-way adapter or addition tube (Fig. *II, 1,* 8); into the two necks of the latter insert respectively a dropping funnel and a double surface condenser, each carrying a calcium chloride or cotton wool guard tube (compare Fig. *II, 13,* 9). Place 6·1 g. of magnesium turnings (previously washed with anhydrous ether and dried at 100–120°), a small crystal of iodine and 30 ml. of sodium-dried ether (Section **II,47,*l***) in the flask, and a solution of 34 g. (27 ml.) of *n*-butyl bromide (Sections **III,35–III,37**) in 25 ml. of sodium-dried ether in the dropping funnel. Add 3–4 ml. of the bromide solution to the magnesium: a vigorous reaction should occur within a few minutes. When the reaction is well under way introduce 50 ml. of anhydrous ether through the condenser. Continue the addition of the solution of *n*-butyl bromide in ether at such a rate that the ether refluxes gently; if the reaction becomes too vigorous at any time, it may be moderated by immersing the flask in cold water. Shake the reaction flask frequently. After all, or practically all, of the magnesium has disappeared, add slowly, with frequent shaking and cooling of the flask by immersion in cold water, a solution of 15 g. (19 ml.) of A.R. acetone in 15 ml. of anhydrous ether. Each drop of acetone reacts with a hissing noise and eventually the addition product separates from the ethereal solution as a grey viscous solid.

Decompose the addition product by the careful addition of a solution of 32 g. (17·5 ml.) of concentrated sulphuric acid in 175 ml. of water during about 30 minutes. Cool the flask in ice and shake frequently during the addition of the cold, dilute acid; the precipitate will decompose

completely. Transfer the mixture to a separatory funnel, separate the two layers ; keep both layers. Extract the lower aqueous layer with two 40 ml. portions of ether. Combine the ether extracts with the ether layer from the first separation and dry with anhydrous potassium carbonate. Filter the solution, remove the ether using the apparatus of Fig. *II*, *13*, 4, and fractionally distil the residue. Collect the dimethyl *n*-butyl carbinol at 137–141°. The yield is 27 g.

Method B. The apparatus and experimental details are similar to those given in Sections **III,17** and **III,22**. Prepare a Grignard reagent from 24·5 g. of magnesium turnings, a crystal of iodine, 137 g. (107 ml.) of *n*-butyl bromide and 450 ml. of sodium-dried ether. Add slowly with rapid stirring, and cooling with ice if necessary, a solution of 58 g. (73·5ml.) of dry A.R. acetone in 75 ml. of anhydrous ether. Allow the reaction mixture to stand overnight. Decompose the product by pouring it on to 500 g. of crushed ice ; dissolve the precipitated magnesium compounds by the addition of 10 per cent. hydrochloric acid or of 15 per cent. sulphuric acid. Transfer to a separatory funnel, remove the ether layer, and extract the aqueous solution with three 50 ml. portions of ether. Dry the combined ethereal solutions over anhydrous potassium carbonate or anhydrous calcium sulphate, filter, distil off the ether, and fractionate. Collect the dimethyl *n*-butyl carbinol at 137–141°. The yield is 105 g.

COGNATE PREPARATION

Dimethyl *n*-propyl carbinol, $CH_3(CH_2)_2COH(CH_3)_2$. From *n*-propyl magnesium bromide and acetone. Collect the tertiary alcohol at 121–124°.

III,25. TRIETHYL CARBINOL

The apparatus required and the general experimental details are similar to those given in Section **III,17**. The apparatus and reagents must be perfectly dry. Place 36 g. of dry magnesium turnings and 275 ml. of sodium-dried ether in a 1-litre three-necked flask. Commence the reaction by adding 2 ml. (3 g.) of dry ethyl bromide (Section **III,35**) through the separatory funnel without stirring. Set the stirrer in motion and introduce a solution of 160 g. (109·5 ml.) of ethyl bromide in 350 ml. of anhydrous ether at such a rate that the mixture refluxes gently ; the addition occupies about 45 minutes. Cool the flask externally during the addition ; it is a good plan to fold a towel in a narrow strip, wrap it about the flask above the ether level and then to place crushed ice on top of the flask. After the bromide solution has been added, continue the stirring for a further 15 minutes.

Now run in a solution of 52 g. (53·5 ml.) of pure diethyl carbonate (1) in 70 ml. of anhydrous ether, with rapid stirring, over a period of about one hour. A vigorous reaction sets in and the ether refluxes continually. When the diethyl carbonate has been added, heat the flask on a water bath with stirring for another hour. Pour the reaction mixture, with frequent shaking, into a 2-litre round-bottomed flask containing 500 g. of crushed ice and a solution of 100 g. of ammonium chloride in 200 ml. of water. Transfer to a separatory funnel, remove the ether layer, and extract the aqueous solution with two 175 ml. portions of ether. Dry

the combined ethereal extracts with anhydrous potassium carbonate or with anhydrous calcium sulphate, and remove the ether on a water bath. Distil the alcohol, preferably from a Claisen flask with a fractionating side arm or through a short column. Collect the fraction boiling at 139–142° as pure triethyl carbinol (3-ethyl-3-pentanol). A further small quantity may be obtained by drying the low-boiling fraction with 2 g. of anhydrous potassium carbonate or anhydrous calcium sulphate, filtering and redistilling. The total yield is 44 g.

Note.

(1) Commercial diethyl carbonate may be purified by the following process. Wash 100 ml. of diethyl carbonate successively with 20 ml. of 10 per cent. sodium carbonate solution, 20 ml. of saturated calcium chloride solution, and 25 ml. of water. Allow to stand for one hour over anhydrous calcium chloride with occasional shaking, filter into a dry flask containing 5 g. of the same desiccant, and allow to stand for a further hour. Distil and collect the fraction boiling at 125–126°. Diethyl carbonate combines with anhydrous calcium chloride slowly and prolonged contact should therefore be avoided. Anhydrous calcium sulphate may also be used.

COGNATE PREPARATIONS

The following tertiary alcohols may be prepared from the appropriate Grignard reagent and diethyl carbonate in yields of 75–80 per cent.

Tri-*n*-propyl carbinol. B.p. 89–92°/20 mm.

Tri-*n*-butyl carbinol. B.p. 129–131°/20 mm.

Tri-*n*-amyl carbinol. B.p. 160–163°/19 mm.

III,26. DIMETHYL *n*-PROPYL CARBINOL

The broad experimental details will be evident from those described in the previous experiments, particularly Sections **III,17** and **III,22**. Place 49 g. of dry magnesium turnings and 100 ml. of sodium-dried ether in a 1-litre three-necked flask and a solution of 284 g. (124·5 ml.) of dry methyl iodide (Section **III,40**) in 300 ml. of anhydrous ether in the separatory funnel protected by a cotton wool or calcium chloride guard tube. Run in about 15 ml. of the iodide solution. The reaction should start within a few minutes: if it does not, warm gently on a water bath and add a crystal of iodine, if necessary. Once the reaction has commenced, remove the water bath, add the iodide solution, with stirring, at such a rate that the mixture refluxes gently; if the reaction becomes too vigorous, cool the flask in ice water. Finally reflux the reaction mixture until all, or most, of the magnesium has reacted. Allow to cool, and slowly add a solution of 116 g. (132 ml.) of ethyl *n*-butyrate (1) in 100 ml. of anhydrous ether into the vigorously stirred solution of the Grignard reagent. Reflux the mixture on a water bath for one hour to complete the reaction. Pour the ethereal solution into a mixture of 200 ml. of approximately 4*N*-sulphuric acid and 750 g. of crushed ice. Separate the upper ethereal layer and extract the aqueous solution with two 150 ml. portions of ether. Wash the combined ethereal extracts with dilute sodium bicarbonate solution, followed by a little water, then dry with anhydrous potassium carbonate or anhydrous calcium sulphate, distil off the ether on a water bath, and distil the residue from a Claisen flask with fractionating side arm or through a short column. Collect

the dimethyl-*n*-propyl carbinol (2-methyl-2-pentanol) at 117–120°. A further small quantity of the tertiary alcohol may be obtained by redrying the low-boiling distillate, filtering and redistilling. The yield is 90 g.

Note.

(1) Ethyl *n*-butyrate may be prepared as described in Section III,95.

COGNATE PREPARATION

Dimethyl ethyl carbinol (2-methyl-2-butanol or *tert.*-amyl alcohol), $CH_3CH_2COH(CH_3)_2$. From ethyl propionate and methyl magnesium iodide. Collect the tertiary alcohol at 100–102°.

III,27. REACTIONS AND CHARACTERISATION OF ALIPHATIC ALCOHOLS

Carry out the following simple experiments ; these have been selected to illustrate some of the general properties of alcohols.

(i) **Miscibility with water.** Measure out 3·1 ml. (2·5 g.) of *n*-butyl alcohol into a dry 100 ml. conical or flat-bottomed flask provided with a well-fitting stopper. From a burette add distilled water to the alcohol, a few drops at a time and shake vigorously after each addition, until a slight but permanent turbidity is produced. Note the volume of water added and calculate the solubility of water in *n*-butyl alcohol at the temperature of the laboratory. Continue the addition of water, 2–3 ml. at a time and with vigorous shaking, until the contents of the flask are just homogeneous : near the point of homogeneity the additions should be reduced to portions of 1 ml. Note the *total* volume of water which has been added from the burette, and calculate the solubility of *n*-butanol in water at the temperature of the laboratory.

The student will doubtless be aware of the fact that methyl, ethyl, *n*-propyl and *iso*-propyl alcohols are completely miscible with water. The solubilities of the higher alcohols decrease progressively as the carbon content increases. The solubilities of all types of alcohols with five carbon atoms or more are quite small. For the isomeric butyl alcohols the solubilities (g. per 100 g. of water at 20°) are: *n*-butyl, 8; *iso*-butyl, 23; *sec.*-butyl, 13; *tert.*-butyl, completely miscible.

Divide the saturated solution of *n*-butyl alcohol in water into three approximately equal parts. Treat these respectively with about 2·5 g. of sodium chloride, potassium carbonate and sodium hydroxide, and shake each until the solids have dissolved. Observe the effect of these compounds upon the solubility of *n*-butanol in water. These results illustrate the phenomenon of **salting out** of organic compounds, *i.e.*, the decrease of solubility of organic compounds in water when the solution is saturated with an inorganic compound. The alcohol layer which separates is actually a saturated solution of water in *n*-butyl alcohol.

(ii) **Miscibility with hydrocarbons.** Mix 2 ml. of liquid paraffin or paraffin oil with 2 ml. of absolute ethyl alcohol (or absolute methylated spirit) in a dry test-tube and determine whether they are completely miscible. Add a drop of water, shake and observe the result (compare Section I,8).

Shake 2 ml. of paraffin oil or liquid paraffin with an equal volume of rectified spirit (95 per cent. ethyl alcohol). Explain the result.

Shake 1 ml. of anhydrous methyl alcohol with 1 ml. of paraffin oil. Repeat the experiment with 1 ml. of *n*-butyl alcohol. From your results state which is the better solvent for paraffin oil (a mixture of higher hydrocarbons) and thus explain why *n*-butanol and higher alcohols are incorporated in pyroxylin lacquers in preference to methyl and ethyl alcohols.

(iii) **Drying of alcohols.** Place 2 ml. of methyl alcohol, *n*-butyl alcohol and *cyclo*hexanol in three separate test-tubes, and add about 0·5 g. of anhydrous calcium chloride to each. Shake and observe the result (evolution of heat and chemical reaction). Stopper the tubes and leave overnight. Do your results explain why anhydrous calcium chloride cannot be employed for drying alcohols ?

(iv) **Reaction with sodium.** Treat 2 ml. of absolute methyl alcohol with a small thin slice of dry, freshly-cut sodium (handle with tongs or a penknife). Observe the result. Cool the solution when *all* the sodium has reacted. Add a little water and test the solution with litmus paper.

Obtain five small dry test-tubes (75 × 10 mm.) and introduce 1 ml. of the following alcohols into each : ethyl alcohol, *n*-butyl alcohol, *sec.*-butyl alcohol, *cyclo*hexanol and *tert.*-butyl alcohol. Add a minute fragment of sodium to each and observe the rate of reaction. Arrange the alcohols in the order of decreasing reactivity towards sodium.

The reaction with sodium is by no means an infallible practical test for alcohols since, strictly speaking, it is applicable only to pure anhydrous liquids. Traces of water, present as impurities, would give an initial evolution of hydrogen, but reaction would stop after a time if an alcohol is absent : furthermore, certain esters and ketones also evolve hydrogen when treated with sodium (compare Section **XI,7,6**). It may, however, be assumed that if no hydrogen is evolved in the test, the substance is not an alcohol.

(v) **Reaction with acetyl chloride.** Treat 1 ml. of the alcohols enumerated in (iv) cautiously with 0·5–0·7 ml. of acetyl chloride. Observe the reaction which occurs. After 2–3 minutes, pour the contents of the various test-tubes into 3 ml. portions of water, neutralise the aqueous layer with solid sodium bicarbonate, and examine the residual liquids for odour and density (relative to water).

(vi) **Differentiation between primary, secondary and tertiary alcohols (Lucas' test).** The test depends upon the different rates of formation of the alkyl chlorides upon treatment with a hydrochloric acid - zinc chloride reagent * (containing 1 mole of acid to 1 mole of anhydrous zinc chloride) and with hydrochloric acid. It applies only to aliphatic and *cyclo*aliphatic alcohols.

To 1 ml. of the alcohol in a small test-tube, add quickly 6 ml. of Lucas' reagent at 26–27°, close the tube with a cork, shake, and allow to stand. Observe the mixture during 5 minutes. The following results may be obtained :—

* **Lucas' reagent is prepared** by dissolving 68 g. (0·5 mole) of anhydrous zinc chloride (fused sticks, powder, etc.) in 52·5 g. (0·5 mole) of concentrated hydrochloric acid with cooling to avoid loss of hydrogen chloride.

(*a*) Primary alcohols, lower than hexyl, dissolve; there may be some darkening, but the solution remains clear.

(*b*) Primary alcohols, hexyl and higher, do not dissolve appreciably; the aqueous phase remains clear.

(*c*) Secondary alcohols: the clear solution becomes cloudy owing to the separation of finely-divided drops of the chloride (see Section **III,29**).* A distinct upper layer is visible *after one hour* except for *iso*-propyl alcohol (probably because of the volatility of the chloride).

(*d*) Tertiary alcohols: two phases separate *almost immediately* owing to the formation of the tertiary chloride (see Section **III,33**).

If a turbid solution is obtained, suggesting the presence of a secondary alcohol but not excluding a tertiary alcohol, a further test with concentrated hydrochloric acid must be made. Mix 1 ml. of the alcohol with 6 ml. of concentrated hydrochloric acid, and observe the result:—

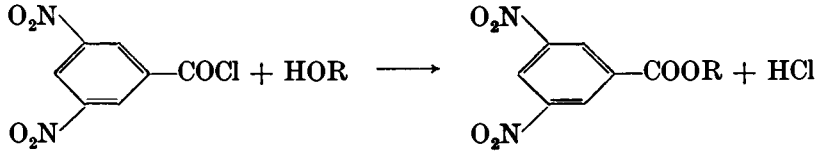
(*e*) Tertiary alcohols: immediate reaction to form the insoluble chloride which rises to the surface in a few minutes.

(*f*) Secondary alcohols: the solution remains clear.

Carry out the Lucas test with *iso*-propyl alcohol, *n*-butyl alcohol, *sec.*-butyl alcohol, *cyclo*hexanol and *tert.*-butyl alcohol. Obtain an "unknown" alcohol from the instructor for test.

Crystalline Derivatives of Aliphatic Alcohols

1. **3 : 5-Dinitrobenzoates.** 3 : 5-Dinitrobenzoyl chloride reacts with alcohols to form solid esters which possess sharp melting points and are therefore admirably suited for purposes of characterisation:



The acid chloride is available commercially, but it is more economical to prepare it from the acid as and when required. Furthermore, 3 : 5-dinitrobenzoyl chloride tends to undergo hydrolysis if kept for long periods, particularly if the stock bottle is frequently opened. The substance may, however, be stored under light petroleum.

Method 1. Mix 1·0 g. of 3 : 5-dinitrobenzoic acid (Section **IV,168**) with 4 ml. of thionyl chloride in a dry 50 ml. conical flask; fit a reflux condenser, carrying a plug of cotton wool at the upper end, into the flask and heat on a water bath for 15–30 minutes, Remove the condenser and heat the flask in a boiling water bath (*FUME CUPBOARD!*) until the excess of thionyl chloride has evaporated. Use the resulting 3 : 5-dinitrobenzoyl chloride (about 1·0 g.) immediately.

Add 0·5–1 ml. of the alcohol, cork the flask loosely, and heat on a water bath for 10 minutes: secondary and tertiary alcohols require longer heating (up to 30 minutes). Cool the mixture, add 10 ml. of 5 per cent. (or saturated) sodium bicarbonate solution, break up the resulting solid ester with a stirring rod (alternatively, stir until crystalline), and filter at the pump; wash with a little sodium bicarbonate solution, followed by water, and then suck as dry as possible. Dissolve the crude

* Allyl alcohol behaves like a secondary alcohol and reacts within 7 minutes.

ester in the minimum volume of hot rectified (or methylated) spirit. Add hot water, drop by drop, with agitation, until the solution *just* develops a slight turbidity that does not disappear on shaking ; immerse the mixture in a hot water bath during the recrystallisation. Allow to cool slowly (in order to avoid the formation of oily drops for esters of low melting point). Filter the crystals, and dry them upon a few thicknesses of filter paper or upon a piece of porous plate. Determine the melting point of the crystals when thoroughly dry. Acetone and petroleum ether may also be employed for recrystallisation.

The above procedure may also be carried out in the presence of 1 ml. of dry pyridine ; with some alcohols improved yields may be obtained by this modification.

Method 2. Mix 1·0 g. of 3 : 5-dinitrobenzoic acid with 1·5 g. of phosphorus pentachloride in a small, dry test-tube. Warm the mixture gently over a small smoky flame to start the reaction ; when the reaction has subsided (but not before), boil for 1–2 minutes or until the solid matter has dissolved. Pour the mixture while still liquid on a dry watch glass (*CAUTION :* the fumes are irritating to the eyes). When the product has solidified, remove the liquid by-product (phosphorus oxychloride) by transferring the pasty mixture to a pad of several thicknesses of filter paper or to a small piece of porous tile. Spread the material until the liquid has been absorbed and the residual solid is dry. Transfer the 3 : 5-dinitrobenzoyl chloride to a test-tube, add 0·5–1 ml. of the alcohol, and continue as in *Method 1.*

2. **p-Nitrobenzoates.** Alcohols react readily with *p*-nitrobenzoyl chloride to yield *p*-nitrobenzoates :

$$p\text{-}NO_2C_6H_4COCl + ROH \longrightarrow p\text{-}NO_2C_6H_4COOR + HCl$$

The melting points of these esters are usually much lower than those of the corresponding 3 : 5-dinitrobenzoates : their preparation, therefore, offers no advantages over the latter except for alcohols of high molecular weight and for polyhydroxy compounds. The reagent is, however, cheaper than 3 : 5-dinitrobenzoyl chloride ; it hydrolyses in the air so that it should either be stored under light petroleum or be prepared from the acid, when required, by the thionyl chloride or phosphorus pentachloride method.

The experimental technique is similar to that given under *1* above.

3. **Benzoates.** Alcohols react with benzoyl chloride in the presence of pyridine or of sodium hydroxide solution to produce esters of benzoic acid :

$$C_6H_5COCl + ROH \longrightarrow C_6H_5COOR + HCl$$

These derivatives are generally liquids and hence are of little value for characterisation ; the polyhydric alcohols, on the other hand, afford solid benzoates. Thus the benzoates of ethylene glycol, trimethylene glycol and glycerol melt at 73°, 58°, and 76° respectively (see Section **III,136**).

The experimental technique is similar to that given under *Aromatic Amines*, Section **IV,100,2**. The following alternative method may also be used. Mix together 0·5–0·8 ml. of the polyhydroxy compound, 5 ml. of pyridine and 2·5 ml. of redistilled benzoyl chloride in a 50 ml. flask,

and heat under reflux for 30–60 minutes. Add 25 ml. of 5 per cent. sodium bicarbonate solution to the cold reaction mixture and cool in ice until the precipitate solidifies. Filter and wash with a little water. Recrystallise from dilute alcohol as detailed under *1* above.

4. **Phenyl- and α-naphthyl-urethanes (Phenyl- and α-naphthyl-carbamates).** Both phenyl *iso*cyanate and α-naphthyl *iso*cyanate react with alcohols to yield phenyl-urethanes and α-naphthyl-urethanes respectively:

$$C_6H_5N{=}C{=}O + ROH \longrightarrow C_6H_5NHCOOR$$
$$C_{10}H_7{}^{\alpha}N{=}C{=}O + ROH \longrightarrow C_{10}H_7{}^{\alpha}NHCOOR$$

If the alcohol is not anhydrous, reaction also occurs between the water and the reagent to produce diphenylurea (m.p. 242°) and di-α-naphthylurea (m.p. 284°) respectively, for example:

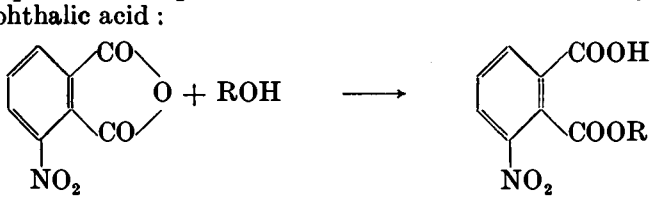
$$2C_6H_5N{=}C{=}O + H_2O \longrightarrow C_6H_5NHCONHC_6H_5 + CO_2$$

The ureas are less soluble than the corresponding urethanes, but their separation is not always easy. For this reason the urethanes are generally prepared from alcohols which are insoluble in water and can therefore be easily obtained in the anhydrous condition.

α-Naphthyl *iso*cyanate is usually preferred to phenyl *iso*cyanate for the following reasons:—(*a*) it is much less lachrymatory; (*b*) it is not so readily decomposed by cold water and thus possesses better keeping qualities; and (*c*) the melting points of the α-naphthyl-urethanes are generally higher than those of the corresponding phenyl-urethanes. Furthermore, with primary alcohols, which react readily in the cold, only small amounts of the urea are produced and these may be removed by taking advantage of the extreme insolubility of di-α-naphthylurea in hot ligroin.

Place 1 g. of the anhydrous alcohol in a dry test-tube and add 0·5 ml. of α-naphthyl *iso*cyanate * (if the molecular weight is known, use a 10 per cent. excess of the reagent); insert a loose plug of cotton wool in the mouth of the tube. If no solid separates after shaking and standing for 5 minutes, warm on a water bath for 5–10 minutes, and then cool in ice. If no solid is now obtained, " scratch " the sides of the tube with a glass rod to induce crystallisation. Extract the solid with 5–10 ml. of boiling ligroin (light petroleum, b.p. 100–120°); this rapidly dissolves the α-naphthylurethane but not the di-α-naphthylurea. Remove the urea (if any) by filtration and allow the hot ligroin solution to cool. If the urethane does not crystallise out, evaporate the solution to half its original volume, and allow to cool. Collect the crystals on a filter, dry, and determine the melting point. If the latter is not sharp, recrystallise from light petroleum (b.p. 100–120°), alcohol, chloroform or carbon tetrachloride.

5. **Hydrogen 3-nitrophthalates.** 3-Nitrophthalic anhydride, a yellow crystalline powder of m.p. 163–164°, reacts with alcohols to yield esters of 3-nitrophthalic acid:



* The procedure for phenyl *iso*cyanate is similar, but great care must be taken to protect both the reagent and the reaction mixture from moisture.

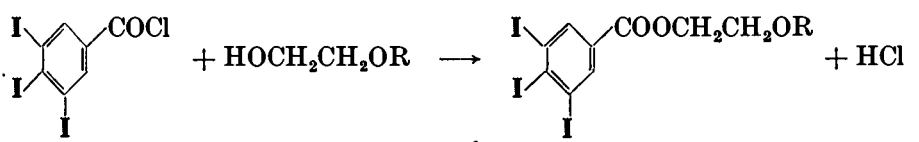
Although two isomeric esters are theoretically possible, the main product is the 2-ester (formulated above); traces of the isomeric 1-ester are eliminated during purification. These derivatives possess a free carboxyl group; their equivalent weights may therefore be determined by titration with standard alkali and thus serve as an additional check upon the identity of the compound.

The reagent must be carefully protected from moisture as it is comparatively easily hydrated to the acid, m.p. 216–218° (sealed capillary tube). Dilute aqueous solutions of an alcohol should be treated with solid potassium carbonate and the alcohol layer used for the test.

Phthalic anhydride reacts similarly, but the acid phthalates are somewhat more difficult to isolate and the melting points are considerably lower.

For alcohols of b.p. below 150°, mix 0·5 g. of 3-nitrophthalic anhydride (Section **VII,19**) and 0·5 ml. (0·4 g.) of the dry alcohol in a test-tube fitted with a short condenser, and heat under reflux for 10 minutes after the mixture liquefies. For alcohols boiling above 150°, use the same quantities of reactants, add 5 ml. of dry toluene, heat under reflux until all the anhydride has dissolved and then for 20 minutes more: remove the toluene under reduced pressure (suction with water pump). The reaction product usually solidifies upon cooling, particularly upon rubbing with a glass rod and standing. If it does not crystallise, extract it with dilute sodium bicarbonate solution, wash the extract with ether, and acidify. Recrystallise from hot water, or from 30 to 40 per cent. ethanol or from toluene. It may be noted that the m.p. of 3-nitrophthalic acid is 218°.

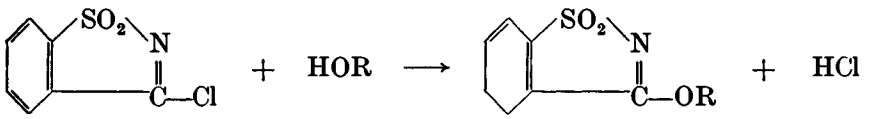
6. **3 : 4 : 5-Triiodobenzoates.** The derivatives enumerated above are unsatisfactory for alcohol-ethers, *e.g.*, the mono-ethers of ethyleneglycol ("cellosolves") and the mono-ethers of diethyleneglycol ("carbitols") (see Table **III,27**). **Crystalline derivatives of alcohol-ethers** are readily obtained with 3 : 4 : 5-triiodobenzoyl chloride (for preparation, see Section **VII,21**), for example:



Place 0·5 g. of 3 : 4 : 5-triiodobenzoyl chloride in a small test-tube, add 0·25 ml. of the alcohol-ether and heat the mixture gently over a micro burner until the evolution of hydrogen chloride ceases (3–5 minutes). Pour the molten mass into 10 ml. of 20 per cent. alcohol to which crushed ice has been added. Some derivatives solidify instantly; those which separate as oils change to solids in a few minutes without further manipulation. Recrystallise from rectified spirit (use 50 per cent. alcohol for esters of methyl and butyl "carbitol").

The following melting points have been recorded:—methyl cellosolve, 152°; cellosolve, 128°; *iso*-propyl cellosolve, 80°; butyl cellosolve, 85°; phenyl cellosolve, 145°; benzyl cellosolve, 104°; methyl carbitol, 82°; ethyl carbitol, 76°; butyl carbitol, 54°.

7. **Pseudo-saccharin ethers.** Pseudo-saccharin chloride (Section **VII,26**) reacts with alcohols to give ethers (*O*-alkyl derivatives of saccharin):



Heat a little pseudo-saccharin chloride with excess of the anhydrous alcohol in a test-tube until hydrogen chloride is no longer evolved. Recrystallise from alcohol or other organic solvent.

With the lower primary alcohols, heating at 100° for 10 minutes suffices: for higher alcohols, a temperature of 125° is preferable. Secondary alcohols require longer heating at 125°. A large excess of alcohol should be used when identifying the lower alcohols and the excess removed by evaporation; for the higher alcohols, it is better to employ an excess of pseudo-saccharin chloride and the product washed free from the reagent with dilute aqueous alkali.

The melting points of derivatives of selected alcohols are collected in Table **III,27**.

TABLE III,27. **ALIPHATIC ALCOHOLS**

Alcohol	B.P.	M.P.	3 : 5-Dinitrobenzoate	*p*-Nitrobenzoate	Phenyl urethane	α-Naphthylurethane	Hydrogen 3-nitrophthalate	*O*-Alkyl saccharin	Other Derivatives
Methyl	64·5°	—	109°	96°	47°	124°	153°	182°	—
Ethyl	78	—	94	57	52	79	157	219	—
n-Propyl	97	—	75	35	57	80	145	125	—
iso-Propyl	82	—	122	110	86	106	153	137	—
n-Butyl	118	—	64	36	61	72	147	96	—
iso-Butyl	108	—	88	68	86	104	179	100	—
sec.-Butyl	99·5	—	76	26	64	98	131	66	—
tert.-Butyl	82·5	25	142	116	136	101	—	—	—
n-Amyl	138	—	46	11	46	68	136	62	—
iso-Amyl	131·5	—	62	21	57	68	166	64	—
2-Pentanol (1)	119	—	62	17	—	76	103	—	—
3-Pentanol (2)	116	—	100	17	49	95	121	—	—
Active Amyl (3)	129	—	70	—	—	82	158	—	—
tert.-Amyl	102	—	118	85	42	72	—	—	—
n-Hexyl	156	—	61	5	42	59	124	60	—
n-Heptyl	176	—	48	10	65	62	127	55	—
n-Octyl	194	—	62	12	74	66	128	46	—
n-Nonyl	214	—	52	10	69	65	125	49	—
n-Decyl	231	6	57	30	60	71	123	48	—
n-Undecyl	243	16	55	29	62	73	123	59	—
n-Dodecyl (4)	259	24	60	45	74	80	124	54	—
n-Tetradecyl (5)	160°/10	39	67	51	74	82	123	62	—
n-Hexadecyl (6)	190°/15	50	66	52	73	82	120	70	—
n-Octadecyl (7)	—	59	66	64	80	89	119	75	—
Neo-pentyl (8)	113	52	—	—	144	100	—	—	—
2-Ethyl-*n*-butyl	149	—	52	—	—	—	—	—	—
2-Heptanol	159	—	49	—	—	54	—	—	—
2-Octanol	179	—	32	28	114	64	—	—	—
*cyclo*Pentanol	141	—	115	62	132	118	—	—	—
*cyclo*Hexanol	161	25	113	50	82	129	160	—	—
Furfuryl	170	—	81	76	45	129	—	—	—
Tetrahydrofurfuryl	177	—	84	47	61	90	—	—	Diphenylcarbamate, 81
Allyl	97	—	50	29	70	109	124	—	—

TABLE III,27. ALIPHATIC ALCOHOLS (*continued*)

Alcohol	B.P.	M.P.	3 : 5-Dinitrobenzoate	p-Nitrobenzoate	Phenylurethane	α-Naphthylurethane	Hydrogen-3-nitrophthalate	Other Derivatives
Diacetone alcohol	166°	—	55°	48°	—	—	—	2 : 4-Dinitrophenylhydrazone, 203°
l-Menthol	216	43	153	62	112	126	—	Benzoate, 54
α-Terpineol	219	35	79	97	113	152	—	—
Geraniol	230	—	63	35	—	48	117	Diphenylcarbamate, 82
d-Borneol	212	205	154	153	138	127	—	—
Ethylene bromohydrin	149	—	86	—	86	—	172	$d_{4°}^{20°}$ 1·763, $n_D^{20°}$ 1·492
Ethylene chlorohydrin	128·5	—	92	—	51	101	98	$d_{4°}^{20°}$ 1·202, $n_D^{20°}$ 1·442
Trimethylene chlorohydrin	161	—	77	—	—	76	—	$d_{4°}^{20°}$ 1·131, $n_D^{20°}$ 1·447
Glycerol α-monochlorohydrin	213	—	—	108	—	—	—	—
Glycerol αγ-dichlorohydrin	176	—	—	—	73	115	—	$d_{4°}^{20°}$ 1·353, $n_D^{20°}$ 1·480
Glycerol βγ-dichlorohydrin	182	—	—	38	73	—	—	—
Glycerol αγ-dibromohydrin	219 (d)	—	—	78	81	—	—	$d_{4°}^{25°}$ 2·120, $n_D^{25°}$ 1·550
Ethylene glycol	197	—	169	141	157	176	—	Dibenzoate, 73
Propylene glycol	187	—	—	127	153	—	—	—
Trimethylene glycol	215	—	178	119	137	164	—	Dibenzoate, 59
Tetramethylene glycol	230	19	—	175	183	198	—	Dibenzoate, 82
Pentamethylene glycol	239	—	—	105	176	147	—	—
Hexamethylene glycol	250	42	—	—	—	—	—	—
Glycerol	290 (d)	—	—	188	180	192	—	Tribenzoate, 72
Diethylene glycol (9)	244	—	149	—	—	—	—	$d_{4°}^{20°}$ 1·116, $n_D^{20°}$ 1·448
Ethyleneglycol monomethyl ether (10)	124	—	—	50	—	113	129	$d_{4°}^{20°}$ 0·966, $n_D^{20°}$ 1·402; 3 : 4 : 5-triiodobenzoate, 152
Ethyleneglycol monethyl ether (11)	135	—	75	—	—	67	118	$d_{4°}^{20°}$ 0·930, $n_D^{20°}$ 1·408; 3 : 4 : 5-triiodobenzoate, 128

TABLE III,27. ALIPHATIC ALCOHOLS (*continued*)

Alcohol	B.P.	M.P.	3 : 5-Dinitrobenzoate	*p*-Nitrobenzoate	Phenylurethane	α-Naphthylurethane	Hydrogen 3-nitrophthalate	Other Derivatives
Ethyleneglycol mono-*n*-propyl ether	151°	—	—	—	—	—	—	$d_{4°}^{20°}$ 0·911, $n_D^{20°}$ 1·413
Ethyleneglycol mono-*iso*-propyl ether	142	—	—	—	—	—	—	$d_{4°}^{20°}$ 0·903, $n_D^{20°}$ 1·410; 3 : 4 : 5-triiodobenzoate, 80
Ethyleneglycol mono-*n*-butyl ether (12)	168	—	—	120	—	—	—	$d_{4°}^{20°}$ 0·902, $n_D^{20°}$ 1·420; 3 : 4 : 5-triiodobenzoate, 85
Ethyleneglycol monophenyl ether (13)	245	—	—	113	—	—	—	$d_{4°}^{20°}$ 1·104, $n_D^{20°}$ 1·534; 3 : 4 : 5-triiodobenzoate, 145; *p*-toluenesulphonate, 80
Ethyleneglycol monobenzyl ether	265	—	—	—	—	—	—	$d_{4°}^{20°}$ 1·070, $n_D^{20°}$ 1·523; 3 : 4 : 5-triiodobenzoate, 104
Diethyleneglycol monomethyl ether (14)	194	—	—	—	—	—	89	$d_{4°}^{20°}$ 1·036, $n_D^{20°}$ 1·424; 3 : 4 : 5-triiodobenzoate, 82
Diethyleneglycol monoethyl ether (15)	202	—	—	—	—	—	—	$d_{4°}^{20°}$ 1·024, $n_D^{20°}$ 1·430; 3 : 4 : 5-triiodobenzoate, 76
Diethyleneglycol mono-*n*-butyl ether (16)	232	—	—	—	—	—	—	$d_{4°}^{20°}$ 0·958, $n_D^{20°}$ 1·434; 3 : 4 : 5-triiodobenzoate, 54
Monoethanolamine (17) . .	171	—	—	—	—	—	—	$d_{4°}^{20°}$ 1·022, $n_D^{20°}$ 1·454; Picrate, 160
Diethanolamine (18) . .	270	28	—	—	—	—	—	$d_{4°}^{20°}$ 1·097, $n_D^{20°}$ 1·478; Picrate, 110
Triethanolamine (19) . .	360	—	—	—	—	—	—	$d_{4°}^{20°}$ 1·124, $n_D^{20°}$ 1·485; Hydrochloride, 177

(1) Methyl *n*-propyl carbinol
(2) Diethyl carbinol
(3) *sec.*-Butyl carbinol
(4) Lauryl alcohol
(5) Myristyl alcohol
(6) Cetyl alcohol
(7) Stearyl alcohol
(8) *tert.*-Butyl carbinol
(9) 2 : 2′-Dihydroxydiethyl ether
(10) "Methyl cellosolve"
(11) "Ethyl cellosolve"
(12) "Butyl cellosolve"
(13) "Phenyl cellosolve"
(14) "Methyl carbitol"
(15) "Carbitol"
(16) "Butyl carbitol"
(17) 2-Aminoethyl alcohol
(18) 2 : 2′-Dihydroxydiethylamine
(19) 2 : 2′ : 2″-Trihydroxytriethylamine

ALKYL HALIDES

CHLORIDES

The chlorides of primary aliphatic alcohols are prepared :

1. By refluxing the alcohol with a mixture of concentrated hydrochloric acid and anhydrous zinc chloride, for example :

$$\underset{n\text{-Butyl alcohol}}{CH_3(CH_2)_2CH_2OH} + HCl \xrightarrow{ZnCl_2} \underset{n\text{-Butyl chloride}}{CH_3(CH_2)_2CH_2Cl} + H_2O$$

2. By the action of thionyl chloride upon the alcohol alone or mixed with pyridine (to absorb the hydrogen chloride formed in the reaction), for example :

$$\underset{n\text{-Hexyl alcohol}}{CH_3(CH_2)_4CH_2OH} \xrightarrow{SOCl_2} \underset{n\text{-Hexyl chloride}}{CH_3(CH_2)_4CH_2Cl} + SO_2 + HCl$$

$$\underset{iso\text{-Butyl alcohol}}{(CH_3)_2CHCH_2OH} \xrightarrow[C_5H_5N]{SOCl_2} \underset{iso\text{-Butyl chloride}}{(CH_3)_2CHCH_2Cl} + SO_2 + HCl$$

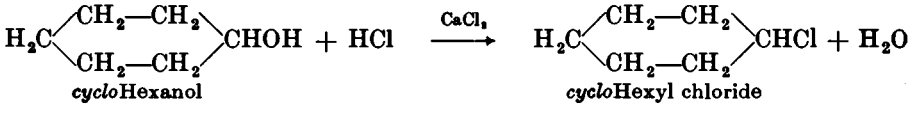
The dichlorides of aliphatic glycols are obtained by reaction with thionyl chloride in the presence of a small quantity of pyridine, for example :

$$\underset{1:4\text{-Butanediol}}{HO(CH_2)_4OH} + 2SOCl_2 \xrightarrow{C_5H_5N} \underset{1:4\text{-Dichlorobutane}}{Cl(CH_2)_4Cl} + 2SO_2 + 2HCl$$

The chlorides of secondary aliphatic alcohols are prepared by method 1, for example :—

$$\underset{sec.\text{-Butyl alcohol}}{CH_3CH_2CHOHCH_3} + HCl \xrightarrow{ZnCl_2} \underset{sec.\text{-Butyl chloride}}{CH_3CH_2CHClCH_3} + H_2O$$

The chlorides of *cyclo*aliphatic alcohols may be prepared by heating the alcohol with concentrated hydrochloric acid and anhydrous calcium chloride, for example :—



*cyclo*Hexanol — *cyclo*Hexyl chloride

The chlorides of tertiary aliphatic alcohols are readily prepared by the action of concentrated hydrochloric acid upon the alcohol at the laboratory temperature, for example :

$$\underset{tert.\text{-Butyl alcohol}}{(CH_3)_3COH} + HCl \longrightarrow \underset{tert.\text{-Butyl chloride}}{(CH_3)_3CCl} + H_2O$$

BROMIDES

Alkyl bromides may be prepared :—

1. By slow distillation of the alcohol with constant boiling point (48 per cent.) hydrobromic acid, for example :

$$\underset{iso\text{-Propyl alcohol}}{(CH_3)_2CHOH} + HBr \longrightarrow \underset{iso\text{-Propyl bromide}}{(CH_3)_2CHBr} + H_2O$$

2. By treatment of the alcohol with a mixture of constant boiling point hydrobromic acid and concentrated sulphuric acid ; the presence of sulphuric acid results, as a rule, in more rapid reaction and improved yields. A typical example is :

$$\underset{n\text{-Butyl alcohol}}{CH_3(CH_2)_2CH_2OH} + HBr \xrightarrow{H_2SO_4} \underset{n\text{-Butyl bromide}}{CH_3(CH_2)_2CH_2Br} + H_2O$$

The hydrobromic acid - sulphuric acid solution may be prepared by the reduction of bromine with sulphurous acid (Section II,49, *1*); distillation of the reaction product is unnecessary:

$$SO_2 + 2H_2O + Br_2 \longrightarrow H_2SO_4 + 2HBr$$

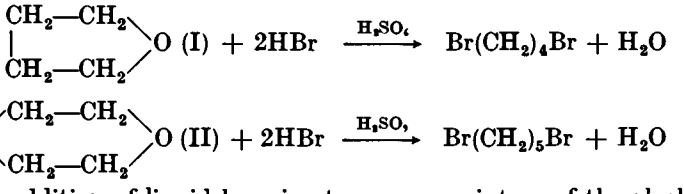
Alternatively, the acid mixture may be obtained from the reaction between potassium bromide solution and concentrated sulphuric acid below 75°; the potassium hydrogen sulphate crystallises out and is removed by filtration:

$$KBr + H_2SO_4 \longrightarrow KHSO_4 + HBr$$

The **dibromides of aliphatic glycols** are best prepared by mixing the glycol with a cold hydrobromic acid - sulphuric acid mixture, allowing to stand for 24 hours, and heating on a steam bath for three hours:

$$\underset{\text{1 : 6-Hexanediol}}{HO(CH_2)_6OH} + 2HBr \xrightarrow[100°]{H_2SO_4} \underset{\text{1 : 6-Dibromohexane}}{Br(CH_2)_6Br} + 2H_2O$$

1 : 4-Dibromobutane and 1 : 5-dibromopentane are conveniently prepared from the readily available tetrahydrofuran (I) and tetrahydropyran (II) respectively:



3. By the addition of liquid bromine to a warm mixture of the alcohol and purified red phosphorus:

$$2P + 10ROH + 5Br_2 \longrightarrow 2H_3PO_4 + 10RBr + 2H_2O$$

The reaction is of general application: with primary alcohols (*n*-propyl to *n*-hexadecyl) the yields are over 90 per cent. of the theoretical, but with secondary alcohols the yields are 50–80 per cent.; in the latter case a small quantity of high boiling point by-product is also formed which can, however, be readily removed by fractional distillation. The reaction is conveniently carried out in a special all-glass apparatus.

4. By the action of phosphorus tribromide upon the alcohol:

$$3ROH + PBr_3 \longrightarrow 3RBr + H_3PO_3$$

This mode of preparation must be regarded as superseded by 3, which is far more economical.

IODIDES

Three general methods are available for the preparation of iodides from alcohols:—

1. By the slow distillation of the alcohol with constant boiling point (57 per cent.) hydriodic acid, for example:

$$\underset{\textit{iso}\text{-Butyl alcohol}}{(CH_3)_2CHCH_2OH} + HI \longrightarrow \underset{\textit{iso}\text{-Butyl iodide}}{(CH_3)_2CHCH_2I} + H_2O$$

2. By the addition of a hot solution of iodine in the alcohol to a boiling (or hot) suspension of purified red phosphorus in the alcohol:

$$2P + 10ROH + 5I_2 \longrightarrow 2H_3PO_4 + 10RI + 2H_2O$$

The reaction is of general application; the yields of primary alcohols approach the theoretical values, and for secondary alcohols are 85–95 per cent. The process is best carried out with the aid of a special apparatus.

3. By the interaction of alcohols or glycols with potassium iodide and 95 per cent. orthophosphoric acid (the last named is prepared from the commercial 85 per cent. acid and phosphoric oxide), for example:

$$\underset{\text{1 : 4-Butanediol}}{HO(CH_2)_4OH} + 2KI + 2H_3PO_4 \longrightarrow \underset{\text{1 : 4-Diiodobutane}}{I(CH_2)_4I} + 2KH_2PO_4 + 2H_2O$$

1 : 4-Diiodobutane and 1 : 5-diiodopentane are conveniently obtained from tetrahydrofuran and tetrahydropyran respectively (compare corresponding bromides above).

FLUORIDES

Alkyl fluorides may be prepared in moderate yield by interaction of an alkyl bromide with anhydrous potassium fluoride in the presence of dry ethylene glycol as a solvent for the inorganic fluoride, for example:

$$\underset{n\text{-Hexyl bromide}}{CH_3(CH_2)_4CH_2Br} + KF \xrightarrow[\text{glycol}]{\text{Ethylene}} \underset{n\text{-Hexyl fluoride}}{CH_3(CH_2)_4CH_2F} + KBr$$

A little olefine accompanies the alkyl fluoride produced and is readily removed by treatment with KBr—Br_2 solution.

III,28. *n*-BUTYL CHLORIDE (*$ZnCl_2$–HCl Method*)

Place 40 ml. (47·5 g.) of concentrated hydrochloric acid in a 200 ml. distilling flask and add 68 g. of anhydrous zinc chloride (*e.g.*, sticks). Fit

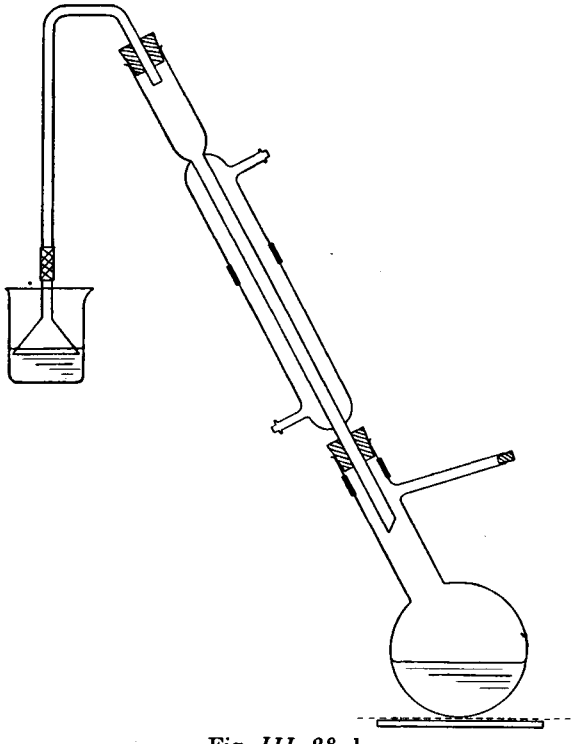


Fig. *III, 28,* 1.

a reflux condenser into the mouth of the distilling flask, and attach to the top of the condenser a tube connected to an inverted funnel dipping just

below the surface of about 250 ml. of water in a beaker (Fig. *III*, *28*, 1).* Close the side arm of the distilling flask with a small cork or by means of a short length of rubber tubing and glass rod plug. Introduce 18·5 g. (23 ml.) of *n*-butyl alcohol into the distilling flask and reflux the contents gently on a wire gauze or in an air bath for 2 hours; the flask must be inclined during the refluxing period as shown in the figure. After cooling, arrange the flask for distillation, and collect the liquid boiling below 115° (1). Separate the upper layer of the distillate, mix it with an equal volume of concentrated sulphuric acid (2), transfer the mixture to a 200 ml. distilling flask, close the side arm and connect the neck with a reflux condenser as before. Reflux gently for 15–30 minutes, and then distil the chloride from the acid; it will pass over at 76–79°. Wash the distillate successively with 25 ml. of water, 10 ml. of 5 per cent. sodium hydroxide solution and 25 ml. of water; dry over 1–2 g. of anhydrous calcium chloride, filter, and distil from a small distilling flask. Collect the *n*-butyl chloride at 75–78°. The yield is 15–16 g.

Notes.

(1) After the butyl chloride fraction has been collected, change the receiver and continue the distillation until the zinc chloride commences to crystallise. Allow to cool and stopper the flask. The anhydrous zinc chloride thus obtained may be used in another preparation and recovered repeatedly. This results in considerable economy when the preparation is conducted by a large number of students.

(2) The sulphuric acid treatment removes high-boiling impurities which are not easily separated by distillation.

COGNATE PREPARATION

***n*-Amyl Chloride.** Use 40 ml. of concentrated hydrochloric acid, 68 g. of anhydrous zinc chloride and 21·5 g. (26·5 ml.) of *n*-amyl alcohol. Distil until the temperature rises to 130°, etc. Collect the fraction, b.p. 104–107°. The yield is 19 g.

III,29. *sec.*-BUTYL CHLORIDE (*$ZnCl_2$–HCl Method*)

Reflux a mixture of 68 g. of anhydrous zinc chloride (*e.g.*, sticks), 40 ml. (47·5 g.) of concentrated hydrochloric acid and 18·5 g. (23 ml.) of *sec.*-butyl alcohol (b.p. 99–100°) in the apparatus of Fig. *III*, *28*, 1 for 2 hours. Distil off the crude chloride until the temperature rises to 100°. Separate the upper layer of the distillate, wash it successively with water, 5 per cent. sodium hydroxide solution and water; dry with anhydrous calcium chloride. Distil through a short column or from a Claisen flask with fractionating side arm, and collect the fraction of b.p. 67–70°; some high boiling point material remains in the flask. Redistil and collect the pure *sec.*-butyl chloride at 67–69°. The yield is 15 g.

COGNATE PREPARATIONS †

***iso*-Amyl Chloride.** Use 68 g. of anhydrous zinc chloride, 40 ml. of concentrated hydrochloric acid and 22 g. (27 ml.) of *iso*-amyl alcohol (b.p. 131°). Collect the *iso*-amyl chloride at 98–100°.

* Alternatively, the tube from the top of the condenser may be supported just *above* the surface of water in a filter flask (as in Fig. *II*, *13*, 8).

† The yields are about 80 per cent. of the theoretical values.

2-Chloropentane. Use the quantities given in the previous preparation, but substitute 22 g. (27 ml.) of methyl *n*-propyl carbinol (b.p. 118·5°) for *iso*-amyl alcohol. Collect the 2-chloropentane at 96–98°.

3-Chloropentane. Use the quantities as for *iso*-amyl chloride, but with 22 g. (27 ml.) of diethyl carbinol (b.p. 115·5–116°). Collect the 3-chloropentane at 95–97°.

III,30. *iso*-BUTYL CHLORIDE (*$SOCl_2$–Pyridine Method*)

Fit a 500 ml. round-bottomed flask with a dropping funnel and a double surface condenser; alternatively, the flask may be provided with a two-way addition tube (Fig. *II*, *13*, 9) and the dropping funnel and condenser inserted into the latter. Place 37 g. (46 ml.) of *iso*-butyl alcohol (b.p. 106–108°) and 40 g. (41 ml.) of pure pyridine in the flask and 119 g. (73 ml.) of redistilled thionyl chloride in the dropping funnel. Insert a cotton wool or calcium chloride guard tube into the mouth of the funnel. Introduce the thionyl chloride during 3–4 hours; a white solid separates, which partially dissolves as the reaction proceeds. Reflux for 45 minutes: the solid will dissolve completely. Allow to cool and remove the upper layer (1). Wash the latter cautiously with water, 5 per cent. sodium hydroxide solution, and twice with water; dry with anhydrous calcium chloride. Distil from a Claisen flask with a fractionating side arm. Collect the *iso*-butyl chloride at 68–69°. The yield is 26 g.

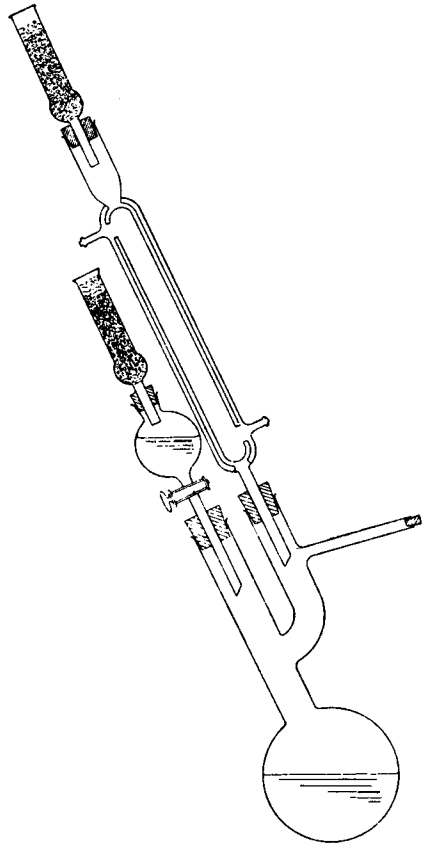


Fig. *III*, *31*, 1.

Note.

(1) The lower pyridine layer contains most of the excess of thionyl chloride; it may be recovered by distillation through an efficient fractionating column.

III,31. *n*-HEXYL CHLORIDE (*$SOCl_2$ Method*)

Use the apparatus shown in Fig. *III*, *31*, 1. Place 179 g. (109·5 ml.) of redistilled thionyl chloride in the 250 ml. Claisen flask and 51 g. (62·5 ml.) of *n*-hexyl alcohol, b.p. 156–158°, in the separatory funnel. Add the *n*-hexyl alcohol during 2 hours; there is a slight evolution of heat, sulphur dioxide is evolved (hence carry out the preparation in the fume cupboard), and the liquid darkens considerably. When all the alcohol has been added, reflux the mixture for 2 hours. Rearrange the apparatus for distillation, and distil slowly; the excess of thionyl

chloride passes over below 80°, followed by a small fraction up to 120°, and finally the crude *n*-hexyl chloride at 132–134°. Wash the last-named successively with water, 10 per cent. sodium carbonate solution, and twice with water. Dry with anhydrous calcium chloride and distil from a 50 ml. Claisen flask with fractionating side arm. Pure *n*-hexyl chloride passes over at 133–134°. The yield is 36 g.

COGNATE PREPARATIONS

***n*-Heptyl Chloride.** From 58 g. (70·5 ml.) of *n*-heptyl alcohol (b.p. 175–177°) (Section **III,16**) and 179 g. (109·5 ml.) of redistilled thionyl chloride; refluxing period, 4 hours. The yield of *n*-heptyl chloride, b.p. 159–160°, is 52 g.

***n*-Dodecyl Chloride.** From 46·5 g. of *n*-dodecyl alcohol (lauryl alcohol), m.p. 24°, and 119 g. (73 ml.) of redistilled thionyl chloride; refluxing period, 6 hours. The crude chloride passes over at 252–257°, mainly at 255–257°. Upon purification as above, 35 g. of *n*-dodecyl chloride, b.p. 116·5°/5 mm., are obtained.

1 : 4-Dichlorobutane. Place 22·5 g. of redistilled 1 : 4-butanediol and 3 ml. of dry pyridine in a 500 ml. three-necked flask fitted with a reflux condenser, mechanical stirrer and thermometer. Immerse the flask in an ice bath. Add 116 g. (71 ml.) of redistilled thionyl chloride dropwise from a dropping funnel (inserted into the top of the condenser) to the vigorously stirred mixture at such a rate that the temperature remains at 5–10°. When the addition is complete, remove the ice bath, keep the mixture overnight, and then reflux for 3 hours. Cool, add ice water cautiously and extract with ether. Wash the ethereal extract successively with 10 per cent sodium bicarbonate solution and water, dry with anhydrous magnesium sulphate and distil. Collect the 1 : 4-dichlorobutane at 55·5–56·5°/14 mm.; the yield is 35 g. The b.p. under atmospheric pressure is 154–155°.

III,32. *cyclo*HEXYL CHLORIDE (*HCl–$CaCl_2$ Method*)

In a 1500 ml. round-bottomed flask, carrying a reflux condenser, place 100 g. of pure *cyclo*hexanol, 250 ml. of concentrated hydrochloric acid and 80 g. of anhydrous calcium chloride: heat the mixture on a boiling water bath for 10 hours with occasional shaking (1). Some hydrogen chloride is evolved, consequently the preparation should be conducted in the fume cupboard. Separate the upper layer from the cold reaction product, wash it successively with saturated salt solution, saturated sodium bicarbonate solution, saturated salt solution, and dry the crude *cyclo*hexyl chloride with excess of anhydrous calcium chloride for at least 24 hours. Distil from a 150 ml. Claisen flask with fractionating side arm, and collect the pure product at 141·5–142·5°. The yield is 90 g.

Note.

(1) The refluxing period may be reduced to 6 hours and the yield improved slightly by mechanical stirring; a three-necked flask should be used.

An alternative method of conducting the preparation consists in treating 100 g. of *cyclo*hexanol with 250 ml. of concentrated hydrochloric acid, refluxing slowly whilst a stream of hydrogen chloride gas is passed into the mechanically stirred

mixture for 3 hours. (The apparatus required is similar to that described for a Clemmensen reduction in Section III, 9). The *cyclo*hexyl chloride, b.p. 141–143°, is isolated as above; the yield is 80 g.

COGNATE PREPARATION

***cyclo*Pentyl Chloride.** Use 43 g. of *cyclo*pentanol (Section **III,21**), 125 ml. of concentrated hydrochloric acid and 50 g. of anhydrous calcium chloride. Thirty grams of *cyclo*pentyl chloride, b.p. 113–115°, are obtained.

III,33. *tert.*-BUTYL CHLORIDE (*HCl Method*)

In a 250 ml. separatory funnel place 25 g. of anhydrous *tert.*-butyl alcohol (b.p. 82–83°, m.p. 25°) (1) and 85 ml. of concentrated hydrochloric acid (2) and shake the mixture from time to time during 20 minutes. After each shaking, loosen the stopper to relieve any internal pressure. Allow the mixture to stand for a few minutes until the layers have separated sharply; draw off and discard the lower acid layer. Wash the halide with 20 ml. of 5 per cent. sodium bicarbonate solution and then with 20 ml. of water. Dry the preparation with 5 g. of anhydrous calcium chloride or anhydrous calcium sulphate. Decant the dried liquid through a funnel supporting a fluted filter paper or a small plug of cotton wool into a 100 ml. distilling flask, add 2–3 chips of porous porcelain, and distil. Collect the fraction boiling at 49–51°. The yield of *tert.*-butyl chloride is 28 g.

Notes.

(1) The commercial constant boiling point alcohol, b.p. 80°/760 mm., containing 88 per cent. of *tert.*-butyl alcohol, may be used; 28·5 g. are required.

(2) The addition of 10 g. of anhydrous calcium chloride tends to concentrate the acid and assists the separation of the chloride; the yield is slightly improved.

COGNATE PREPARATIONS

***tert.*-Amyl Chloride.** Use 22 g. (27 ml.) of *tert.*-amyl alcohol (dimethyl-ethyl carbinol), b.p. 101–101·5°, and 65 ml. of concentrated hydrochloric acid. Distil the chloride twice from a Claisen flask with fractionating side arm or through a short column. Collect the *tert.*-amyl chloride at 83–85°; the yield is 18 g.

Allyl Chloride. Comparatively poor yields are obtained by the zinc chloride - hydrochloric acid method, but the following procedure, which employs cuprous chloride as a catalyst, gives a yield of over 90 per cent. Place 100 ml. of allyl alcohol (Section **III,140**), 150 ml. of concentrated hydrochloric acid and 2 g. of freshly prepared cuprous chloride (Section **II,50,*1***; one tenth scale) in a 750 ml. round-bottomed flask equipped with a reflux condenser. Cool the flask in ice and add 50 ml. of concentrated sulphuric acid dropwise through the condenser with frequent shaking of the flask. A little hydrogen chloride may be evolved towards the end of the reaction. Allow the turbid liquid to stand for 30 minutes in order to complete the separation of the allyl chloride. Remove the upper layer, wash it with twice its volume of water, and dry over anhydrous calcium chloride. Distil; the allyl chloride passes over at 46–47°.

III,34. *iso*PROPYL BROMIDE (*HBr Method*)

Mix 40 g. (51 ml.) of *iso*propyl alcohol with 460 g. (310 ml.) of constant boiling point hydrobromic acid in a 500 ml. distilling flask, attach a double surface (or long Liebig) condenser and distil slowly (1–2 drops per second) until about half of the liquid has passed over. Separate the lower alkyl bromide layer (70 g.), and redistil the aqueous layer when a further 7 g. of the crude bromide will be obtained (1). Shake the crude bromide in a separatory funnel successively with an equal volume of concentrated hydrochloric acid (2), water, 5 per cent. sodium bicarbonate solution, and water, and dry with anhydrous calcium chloride. Distil from a 100 ml. flask; the *iso*propyl bromide passes over constantly at 59°. The yield is 66 g.

Notes.

(1) The residue in the flask may be mixed with the aqueous layer of the first distillate, 40 g. of *iso*propyl alcohol added, and the slow distillation repeated. The yield of crude *iso*propyl bromide in the second distillation is only slightly less than that obtained in the original preparation. Subsequently most of the residual hydrobromic acid may be recovered by distillation as the constant boiling point acid (126°).

(2) The hydrochloric acid washing removes any unchanged alcohol which may be present.

Cognate Preparations

***n*-Propyl Bromide.** The quantities and experimental details are similar to those given above. B.p. 71°.

***cyclo*Hexyl Bromide.** Use 50 g. of *cyclo*hexanol and 260 g. (176 ml.) of 48 per cent. hydrobromic acid in a 500 ml. distilling flask, and distil *all* the mixture slowly (6 hours). Add a little water to the distillate, separate the lower layer of crude bromide, and purify as for *iso*propyl bromide. Collect the *cyclo*hexyl bromide at 163–165° (60 g.).

***cyclo*Pentyl Bromide.** Use 43 g. of *cyclo*pentanol (Section **III,21**) and 260 g. (176 ml.) of 48 per cent. hydrobromic acid. Collect the *cyclo*pentyl bromide at 135–137° (55 g.).

III,35. *n*-BUTYL BROMIDE (*HBr–H_2SO_4 Method*)

To 250 g. of 48 per cent. hydrobromic acid contained in a 500 ml. round-bottomed flask add 75 g. (41 ml.) of concentrated sulphuric acid in portions with shaking (1); some hydrogen bromide may be evolved. Add 88 g. (110 ml.) of *n*-butyl alcohol, followed by 60 g. (32·5 ml.) of concentrated sulphuric acid in several portions with shaking, and finally a few chips of broken glass. Attach a reflux condenser to the flask and reflux the mixture gently on a wire gauze for 2–3 hours; during this period the formation of *n*-butyl bromide is almost complete and a layer separates above the acid. If the preparation is carried out in the open laboratory, fit an absorption device (compare Fig. *II*, *13*, 8 and Fig. *III*, *28*, 1) to the top of the condenser in order to absorb any hydrogen bromide and sulphur dioxide which may be evolved. Allow the contents of the flask to cool, remove the condenser and set it for downward distillation; connect the condenser to the flask by means of a wide (7–8 mm. diameter bent glass tube. Distil the mixture until no more oily drops of *n*-butyl

bromide pass over (30–40 minutes). Transfer the distillate to a separatory funnel and remove the halide which forms the lower layer. Wash it successively with water, an equal volume of concentrated hydrochloric acid (2), water, 5 per cent. sodium bicarbonate or sodium carbonate solution, and water. Separate the water as completely as possible and dry with 2–3 g. of anhydrous calcium chloride or anhydrous magnesium sulphate; the desiccant should be left in contact with the bromide for at least 30 minutes and shaken occasionally. Filter the dried product through a small funnel supporting a fluted filter paper or small cotton wool plug into a 200 ml. distilling flask, add a few chips of porous porcelain and distil either from an air bath (Fig. *II*, *5*, 3) or on an asbestos-centred wire gauze. Collect the portion boiling at 100–103°. The yield is 155 g.

Notes.

(1) This acid mixture may be prepared (compare Section **II,49**, *1*) by placing 120 g. (37·5 ml.) of bromine and 130 g. of crushed ice in a 500 ml. flask, cooling the latter in ice, and passing sulphur dioxide (from a siphon of the liquefied gas) into the bromine layer at such a rate that the gas is completely absorbed. The flask is shaken occasionally, and the flow of gas is stopped immediately the red colour due to free bromine has disappeared; the mixture will then have a yellow colour. The resulting acid mixture is equivalent to 250 g. of 48 per cent. hydrobromic acid to which 75 g. of concentrated sulphuric acid have been added; it need not be distilled for the preparation of *n*-butyl bromide.

Owing to the comparatively negligible difference in the cost of bromine and the equivalent quantity of constant boiling point hydrobromic acid, there is little to be gained—apart from the instructional value—in preparing the hydrobromic acid from bromine in the preparation of alkyl bromides.

CAUTION. Bromine must be handled with great care and in the fume cupboard. The liquid produces painful burns and the vapour is unpleasant. Bromine burns should be treated immediately with a liberal quantity of glycerine. If the vapour is inhaled, relief may be obtained by soaking a handkerchief in alcohol and holding it near the nose.

(2) The crude bromide contains a little unchanged alcohol and is said to contain some *n*-butyl ether (b.p. 141°). The former is removed by washing with concentrated hydrochloric acid and this purification process is satisfactory for most purposes. Both the alcohol and the ether are removed by washing with 11–12 ml. of concentrated sulphuric acid; the butyl bromide is not affected by this reagent.

Cognate Preparations

sec.-Butyl Bromide. The quantities required are as for *n*-butyl bromide but with *sec.*-butyl alcohol (b.p. 99–100°) replacing the *n*-butyl alcohol. Two to three washings with concentrated hydrochloric acid are necessary, *i.e.*, until the volume of the acid layer remains unchanged on shaking with the halide. The yield of *sec.*-butyl bromide, b.p. 90·5–92·5°, is 150 g.

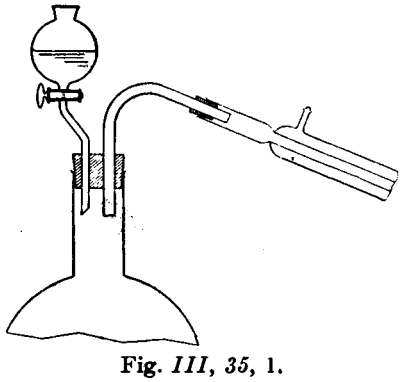


Fig. *III*, *35*, 1.

Ethyl Bromide. Fit a 1-litre round-bottomed flask with a two-holed cork carrying a separatory funnel and a wide (6–8 mm.) bent tube connected to a long efficient condenser set for downward distillation (Fig. *III*,*35*, 1); alternatively, a two-way addition tube (Fig. *II*, *1*, 8)

may be used and the necessary modifications made. Place 415 g. (281 ml.) of 48 per cent. hydrobromic acid in the flask and add 120 g. (65 ml.) of concentrated sulphuric acid in portions, with shaking. When cold, add 100 g. (145 ml.) of rectified spirit (95 per cent. ethyl alcohol) and assemble the apparatus completely. Connect the end of the condenser to an adapter dipping into water contained in a 500 ml. flask; the latter is surrounded by ice. Introduce 200 g. (109 ml.) of concentrated sulphuric acid slowly from the tap funnel and distil the mixture slowly. Wash the crude ethyl bromide with an equal volume of concentrated hydrochloric acid, then with water, a little 5 per cent. sodium bicarbonate solution, and finally with water. Dry with anhydrous calcium chloride. Distil the dry bromide, to which a few chips of porous porcelain have been added, from a water bath and collect the ethyl bromide, b.p. 38–39°, in a receiver cooled in ice. The yield is 205 g.

***n*-Propyl Bromide.** Use the procedure described for *Ethyl Bromide* substituting the following quantities of reagents: 500 g. (338 ml.) of 48 per cent. hydrobromic acid and 150 g. (82 ml.) of concentrated sulphuric acid; 144 g. (179 ml.) of *n*-propyl alcohol (b.p. 96·5–97·5°). Introduce 120 g. (65 ml.) of concentrated sulphuric acid gradually through the separatory funnel and distil slowly over a wire gauze until no more oily drops pass over. The yield of *n*-propyl bromide, b.p. 70–72°, is 255 g.

***n*-Amyl Bromide.** Use 210 g. (142 ml.) of 48 per cent. hydrobromic acid, 60 g. (33 ml.) of concentrated sulphuric acid, followed by 88 g. (108 ml.) of *n*-amyl alcohol (b.p. 135–136°) and 10 g. (5·5 ml.) of concentrated sulphuric acid. Distil the product through a short fractionating column, and collect the *n*-amyl bromide at 127–130° (135 g.).

***iso*-Amyl Bromide.** Proceed as for n-*Amyl Bromide*, but use 88 g. (109 ml.) of synthetic (Sharples) *iso*amyl alcohol, b.p. 129·5–131°. Distil the purified product through a fractionating column and collect the *iso*amyl bromide at 117–120° (125 g.).

2-Bromopentane. Proceed as for n-*Amyl Bromide*, but use 88 g. (108 ml.) of methyl *n*-propyl carbinol (2-pentanol), b.p. 118·5°. During the washing with concentrated hydrochloric acid, difficulty may be experienced in separating the acid layer; this is overcome by adding a little water to decrease the density of the acid. Distil the purified product through a fractionating column; some amylene passes over first, followed by the 2-bromopentane at 115–118° (120 g.).

3-Bromopentane. Proceed as for n-*Amyl Bromide*, but use 88 g. (108 ml.) of diethyl carbinol (3-pentanol), b.p. 115·5–116°. The experimental observations are similar to those given for *2-Bromopentane*. Collect the 3-bromopentane at 116–119° (120 g.).

Trimethylene Dibromide. In a 1-litre round-bottomed flask place 500 g. (338 ml.) of 48 per cent. hydrobromic acid and add 150 g. (82 ml.) of concentrated sulphuric acid in portions, with shaking. Then add 91 g. of trimethylene glycol (b.p. 210–215°), followed by 240 g. (130·5 ml.) of concentrated sulphuric acid slowly and with shaking. Attach a reflux condenser to the flask and reflux the mixture for 3–4 hours. Arrange for downward distillation and distil, using a wire gauze, until no more oily drops pass over (30–40 minutes). Purify the trimethylene dibromide

as detailed for n-*Butyl Bromide* above. About 220 g. of the pure dibromide b.p. 162–165°, are obtained.

Allyl Bromide. Introduce into a 1-litre three-necked flask 250 g. (169 ml.) of 48 per cent. hydrobromic acid and then 75 g. (40·5 ml.) of concentrated sulphuric acid in portions, with shaking ; finally add 58 g. (68 ml.) of pure allyl alcohol (Section **III,140**). Fit the flask with a separatory funnel, a mechanical stirrer and an efficient condenser (preferably of the double surface type) set for downward distillation ; connect the flask to the condenser by a wide (6–8 mm.) bent tube. Place 75 g. (40·5 ml.) of concentrated sulphuric acid in the separatory funnel, set the stirrer in motion, and allow the acid to flow slowly into the warm solution. The allyl bromide will distil over (< 30 minutes). Wash the distillate with 5 per cent. sodium carbonate solution, followed by water, dry over anhydrous calcium chloride, and distil from a Claisen flask with a fractionating side arm or through a short column. The yield of allyl bromide, b.p. 69–72°, is 112 g. There is a small high-boiling fraction containing propylene dibromide.

1 : 4-Dibromobutane (*from 1 : 4-butanediol*). In a 500 ml. three-necked flask fitted with a stirrer, reflux condenser and dropping funnel, place 154 g. (105 ml.) of 48 per cent. hydrobromic acid. Cool the flask in an ice bath. Add slowly, with stirring, 130 g. (71 ml.) of concentrated sulphuric acid. To the resulting ice-cold solution add 30 g. of redistilled 1 : 4-butanediol dropwise. Leave the reaction mixture to stand for 24 hours ; heat for 3 hours on a steam bath. The reaction mixture separates into two layers. Separate the lower layer, wash it successively with water, 10 per cent. sodium carbonate solution and water, and then dry with anhydrous magnesium sulphate. Distil and collect the 1 : 4-dibromobutane at 83–84°/12 mm. The yield is 55 g.

1 : 4-Dibromobutane (*from tetrahydrofuran*). Placea mixture of 250 g. (170 ml.) of 48 per cent. hydrobromic acid and 75 g. (41 ml.) of concentrated sulphuric acid, prepared as in *Note 1*, in a 500 ml. round-bottomed flask, add 18·1 g. (20·5 ml.) of redistilled tetrahydrofuran (b.p. 65–66°), attach a reflux condenser and reflux gently for 3 hours. Separate the lower layer of dibromide and purify as in the previous preparation. The yield of 1 : 4-dibromobutane, b.p. 83–84°/12 mm., is 40 g.

1 : 5-Dibromopentane (*from 1 : 5-pentanediol*). Proceed as for 1 : 4-dibromobutane but use 35 g. of redistilled commercial 1 : 5-pentanediol. The yield of 1 : 5-dibromopentane, b.p. 99°/13 mm., is 39 g.

1 : 5-Dibromopentane (*from tetrahydropyran*). Proceed as for 1 : 4-dibromobutane (from tetrahydrofuran) but use 21·5 g. (24·4 ml.) of redistilled tetrahydropyran (b.p. 86·5–87·5°). The yield of 1 : 5-dibromopentane, b.p. 99°/13 mm. is 46 g.

III,36. *n*-BUTYL BROMIDE (*KBr–H_2SO_4 Method*)

Dissolve 30 g. of potassium bromide in 50 ml. of water in a 350 ml. conical flask ; *gentle* warming may be necessary. Cool the flask with running water from the tap so that the contents attain room temperature. Add 25 ml. of concentrated sulphuric acid slowly and with constant rotation of the flask to ensure thorough mixing ; cool under the tap from

time to time and do not allow the temperature to rise above 40 during the addition of the acid. Cool to about 15° (under a running water tap), and filter off the precipitated potassium bisulphate using a Buchner funnel and a dry filter flask. Press the precipitate on the filter firmly with the aid of the wide end of a large glass stopper; it is unnecessary to wash the solid with water. Transfer the filtrate to a 250 ml. round-bottomed flask and add 11 g. (14 ml.) of *n*-butyl alcohol. Introduce 28 g. (15 ml.) of concentrated sulphuric acid slowly and with constant rotation of the contents of the flask; if this operation is carried out carefully, very little hydrogen bromide will be evolved. Add a few small chips of porous porcelain, attach a reflux condenser to the flask, and reflux for 3–4 hours. Remove the reflux condenser, attach a bent tube to the mouth of the flask and set the condenser for downward distillation (Fig. *II*, *13*, 3, but without the thermometer). Distil slowly on a wire gauze until no more oily drops are visible in the condenser. Transfer the distillate to a separatory funnel, remove the lower layer of crude butyl bromide, and discard the upper aqueous layer. Wash the crude halide in the separatory funnel successively with 10–15 ml. of concentrated hydrochloric acid (this will remove any unchanged *n*-butyl alcohol), 25 ml. of water, 20 ml. of *ca.* 10 per cent. sodium carbonate solution and finally with 25 ml. of water: the bromide layer is the lower layer in all cases. Dry the product with 2–3 g. of anhydrous calcium chloride; it is best to leave the halide in contact with the desiccant for about 30 minutes and shake occasionally after an initial shaking of 2–3 minutes. Filter the dried product through a fluted filter paper or a small cotton wool plug supported in a funnel into a dry 50 ml. distilling flask, and distil on a wire gauze or from an air bath (Fig. *II*, *5*, 3). Collect the fraction, b.p. 100–103°. The yield of *n*-butyl bromide is 18–19 g.

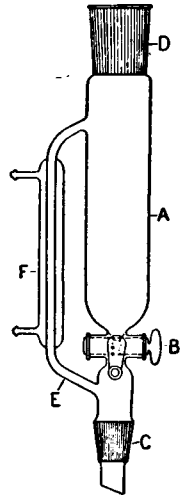


Fig. *III*, *37*, 1.

III,37. *n*-BUTYL BROMIDE (*Red P - Br_2 Method*)

Owing to the corrosive action of bromine upon corks and rubber stoppers, ground glass joints are recommended in this preparation. The apparatus, depicted in Fig. *III*, *37*, 1,* is particularly convenient for the preparation of bromides from alcohols. A double surface condenser is fitted into *D* and a round-bottomed flask is fitted on to the ground glass joint at *C*; *B* is a "three-way" stopcock † which permits the removal of the contents of *A* without disconnecting the apparatus. For preparations of moderate size, *A* has a capacity of 60 or 100 ml. and a 250 or 500 ml. flask is attached at *C*.

Place 92·5 g. (114·5 ml.) of *n*-butyl alcohol and 8·55 g. of purified red phosphorus (Section **II,50**,*5*) in a 500 ml. round-bottomed flask (attached at *C*) and 100 g. (32 ml.) of bromine in *A*. Pass a stream of cold water through the condenser *F* and through the double surface condenser fitted at *D*; the condenser *F* prevents the volatilisation of the alcohol from the

* Obtainable from A. Gallenkamp and Co. Ltd.

† For a side view of the "three-way" stopcock *B*, see Fig. *III*, *40*, 2, *b*.

flask into the bromine in *A* (for precautions in the use of bromine, see Section **III,35,** *Note 1*), and also serves to condense unreacted bromine from the flask. Heat the flask gently and introduce the liquid bromine, by suitably turning the stopcock *B*, into the phosphorus - alcohol mixture at such a rate that it appears to react almost completely so that there is little bromine vapour above the surface of the reaction mixture and the reaction is under control. When all the bromine has been added, reflux the mixture gently for 15–30 minutes; during this process the water should be emptied from *F* and tap *B* turned so that it connects the flask and the reservoir *A*. Close the tap *B* and collect most (about 90 per cent. of the butyl bromide in *A* (1); remove the crude bromide into a 350 ml. flask by suitably rotating the stopcock *B*. Now add 50 ml. of water through the condenser and reservoir *A* into the flask and continue the distillation; the residual bromide in the flask, together with water, will collect in *A* and is transferred, as before, to the flask containing the main yield of halide. When the apparatus is cold, separate the flask and the condenser at the ground joints; "sticking" is thus avoided. Pour the crude bromide into a separatory funnel, discard the upper aqueous layer, and wash successively with water, an approximately equal volume of concentrated hydrochloric acid, water, 10 per cent. sodium carbonate solution, water, and then dry it with anhydrous calcium chloride. Distil from a flask of appropriate size. The *n*-butyl bromide (154 g.) passes over at 100–103°.

Note.

(1) It is not advisable to distil the mixture almost to dryness, since, towards the end of the distillation, the inflammable butylene is formed. Butylene formation is avoided by conducting the distillation in two stages as described.

COGNATE PREPARATIONS *

***n*-Propyl Bromide.** Use 90 g. (112 ml.) of *n*-propyl alcohol, 12·40 g. of purified red phosphorus and 121 g. (39 ml.) of bromine. B.p. 71–72·5°.

***iso*-Butyl Bromide.** Use 92·5 g. (115·5 ml.) of *iso*-butyl alcohol, 8·55 g. of purified red phosphorus and 105 g. (34 ml.) of bromine. B.p. 91–94°.

***n*-Hexyl Bromide.** Use 152·5 g. (186·5 ml.) of *n*-hexyl alcohol, 8·55 g. of purified red phosphorus and 110 g. (35·5 ml.) of bromine.† B.p. 154–156°.

***n*-Octyl Bromide.** Use 81 g. (98·5 ml.) of *n*-octyl alcohol (b.p. 193–194°), 5·18 g. of purified red phosphorus and 55 g. (18 ml.) of bromine. B.p. 198–201°.

***n*-Dodecyl Bromide.** Use 116 g. of *n*-dodecyl alcohol (lauryl alcohol), m.p. 24°, 5·18 g. of purified red phosphorus and 55 g. (18 ml.) of bromine. Allow the mixture to cool after all the bromine has been introduced. Dilute with water, add ether, filter off the excess of phosphorus, separate the ethereal solution of the bromide, wash it with water and dry over anhydrous potassium carbonate. Remove the ether on a water bath, and distil the residue under reduced pressure. B.p. 149–151°/18 mm.

* Unless otherwise stated, the yields exceed 90 per cent. of the theoretical.

† The slight excess of bromine over that theoretically equivalent to the alcohol in the preparation of high boiling point bromides ensures the absence of unchanged alcohol in the product; any excess of bromine may be removed by the addition of a little sodium bisulphite.

***n*-Tetradecyl Bromide.** Use 107 g. of *n*-tetradecyl alcohol (m.p. 38°), 3·41 g. of purified red phosphorus and 44 g. (14·5 ml.) of bromine. Heat the alcohol - phosphorus mixture to about 250° and add the bromine slowly. Treat the cold reaction mixture with ether, filter off the excess of red phosphorus, and proceed as under n-*Dodecyl Bromide*. B.p. 178·5–179·5°/20 mm., m.p. 5°.

Alternatively, place the mixture of alcohol and red phosphorus in a 500 ml. three-necked flask fitted with a mechanical stirrer, dropping funnel and double surface condenser. Heat the phosphorus - alcohol mixture to about 250°, and add the bromine whilst stirring vigorously. Work up the reaction product as above.

***n*-Hexadecyl Bromide.** Use 121 g. of *n*-hexadecyl alcohol (cetyl alcohol), m.p. 48°, 3·41 g. of purified red phosphorus and 44 g. (14·5 ml.) of bromine. Heat the alcohol - phosphorus mixture to about 250° and add the bromine slowly. Either the apparatus of Fig. *III*, *37*, 1 or a 500 ml. three-necked flask may be used. Isolate the cetyl bromide as described for n-*Tetradecyl Bromide*; filter off the excess of phosphorus at 16–20°. B.p. 202–203°/21 mm.; m.p. 14°.

β-Phenylethyl Bromide. Use 152·5 g. (148 ml.) of β-phenylethyl alcohol (Section **IV,204**), b.p. 216·5–217°, 10·35 g. of purified red phosphorus and 110 g. (35·5 ml.) of bromine. Isolate the β-phenylethyl bromide as detailed for n-*Dodecyl Bromide*. B.p. 98°/12 mm.

1 : 4-Dibromobutane (*from 1 : 4-butanediol*). Use 45 g. of redistilled 1 : 4-butanediol, 6·84 g. of purified red phosphorus and 80 g. (26 ml.) of bromine. Heat the glycol - phosphorus mixture to 100–150° and add the bromine slowly: use the apparatus of Fig. *III*, *37*, 1. Continue heating at 100–150° for 1 hour after all the bromine has been introduced. Allow to cool, dilute with water, add 100 ml. of ether, and remove the excess of red phosphorus by filtration. Separate the ethereal solution of the dibromide, wash it successively with 10 per cent. sodium thiosulphate solution and water, then dry over anhydrous potassium carbonate. Remove the ether on a water bath and distil the residue under diminished pressure. Collect the 1 : 4-dibromobutane at 83–84°/12 mm.; the yield is 73 g.

1 : 6-Dibromohexane. Proceed as for 1 : 4-dibromobutane but use 58 g. of 1 : 6-hexanediol. The yield of 1 : 6-dibromohexane, b.p. 114–115°/12 mm. is 85 g.

1 : 4-Dibromobutane (*from tetrahydrofuran*). Place 18·1 g. (20·5 ml.) of redistilled tetrahydrofuran (b.p. 65–66°), 3·42 g. of purified red phosphorus and 4·5 g. of water in the flask attached to the apparatus of Fig. *III*, *37*, 1. Heat the mixture gently and add 40 g. (13 ml.) of bromine at such a rate that there is little bromine vapour above the surface of the reaction mixture. Heat at 100–150° for 45–60 minutes after all the bromine has been introduced. Work up as for the 1 : 4-butanediol preparation. The yield of 1 : 4-dibromobutane, b.p. 83–84°/12 mm. is 42 g.

1 : 5-Dibromopentane (*from tetrahydropyran*). Proceed as in the previous preparation but replace the tetrahydrofuran by 21·5 g. (24·4 ml.) of redistilled tetrahydropyran (b.p. 86·5–87·5°). The yield of 1 : 5-dibromopentane, b.p. 99°/13 mm., is 43 g.

III,38. 1 : 4-DIIODOBUTANE (*KI - H_3PO_4 Method*)

In a 500 ml. three-necked flask, equipped with a thermometer, a sealed Hershberg stirrer and a reflux condenser, place 32·5 g. of phosphoric oxide and add 115·5 g. (67·5 ml.) of 85 per cent. orthophosphoric acid (1). When the stirred mixture has cooled to room temperature, introduce 166 g. of potassium iodide and 22·5 g. of redistilled 1 : 4-butanediol (b.p. 228–230° or 133–135°/18 mm.). Heat the mixture with stirring at 100–120° for 4 hours. Cool the stirred mixture to room temperature and add 75 ml. of water and 125 ml. of ether. Separate the ethereal layer, decolourise it by shaking with 25 ml. of 10 per cent. sodium thiosulphate solution, wash with 100 ml. of cold, saturated sodium chloride solution, and dry with anhydrous magnesium sulphate. Remove the ether by "flash distillation" (Section **II,13**; compare Fig. *II, 13*, 4) on a steam bath and distil the residue from a Claisen flask with fractionating side arm under diminished pressure. Collect the 1 : 4-diiodobutane at 110°/6 mm.; the yield is 65 g.

Alternatively, add 18·2 g. (20·5 ml.) of redistilled tetrahydrofuran (b.p. 65–66°) to a mixture of 32·5 g. of phosphoric oxide, 115·5 g. (67·5 ml.) of 85 per cent. orthophosphoric acid and 166 g. of potassium iodide, reflux for 3–4 hours, cool and isolate the 1 : 4-diiodobutane as above. The yield of product, b.p. 110°/6 mm., is 70 g.

Note.

(1) The orthophosphoric acid must be adjusted to a concentration of 95 per cent. H_3PO_4. Alternatively, the commercial 100 per cent. orthophosphoric acid may be diluted with water to this concentration. The 95 per cent. acid is claimed to be the most efficient for the preparation of iodides from alcohols and glycols, and for effecting cleavage of tetrahydrofuran and tetrahydropyran. Anhydrous orthophosphoric acid does not give such good results because of the limited solubility of hydrogen iodide in the reagent.

Cognate Preparations

1 : 5-Diiodopentane (*from 1 : 5-pentanediol*). Proceed as for 1 : 4-diiodobutane but use 26 g. (26·5 ml.) of redistilled 1 : 5-pentanediol (b.p. 238–239°) in place of the 1 : 4-butanediol. The yield of 1 : 5-diiodopentane, b.p. 142–143°/16 mm., is 65 g.

1 : 5-Diiodopentane (*from tetrahydropyran*). Use 21·5 g. (24·4 ml.) of redistilled tetrahydropyran (b.p. 86·5–87·5°) in place of the tetrahydrofuran, otherwise proceed as for 1 : 4-diiodobutane. The yield of 1 : 6-diiodopentane, b.p. 142–143°/16 mm., is 71 g.

1 : 6-Diiodohexane. Proceed exactly as detailed for 1 : 4-diiodobutane but replace the 1 : 4-butanediol by 29·5 g. of 1 : 6-hexanediol, m.p. 41–42°. The yield of 1 : 6-diiodohexane, b.p. 150°/10 mm., m.p. 10°, is 70 g.

***n*-Butyl Iodide.** Use 16·3 g. of phosphoric oxide, 58 g. (34 ml.) of 85 per cent. orthophosphoric acid, 83 g. of potassium iodide and 18·5 g. (23 ml.) of redistilled *n*-butyl alcohol in a 250 ml. three-necked flask. Follow the experimental details given for 1 : 4-diiodobutane but stir for 2–3 hours. The yield of *n*-butyl iodide, b.p. 129–131° (largely 130°), is 32 g.

***cyclo*Hexyl Iodide.** Proceed exactly as described for *n*-butyl iodide, but replace the *n*-butyl alcohol by 25 g. of redistilled *cyclo*hexanol (b.p. 160–161°). The yield of *cyclo*hexyl iodide, b.p. 67–69°/9 mm., is 45 g.

III,39. *iso*PROPYL IODIDE (*HI Method*)

Mix 30 g. (38 ml.) of *iso*propyl alcohol with 450 g. (265 ml.) of constant boiling point hydriodic acid (57 per cent.) (Section **II,49,2**) in a 500 ml. distilling flask, attach a condenser for downward distillation, and distil slowly (1–2 drops per second) from an air bath (compare Fig. *II*, *5*, 3). When about half the liquid has passed over, stop the distillation. Separate the lower layer of crude iodide (80 g.). Redistil the aqueous layer and thus recover a further 5 g. of iodide from the first quarter of the distillate (1). Wash the combined iodides with an equal volume of concentrated hydrochloric acid, then, successively, with water, 5 per cent. sodium carbonate solution, and water. Dry with anhydrous calcium chloride and distil. The *iso*propyl iodide distils constantly at 89°.

Note.

(1) A further quantity of *iso*propyl iodide, only slightly less than that obtained in the first distillation, may be prepared by combining the residues in the distilling flask, adding 30 g. (38 ml.) of *iso*propyl alcohol, and repeating the distillation. Finally, the residues should be distilled and the 57 per cent. constant boiling point acid recovered.

Cognate Preparations

***iso*-Butyl Iodide.** Use 30 g. (37·5 ml.) of *iso*-butyl alcohol and 273 g. (161 ml.) of 57 per cent. hydriodic acid ; 65 g. of the crude iodide are obtained. If the crude iodide is dark in colour, add a little sodium bisulphite. B.p. 119–120°.

***sec.*-Butyl Iodide.** Use 30 g. (37·5 ml.) of *sec.*-butyl alcohol and 273 g. (161 ml.) of 57 per cent. hydriodic acid ; 73 g. of crude iodide are obtained. B.p. 117·5–119°.

***cyclo*Pentyl Iodide.** Use 43 g. (45·5 ml.) of *cyclo*pentanol and 340 g. (200 ml.) of 57 per cent. hydriodic acid ; 89 g. of crude iodide are obtained. B.p. 58°/22 mm.

Allyl Iodide. Use 29 g. (34 ml.) of allyl alcohol and 340 g. (200 ml.) of 57 per cent. hydriodic acid ; 84 g. of crude iodide are obtained. Upon adding 29 g. (34 ml.) of allyl alcohol to the combined residue in the flask and the aqueous layer and distilling as before, a further 72 g. of crude allyl iodide may be isolated. B.p. 99–101° (mainly 100°). The compound is very sensitive to light ; the distillation should therefore be conducted in a darkened room and preferably in the presence of a little silver powder.

III,40. *n*-BUTYL IODIDE (*Red P and I_2 Method*)

A special apparatus * (Fig. *III*, *40*, 1) renders the preparation of iodides from alcohols a very simple operation. The special features of the apparatus are :—(i) a wide bored (3–4 mm.) stopcock *A* which considerably reduces the danger of crystallisation in the bore of the tap of the iodine from the hot alcoholic solution ; (ii) a reservoir *B* for the solid iodine and possessing a capacity sufficiently large to hold all the alkyl iodide produced ; (iii) a wide tube *C* which permits the alcohol vapour from the flask *D* to pass rapidly into the reservoir *B*, thus ensuring that the iodine is dissolved by alcohol which is almost at the boiling point. An improved apparatus is shown in Fig. *III*, *40*, 2, *a* and *b* ; here a

* Supplied by A. Gallenkamp and Co. Ltd. in various capacities.

" three-way " stopcock is provided in order to remove the liquid contents of the reservoir without disconnecting the special apparatus from the flask.

Fit up the assembly depicted in Fig. *III*, *40*, 1 ; insert a plug of glass wool at the bottom of *B* (just above the wide bore tap *A*). *D* is a 100 ml. bolt-head flask, *B* has a capacity of about 30 ml. (1) and *E* is a Liebig (but may be a double surface) condenser. Place 15 g. (19 ml.) of *n*-butyl alcohol and 2·75 g. of purified red phosphorus (Section **II,50,5**) in the flask and 25 g. of iodine in the special apparatus. Make sure that all the corks fit tightly and do not leak. Heat the flask gently on a wire

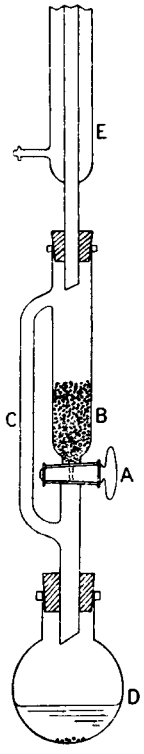


Fig. *III*, *40*, 1.

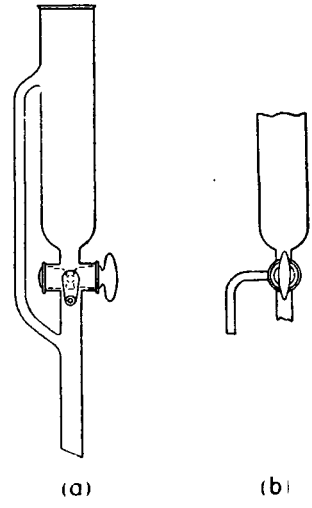


Fig. *III*, *40*, 2.

gauze. The *n*-butyl alcohol vapour will gradually pass into *B* through the wide-bore side tube *C* and eventually the hot alcohol will dissolve a considerable quantity of the iodine. As soon as the liquid (a solution of iodine in *n*-butyl alcohol) has reached the tap, open the latter slightly and allow the solution to flow slowly into the flask. There is usually a fairly vigorous reaction, and it may be necessary to remove the flame from beneath the flask. Arrange the rate of addition so that the mixture in the flask boils gently and the reaction is under control. When all the iodine has been transferred to the flask in this manner, the formation of *n*-butyl iodide is practically complete and little iodine vapour is visible. To ensure absolute completeness of the reaction, distil most (80–90 per cent.) of the iodide into *B* by gently heating the flask. *Stop the heating*

when about 5 ml. of liquid remains in the flask; if the heating is continued beyond this point, butylene may be formed and a fire may result. Disconnect the special apparatus (2) from the bolt-head flask and run off the crude iodide into a flask. Add 25 ml. of water to the residue in the bolt-head flask *D*, assemble the complete apparatus again, and heat *D* gently. The remaining *n*-butyl iodide (and some water) will collect in *B*. Stop the "steam distillation" when no more oily drops pass into *B*. Run the contents of *B* into the flask containing the main bulk of the crude iodide, transfer the mixture to a 50 ml. or 100 ml. separatory funnel, and run off the lower layer of iodide: discard the aqueous layer. Wash the *n*-butyl iodide successively with approximately equal volumes of water, concentrated hydrochloric acid (3), water, 10 per cent. sodium carbonate solution and water. Dry the iodide with about 2·5 g. of anhydrous calcium chloride; it is best to leave the liquid in contact with the desiccant for 15–30 minutes and to shake occasionally. Filter the dried product through a fluted filter paper or a small plug of cotton wool supported in a small funnel into a dry 50 ml. distilling flask, add 2–3 fragments of porous porcelain, and distil on a wire gauze or from an air bath (Fig. *II*, *5*, 3). Collect the fraction boiling at 129–131°. The yield of *n*-butyl iodide is 32–34 g.

Notes.

(1) The small capacity apparatus is especially recommended for the use of students; the consumption of iodine by a large class of students is not unreasonably high. Larger apparatus, *e.g.*, 60 ml. and 100 ml. capacity holding 100 g. and 200 g. respectively of iodine, are generally preferred for routine preparations of alkyl iodides; the bolt-head flask should then be of 250 or 500 ml. capacity. Thus for *n*-butyl iodide a typical preparation would employ 120 g. (148·5 ml.) of *n*-butyl alcohol, 21·75 g. of red phosphorus, and 200 g. of iodine.

(2) If the apparatus of Fig. *III*, *40*, 2 is employed, the iodide is removed by suitably turning the "three-way" stopcock. It is then, of course, unnecessary to disconnect the special apparatus from the flask.

(3) The washing with concentrated hydrochloric acid removes unchanged alcohol, if present.

Cognate Preparations *

Methyl Iodide. Use 38 g. (48 ml.) of methyl alcohol, 8·27 g. of purified red phosphorus and 127 g. of iodine. Cover the iodine completely with the hot methyl alcohol before running the alcoholic solution into the boiling alcohol - phosphorus mixture. B.p. 42–42·5°.

Ethyl Iodide. Use 55 g. (70 ml.) of absolute ethyl alcohol, 8·27 g. of purified red phosphorus and 127 g. of iodine. B.p. 72–73°.

***n*-Propyl Iodide.** Use 98 g. (122 ml.) of *n*-propyl alcohol, 21·00 g. of purified red phosphorus and 200 g. of iodine. B.p. 102–103°.

***iso*Propyl Iodide.** Use 98 g. (125 ml.) of *iso*propyl alcohol, 21·00 g. of purified red phosphorus and 200 g. of iodine. A little hydrogen iodide is evolved. B.p. 89–90°.

* The yields, unless otherwise stated, exceed 90 per cent. of the theoretical. The appropriate size of apparatus (generally of 60 ml. or 100 ml. capacity) should be used; the corresponding bolt-head flask should have a capacity of 250 or 500 ml.

If the iodide is deeply coloured, it may be decolourised with a little sodium bisulphite. A perfectly colourless product can be obtained by distilling in the dark or in diffused light from a little silver powder. The iodide should be preserved in a bottle containing a short coil of copper wire made by wrapping copper wire round a glass rod or tube.

***sec.*-Butyl Iodide.** Use 119 g. (147·5 ml.) of *sec.*-butyl alcohol, 20·40 g. of purified red phosphorus and 200 g. of iodine. Some hydrogen iodide is evolved. The yield of *sec.*-butyl iodide, b.p. 118–120°, is 228 g.

***n*-Amyl Iodide.** Use 139 g. (171 ml.) of *n*-amyl alcohol, 21·75 g. of purified red phosphorus and 200 g. of iodine. B.p. 153–156°.

2-Iodopentane. Use 88 g. (109 ml.) of methyl *n*-propyl carbinol, 11·30 g. of purified red phosphorus and 256 g. of iodine. B.p. 142–144°.

***n*-Hexyl Iodide.** Use 161 g. (197 ml.) of *n*-hexyl alcohol, 21·75 g. of purified red phosphorus and 200 g. of iodine. B.p. 175–180° (mainly 178–180°).

***n*-Heptyl Iodide.** Use 91·5 g. (111·5 ml.) of *n*-heptyl alcohol (b.p. 175–177°), 10·88 g. of purified red phosphorus and 100 g. of iodine. B.p. 198–201° and 62·5°/3·5 mm.

***n*-Octyl Iodide.** Use 111 g. (134·5 ml.) of *n*-octyl alcohol (b.p. 193–194·5°), 10·20 g. of purified red phosphorus and 100 g. of iodine. The arm *C* in Fig. *III*, *40*, 1 should be lagged with asbestos cloth in order to facilitate the distillation of the alcohol into the iodine. B.p. 219–222° and 86·5°/5 mm.

***cyclo*Hexyl Iodide.** Use 158 g. of *cyclo*hexanol, 20·40 g. of purified red phosphorus and 200 g. of iodine. It is best to add ether after all the iodine has been introduced into the flask, filter from the solid, remove the ether on a water bath, and distil under diminished pressure. B.p. 81–83°/20 mm. Yield: 290 g.

Trimethylene Di-iodide. Use 76 g. of trimethylene glycol, 27·52 g. of purified red phosphorus and 254 g. of iodine. Lag the arm *C* (Fig. *III*, *40*, 1) with asbestos cloth. Stop the heating immediately all the iodine has been transferred to the flask. Add water to the reaction mixture, decolourise with a little sodium bisulphite, filter, separate the crude iodide, wash it twice with water, dry with anhydrous potassium carbonate and distil under reduced pressure. B.p. 88–89°/6 mm. Yield: 218 g. (a colourless liquid).

β-Phenylethyl Iodide. Use 146 g. (142 ml.) of β-phenylethyl alcohol (b.p. 216·5–217°), 16·54 g. of purified red phosphorus and 154 g. of iodine. Lag the arm *C* (Fig. *III*, *40*, 1) with asbestos cloth. Heat the alcohol–phosphorus mixture to boiling until sufficient alcohol (usually one-third to one-half of the total volume) passes into the reservoir *B* to dissolve all the iodine. Remove the flame and add the iodine solution at such a rate that the mixture boils gently. A little hydrogen iodide is evolved towards the end of the reaction. Allow the mixture to cool, add water and filter off the excess of phosphorus. Decolourise the filtrate with a little sodium bisulphite and add ether to assist in the separation of the water layer. Wash the ethereal solution with water, dry with anhydrous potassium carbonate, and distil under diminished pressure. B.p. 114–116°/12 mm. Yield: 215 g.

III,41. *n*-HEXYL FLUORIDE

CAUTION: Alkyl fluorides are said to be highly toxic. Great care should be taken not to inhale the vapours.

In a dry 500 ml. three-necked flask, equipped with a mercury-sealed stirrer, a 100 ml. dropping funnel and a short fractionating column (1), place a mixture of 116 g. of anhydrous, finely-powered potassium fluoride (2) and 200 g. of dry ethylene glycol (3). Connect the fractionating

column (which carries a thermometer) to a downward double-surface condenser and a filter flask as receiver. Heat the flask in an oil bath at 160–170° and introduce 165 g. (141 ml.) of *n*-hexyl bromide (Section **III,37**) dropwise, with stirring, during 5 hours. A liquid passes over intermittently at 60–90°. When the addition is complete, allow the bath temperature to fall to 110–120°; replace the dropping funnel by a tube of narrow bore dipping just below the surface of the liquid, attach the side arm of the filter flask to a water pump, and draw a slow stream of air through the apparatus whilst maintaining the stirring. It is advisable to interpose a U-tube cooled in ice between the water pump and receiver in order to recover any uncondensed liquid. Distil the combined distillates through an efficient fractionating column (4) or from a Claisen flask with fractionating side arm (Figs. *II*, *24*, 4–5): after a small forerun (0·5 g.) of 1-hexene, collect the crude *n*-hexyl fluoride at 92–97°. Purify the crude product by cooling in ice and adding 1 ml. portions of a solution containing 9·0 g. of bromine and 6·0 g. of potassium bromide in 50 ml. of water until the organic layer acquires an orange colour: shake the mixture vigorously for a minute or so after each addition. The volume of Br_2—KBr solution required is usually less than 5 ml. Separate the aqueous layer, wash the organic layer with saturated aqueous potassium bromide solution until colourless, and finally with water. Dry the liquid with anhydrous magnesium sulphate and distil from a Claisen flask with fractionating side arm (Figs. *II*, *24*, 4–5). Collect the *n*-hexyl fluoride at 92–94°: the yield is 44 g. The colourless liquid keeps unchanged for long periods.

Notes.

(1) Any fractionating column of moderate efficiency is satisfactory, *e.g.*, a Dufton column (20 cm. long containing a spiral 10 cm. in length, 2 cm. in diameter with 8 turns of the helix) or a Vigreux column (20–25 cm. long).

(2) Grind finely pure laboratory grade, anhydrous potassium fluoride, and heat it in an electrically heated oven at 180–210°; store in a desiccator. Before use, dry the powdered salt at 180° for 3 hours and grind again in a warm (*ca.* 50°) glass mortar.

(3) Redistil laboratory grade ethylene glycol under reduced pressure and collect the fraction of b.p. 85–90°/7 mm. for use as a solvent for the potassium fluoride.

(4) A Widmer column (spiral 18 cm. in length, 1·5 cm. in diameter with 20 turns of the helix) is satisfactory.

Cognate Preparation

***n*-Amyl Fluoride.** Use 116 g. of dry potassium fluoride in 200 g. of dry ethylene glycol: heat in an oil bath at 140–150° and add 302 g. (248 ml.) of *n*-amyl bromide during 5 hours with stirring. The reaction product distils intermittently at 50–85°. The yield of *n*-amyl fluoride, b.p. 63·5–65°, is 50 g.

III,42. REACTIONS AND CHARACTERISATION OF ALKYL HALIDES

The following are some of the most important reactions of alkyl halides which will assist in their identification.

(i) **Beilstein's test.** This test serves to detect the presence of halogens in many organic compounds. It consists in heating the substance in contact with pure copper oxide in the Bunsen flame: the corresponding

copper halide is formed, which, being volatile, imparts an intense green or bluish-green colour to the mantle of the flame.

Push one end of a length of 20 cm. of stout copper wire into a cork (this will serve as a holder); at the other end make two or three turns about a thin glass rod. Heat the coil in the outer mantle of a Bunsen flame until it ceases to impart any colour to the flame. Allow the wire to cool somewhat and, while still warm, dip the coil into a small portion of the substance to be tested and heat again in the non-luminous flame. If the compound contains a halogen element, a green or bluish-green flame will be observed (usually after the initial smoky flame has disappeared). Before using the wire for another compound, heat it until the material from the previous test has been destroyed and the flame is not coloured.

It has been stated that many halogen-free compounds, *e.g.*, certain derivatives of pyridine and quinoline, purines, acid amides and cyano compounds, when ignited on copper oxide impart a green colour to the flame, presumably owing to the formation of volatile cuprous cyanide. The test is therefore not always trustworthy. The test is not given by fluorides.

(ii) **Alcoholic silver nitrate solution.** Shake 0·1 g. of the substance with 2 ml. of alcoholic silver nitrate solution. Alkyl iodides usually yield silver iodide instantly; alkyl bromides react rapidly, but may require warming; alkyl chlorides give very little precipitate in the cold, but a copious precipitate is obtained by warming on a water bath. The order of reactivity is I > Br > Cl and tertiary > secondary > primary.

The alcoholic silver nitrate solution consists of a saturated solution of silver nitrate in absolute alcohol (about 1–2 per cent.).

(iii) **Alcoholic potassium hydroxide solution.** Boil 0·5 ml. of the compound with 4 ml. of 0·5*N* alcoholic potassium hydroxide under reflux for 15 minutes. Most alkyl halides give a crystalline precipitate of the potassium halide. Dilute with 5 ml. of water, acidify with dilute nitric acid, and test with silver nitrate solution.

The 0·5*N* alcoholic potassium hydroxide solution is prepared by dissolving 16 g. of potassium hydroxide pellets in 500 ml. of alcohol (or industrial spirit) contained in a bottle closed by a cork. After standing for 24 hours, the clear solution is decanted or filtered from the residue of potassium carbonate. It is said that a solution in methyl alcohol has better keeping qualities than that in ethyl alcohol.

Crystalline Derivatives of Alkyl Halides

1. **Anilides and α-Naphthalides.** The Grignard reagents prepared from alkyl halides react with phenyl *iso*cyanate ($C_6H_5N{=}C{=}O$) or with α-naphthyl *iso*cyanate ($C_{10}H_7{}^{\alpha}N{=}C{=}O$) to yield addition products that are converted by hydrolysis into anilides and α-naphthalides respectively:

$$RX + Mg \longrightarrow RMgX$$

$$ArN{=}C{=}O + RMgX \rightarrow ArN{=}C(R){-}OMgX \xrightarrow{H_2O} \left[ArN{=}C(R){-}OH\right] + Mg(OH)X$$

$$\longrightarrow ArNHCOR$$

Phenyl *iso*cyanate is a colourless liquid, b.p. 164° or 55°/13 mm.; its vapour is lachrymatory. The liquid reacts readily with water, yielding diphenyl urea, m.p. 241°, and hence must be protected from atmospheric moisture:

$$2C_6H_5NCO + H_2O \longrightarrow C_6H_5NHCONHC_6H_5 + CO_2$$

α-Naphthyl *iso*cyanate, b.p. 269–270° or 153°/18 mm., is not quite so irritant and is somewhat more stable towards water (di-α-naphthyl urea has m.p. 297°). It is therefore to be preferred as a reagent; furthermore the α-naphthalides are less soluble than the corresponding anilides.

In a small dry flask, fitted with a short reflux condenser and a calcium chloride or cotton wool guard tube, place 0·4 g. of dry magnesium turnings, a minute crystal of iodine and a solution of 1 ml. (or 0·01 mol) of the alkyl halide in 10–15 ml. of anhydrous ether. If the reaction does not start immediately (as indicated by the disappearance of the iodine colour), warm for a short period in a beaker of warm water; allow the reaction to proceed spontaneously, moderating it if necessary by immersing the flask in cold water. When the reaction has ceased, decant the nearly clear liquid from any solid material into another flask, and fit the reflux condenser into it. Add, portion-wise, through the condenser a solution of 0·5 ml. of phenyl- or α-naphthyl-*iso*cyanate in 15 ml. of anhydrous ether, shaking the flask after each addition. Allow the mixture to stand for 10 minutes and then add 30 ml. of *N* hydrochloric acid dropwise and with vigorous shaking and cooling in ice. (Alternatively, pour the reaction mixture cautiously into 20 ml. of ice water containing 1 ml. of concentrated hydrochloric acid, and shake the mixture well.) Transfer to a separatory funnel, shake well, then discard the lower aqueous layer. Dry the ethereal solution with a little anhydrous magnesium sulphate and distil off the ether. Recrystallise the residue: methyl alcohol, ethyl alcohol, petroleum ether, ether or hot water are suitable recrystallisation solvents.

If dry apparatus and dry reagents have not been used, diphenyl urea (m.p. 241°) or di-α-naphthyl urea (m.p. 297°) are obtained.

2. **Alkyl mercuric halides.** Grignard reagents, prepared from alkyl halides, react with a mercuric halide that contains the *same halogen* as the reagent to form alkyl mercuric halides:

$$RMgX + HgX_2 \longrightarrow RHgX + MgX_2$$

The reaction is applicable to primary and secondary halides only; tertiary halides do not react.

Filter the Grignard solution, prepared as in *1*, rapidly through a little glass wool into a test-tube containing 4–5 g. of mercuric chloride, bromide or iodide, depending upon the halogen in the original alkyl halide. Shake the reaction mixture vigorously for a few minutes and then evaporate the ether. Boil the residue with 20 ml. of rectified spirit, filter the solution, dilute it with 10 ml. of distilled water, reheat to dissolve any precipitated solid, and allow to cool. Recrystallise the alkyl mercuric halide from dilute alcohol.

3. **S-Alkyl-*iso*-thiuronium picrates.** Alkyl bromides or iodides react with thiourea in alcoholic solution to produce S-alkyl-*iso*-thiuronium salts, which yield picrates of sharp melting point:

$$RX + S{=}C(NH_2){-}NH_2 \longrightarrow [R{-}S{-}C(NH_2){=}NH_2]^+ X$$

$$[R{-}S{-}C(NH_2){=}NH_2]^+ X + HPic \longrightarrow [R{-}S{-}C(NH_2){=}NH_2]^+ Pic$$

[HPic ≡ $HOC_6H_2(NO_2)_3$]

Alkyl chlorides react slowly and the yield of the derivative is poor. Tertiary halides give anomalous results.

Place a mixture of 0·5 g. of finely powdered thiourea, 0·5 g. of the alkyl halide and 5 ml. of alcohol in a test-tube or small flask equipped with a reflux condenser. Reflux the mixture for a period depending upon the nature of the halide: primary alkyl bromides and iodides, 10–20 minutes (according to the molecular weight); secondary alkyl bromides or iodides, 2–3 hours; alkyl chlorides, 3–5 hours; polymethylene dibromides or di-iodides, 20–50 minutes. Then add 0·5 g. of picric acid, boil until a clear solution is obtained, and cool. If no precipitate is obtained, add a few drops of water. Recrystallise the resulting S-alkyl-*iso*-thiuronium picrate from alcohol.

The derivatives of ethylene dibromide, propylene dibromide, trimethylene dibromide and *iso*-butylene dibromide melt at 260°, 232°, 229° and 223° respectively.

4. **Picrates of β-naphthyl alkyl ethers.** Alkyl halides react with the sodium or potassium derivative of β-naphthol in alcoholic solution to yield the corresponding alkyl β-naphthyl ethers (which are usually low m.p. solids) and the latter are converted by alcoholic picric acid into the crystalline picrates:

$$RX + C_{10}H_7{}^{\beta}ONa \longrightarrow C_{10}H_7{}^{\beta}OR + NaX$$

Mix together 1·0 g. of pure β-naphthol and the theoretical quantity of 50 per cent. potassium hydroxide solution, add 0·5 g. of the halide, followed by sufficient rectified spirit to produce a clear solution. For alkyl chlorides, the addition of a little potassium iodide is recommended. Heat the mixture under reflux for 15 minutes, and dissolve any potassium halide by the addition of a few drops of water. The β-naphthyl ether usually crystallises out on cooling; if it does not, dilute the solution with 10 per cent. sodium hydroxide solution until precipitation occurs. Dissolve the β-naphthyl ether in the minimum volume of hot alcohol and add the calculated quantity of picric acid dissolved in hot alcohol. The picrate separates out on cooling. Recrystallise it from rectified spirit.

The β-naphthyl ethers of methylene halides have m.p. 133°, of ethylene halides 217°, and trimethylene halides 148°.

Di- and poly-halogenated aliphatic hydrocarbons. No general procedure can be given for the preparation of derivatives of these compounds. Reliance must be placed upon their physical properties (b.p., density and refractive index) and upon any chemical reactions which they undergo.

Table **III,42** deals with a number of aliphatic halogen compounds together with their crystalline derivatives. Some aromatic compounds, which simulate the properties of aliphatic halides in some respects, are included.

TABLE III,42. **ALIPHATIC HALOGEN COMPOUNDS**

Halide	B.P.	M.P.	$d^{20°}_{4°}$	$n^{20°}_{D}$	Anilide	α-Naphthalide	Alkyl Mercuric Halide	S-Alkyl-*iso*-thiuronium Picrate	Picrate of β-naphthyl ether
CHLORIDES									
Ethyl	12°	—	—	—	104°	126°	193°	—	102°
n-Propyl	46	—	0·889	1·388	92	121	140	177°	81
iso-Propyl	35	—	0·863	1·378	104	—	—	—	95
n-Butyl	77	—	0·886	1·402	63	112	128	177	67
iso-Butyl	69	—	0·881	1·398	110	126	—	—	84
sec.-Butyl	68	—	0·874	1·397	108	129	—	—	85
tert.-Butyl	50	—	0·846	1·386	128	147	—	—	—
n-Amyl	105	—	0·882	1·412	96	112	110	154	67
iso-Amyl	99	—	0·872	1·409	110	111	86	173	94
*Neo*pentyl	85	—	0·879	—	126	—	—	—	—
β-Chloropentane	97	—	0·873	1·408	—	—	—	—	—
γ-Chloropentane	96	—	0·872	1·408	—	—	—	—	—
tert.-Amyl	85	—	0·865	1·405	92	138	—	—	—
n-Hexyl	134	—	0·878	1·420	69	106	125	—	—
n-Heptyl	159	—	0·877	1·426	57	95	119	—	—
n-Octyl	182	—	0·875	1·431	57	91	151	—	—
n-Nonyl	202	—	0·870	1·434	—	—	—	—	—
n-Decyl	223	—	0·868	1·437	—	—	—	—	—
n-Undecyl	241	—	0·868	1·440	—	—	—	—	—
n-Dodecyl	130°/15	—	0·867	1·443	—	—	—	—	—
*cyclo*Pentyl	114	—	1·005	1·451	—	—	—	—	—
*cyclo*Hexyl	142	—	0·989	1·462	146	188	—	—	—
Benzyl	179	—	1·100	1·539	117	166	—	188	123
Benzal	207	—	—	—	166	—	—	—	—
Benzo tri-	218	—	—	—	—	—	—	—	—
β-Phenylethyl	198	—	—	—	97	—	—	—	84
Allyl	45	—	0·940	1·416	114	—	—	154	99

TABLE III,42. ALIPHATIC HALOGEN COMPOUNDS (*continued*)

Halide	B.P.	M.P.	$d_{4°}^{20°}$	$n_D^{20°}$	Anilide	α-Naphthalide	Alkyl Mercuric Halide	S-Alkyl-*iso*-thiuronium Picrate	Picrate of β-naphthyl ether
BROMIDES									
Ethyl	38°	—	1·460	1·425	104°	126°	194°	188°	102°
n-Propyl	71	—	1·435	1·355	92	121	138	177	81
iso-Propyl	59	—	1·425	1·314	104	—	94	196	95
n-Butyl	101	—	1·274	1·440	63	112	129	177	67
iso-Butyl	91	—	1·253	1·435	110	126	56	167	84
sec.-Butyl	91	—	1·256	1·437	108	129	39	166	85
n-Amyl	129	—	1·219	1·445	96	112	122	154	67
iso-Amyl	119	—	1·213	1·442	110	111	80	173	94
*Neo*Pentyl	109	—	1·225	—	126	—	—	—	—
β-Bromopentane	117	—	1·212	1·442	93	—	—	—	—
γ-Bromopentane	118	—	1·211	1·443	124	—	—	—	—
n-Hexyl	154	—	1·175	1·448	69	106	119	157	—
n-Heptyl	178	—	1·140	1·451	57	95	115	142	—
n-Octyl	200	—	1·112	1·453	57	91	109	134	—
n-Nonyl	220	—	1·090	1·454	—	—	109	—	—
n-Decyl	103°/6	—	1·066	1·455	—	—	—	—	—
n-Undecyl	114°/5	—	1·054	1·457	—	—	—	—	—
n-Dodecyl	130°/6	—	1·038	1·458	—	—	108	—	—
n-Tetradecyl	179°/20	5°	1·017	1·460	—	—	—	—	—
n-Hexadecyl	201°/19	14	1·001	1·462	—	—	—	137	—
*cyclo*Pentyl	137	—	1·387	1·489	—	—	—	—	—
*cyclo*Hexyl	164	—	1·336	1·495	146	188	153	—	—
Benzyl	198	—	1·438	—	117	166	119	188	123
β-Phenylethyl	218	—	1·359	1·556	97	—	169	—	84
Allyl	70	—	1·432	1·470	114	—	—	—	99

TABLE III,42. ALIPHATIC HALOGEN COMPOUNDS (*continued*)

Halide	B.P.	M.P.	$d_{4}^{20°}$	$n_{D}^{20°}$	Anilide	α-Naphthalide	Alkyl Mercuric Halide	S-Alkyl-*iso*-thluronium Picrate	Picrate of β-naphthyl ether
Iodides									
Methyl	42°	—	2·282	1·532	114°	160°	145°	224°	117°
Ethyl	73	—	1·940	1·514	104	126	182	188	102
n-Propyl	102	—	1·743	1·505	92	121	113	177	81
iso-Propyl	89	—	1·703	1·499	104	—	—	196	95
n-Butyl	129	—	1·616	1·499	63	112	117	177	67
iso-Butyl	119	—	1·602	1·496	110	126	72	167	84
sec.-Butyl	118	—	1·592	1·499	108	129	—	166	85
n-Amyl	155	—	1·512	1·496	96	112	110	154	—
iso-Amyl	147	—	1·503	1·493	110	111	122	173	94
β-Iodopentane	142	—	1·510	1·496	—	—	—	—	—
γ-Iodopentane	142	—	1·511	1·497	—	—	—	—	—
tert.-Amyl	128	—	1·479	—	92	138	—	—	—
n-Hexyl	180	—	1·437	1·493	69	106	110	157	—
n-Heptyl	201	—	1·373	1·490	57	95	103	—	—
n-Octyl	221	—	1·330	1·489	—	—	—	—	—
*cyclo*Pentyl	58°/22	—	1·709	1·547	—	—	—	—	—
*cyclo*Hexyl	82°/20	—	1·624	1·547	—	—	—	—	—
Benzyl	93°/10	24°	—	—	116	—	—	—	123
β-Phenylethyl	116°/12	—	1·632	1·602	—	—	—	—	84
Allyl	100	—	1·777	1·578	114	121	112	154	99
Iodo Compounds									
Methylene iodide	80°/25	—	3·324	1·741					
Ethylene iodide	—	81°	—	—					
Trimethylene iodide	90°/9	—	2·576	1·642					
Iodoform	—	119	—	—					

TABLE III,42. ALIPHATIC HALOGEN COMPOUNDS (*continued*)

Halide	B.P.	M.P.	$d_{4^\circ}^{20^\circ}$	$n_{D}^{20^\circ}$
CHLORO COMPOUNDS				
Methylene chloride	42°	—	1·336	1·425
Dichloroethylene (*trans*)	48	—	1·257	1·444
Ethylidene chloride	57	—	1·176	1·416
Dichloroethylene (*cis*)	60	—	1·282	1·446
Chloroform	61	—	1·489	1·446
2 : 2-Dichloropropane	70	—	1·092	1·412
Methyl chloroform	75	—	1·349	1·438
Carbon tetrachloride	77	—	1·594	1·461
Ethylene chloride	84	—	1·256	1·445
Trichloroethylene	87	—	1·465	1·478
Propylene chloride	96	—	1·155	1·439
Ethylene chlorobromide	107	—	1·689	1·491
1 : 1 : 2-Trichloroethane	114	—	1·443	1·471
Trimethylene chloride	120	—	1·183	1·449
Tetrachloroethylene	121	—	1·623	1·506
Trimethylene chlorobromide	143	—	1·593	1·471
sym.-Tetrachloroethane	147	—	1·597	1·495
1 : 4-Dichlorobutane	153	—	1·139	1·455
1 : 2 : 3-Trichloropropane	157	—	1·394	1·486
Pentachloroethane	162	—	1·680	1·503
1 : 5-Dichloropentane	178d	—	1·100	1·457
1 : 6-Dichlorohexane	204d	—	1·069	1·457
Hexachloroethane	—	187° (sub.)	—	—
BROMO COMPOUNDS				
Methylene bromide	97	—	2·496	1·541
Ethylidene bromide	113	—	2·055	1·513
Ethylene bromide	131	—	2·183	1·539
Propylene bromide	141	—	1·932	1·520
Bromoform	150	—	2·887	1·598
iso-Butylene bromide	150	—	1·783	1·512
2 : 3-Dibromobutane	157	—	1·792	1·515
1 : 3-Dibromopropane	165	—	1·982	1·523
1 : 2-Dibromobutane	166	—	1·820	—
1 : 4-Dibromobutane	198	—	1·826	1·519
1 : 2 : 3-Tribromopropane	220	—	2·402	1·582
1 : 5-Dibromopentane	221	—	1·702	1·513
1 : 6-Dibromohexane	240	—	1·603	1·506
sym.-Tetrabromoethane	124°/19	—	2·967	1·628
Carbon tetrabromide	—	92°	—	—

POLYHALOGEN COMPOUNDS

Acetone (R = CH_3) when treated with sodium hypochlorite or bleaching powder solution yields **chloroform**, probably in accordance with the following mechanism :

$$R—CO—CH_3 + 3NaOCl \longrightarrow R—CO—CCl_3 + 3NaOH$$
$$R—CO—CCl_3 + NaOH \longrightarrow R—CO—ONa + HCCl_3$$

Ethyl alcohol, which is first oxidised to acetaldehyde (R = H), behaves similarly :

$$CH_3CH_2OH + NaOCl \longrightarrow CH_3CHO + NaCl + H_2O$$

Sodium hypobromite and sodium hypoiodite solutions react in an analogous manner and yield **bromoform** ($CHBr_3$) and **iodoform** (CHI_3) respectively. The smooth production of the trihalomethanes by the use of the appropriate hypohalides is termed the **haloform reaction.** It is applicable to all compounds containing the —$COCH_3$ group or which yield a substance containing this group by oxidation (*e.g.*, acetaldehyde from ethyl alcohol). Iodoform is a stable, crystalline, yellow solid, m.p. 119°, with a characteristic odour ; it is only sparingly soluble in water and hence will separate, even in very minute quantity, from an aqueous solution and can easily be identified by m.p. and mixed m.p. determinations.

III,43. CHLOROFORM

Much of the chloroform of commerce is obtained by the action of moist iron upon carbon tetrachloride : the following preparation is, however, instructive.

Fit a 2-litre round-bottomed flask with a two-holed cork carrying a dropping funnel and a glass tube bent at an angle of about 60° to act as a still head (compare Fig. *II*, *13*, 3). Attach the latter to a condenser (set for downward distillation) and insert the end of the condenser through a cork into a filter flask to act as a receiver. Attach a length of 5 mm. glass tubing to the stem of the funnel by means of a short length of rubber " pressure " tubing ; the end of the glass tube should dip just below the surface of the liquid in the flask.

Place 200 g. of bleaching powder in a mortar and add 500 ml. of water in small quantities at a time ; between each addition grind the mixture of bleaching powder and water well together, and decant the suspension into the flask. Only a small quantity of a gritty residue should remain in the mortar when all the water has been introduced. It may be more convenient to prepare the suspension in two operations, each with 100 g. of bleaching powder and 250 ml. of water. Arrange the apparatus for heating on a wire gauze, and place 20 ml. of water in the receiver. Introduce 25 g. (32 ml.) of acetone diluted with an equal volume of water into the separatory funnel. Allow about 5 ml. of the dilute acetone to enter the flask and heat gently. After a short period the contents of the flask commence to froth and chloroform distils into the receiver. At this point great care must be exercised to prevent " frothing over " into the receiver. Shake the flask from time to time and break down the froth ; if the

foaming at any stage appears to be out of control, remove the small flame from beneath the flask and, if necessary, cool the flask by means of a large wet cloth. [A wet cloth should be at hand for this purpose.] As soon as the chloroform passes over into the receiver, continue the addition of the dilute acetone in small portions. When all the acetone has been run into the flask, add 10–15 ml. of water through the separatory funnel and continue heating the flask until the condensate is clear. Separate the lower layer of chloroform from the water, wash it once with an equal volume of 2 per cent. sodium hydroxide solution, and then with an equal volume of water. Carefully run off the lower layer of chloroform into a small conical flask, dry it over 2–3 g. of anhydrous calcium chloride for 15–20 minutes, filter it into a small distilling flask, and distil. Collect the fraction of b.p. 60–63°. The yield is 30 g.

Chloroform undergoes oxidation to the very poisonous phosgene upon exposure to light and air. Commercial specimens are therefore stored in brown bottles and contain 1–2 per cent. of alcohol; the latter converts the toxic phosgene into the harmless substance diethyl carbonate:

$$2CHCl_3 + O_2 \longrightarrow 2COCl_2 + 2HCl$$
$$COCl_2 + 2C_2H_5OH \longrightarrow (C_2H_5O)_2CO + 2HCl$$

CHLORAL HYDRATE, $CCl_3CH(OH)_2$

The student is recommended to carry out the following reactions with chloral hydrate in order to familiarise himself with its general properties.

(i) This substance, m.p. 52°, b.p. 97·5°, is of interest since it yields chloroform upon warming with dilute sodium hydroxide solution:

$$CCl_3CH(OH)_2 + NaOH \longrightarrow CHCl_3 + HCOONa + H_2O$$

Confirm this by treating 0·5 g. of chloral hydrate with 3 ml. of dilute sodium hydroxide solution and warming gently.

(ii) Treat 0·5 g. dissolved in 1 ml. of water with a little Schiff's reagent (Section **III,70**,(iii)): the colour is not restored.

(iii) Dissolve 0·5 g. in 1 ml. of water, add a little ammoniacal silver nitrate solution and warm. Metallic silver is deposited (compare Section **III,70**,(i)).

(iv) Repeat experiment (iii) with Fehling's solution as the reagent; the latter is reduced and some chloroform is produced, due to the action of the alkali present in the Fehling's solution.

(v) Place 5 g. of chloral hydrate and 5 ml. of concentrated sulphuric acid in a small dry distilling flask, and distil slowly. Collect the first 2–3 drops of the distillate in 2 ml. of Schiff's reagent: observe that the colour is immediately restored (this is because chloral, CCl_3CHO, the free aldehyde, is liberated by the acid). Continue the distillation and collect about 3 ml. of the liquid chloral in a dry test-tube; this gives all the reactions of aldehydes (see Section **III,70**). Treat a small portion with a few drops of water; the chloral hydrate is reformed.

III,44. BROMOFORM

Fit a 1000 ml. three-necked flask with a mechanical stirrer (*not* mercury sealed), a dropping funnel (Fig. *II*, *1*, 5,*f*) with stem reaching to almost the bottom of the flask, and another separatory funnel but with a short stem. Clamp the flask in a large beaker containing water maintained at 50°. Introduce into the flask 30 ml. (24 g.) of acetone and 150 ml. of 20 per cent. sodium carbonate solution. Place 75 ml. (234 g.) of bromine in the long-stemmed funnel and 10 per cent. sodium hydroxide solution in the other funnel (about 800 ml. are required). Set the stirrer in motion and allow the bromine to drop slowly into the well-stirred alkaline mixture. Bromoform soon separates out. As soon as the bromine is no longer decolourised, introduce the sodium hydroxide solution from the second separatory funnel slowly and at such a rate that the mixture in the flask does not become strongly alkaline. The correct rate of addition of the sodium hydroxide solution is attained when, on stopping the addition, the liquid immediately assumes the red colour of bromine. The bath should be maintained at 50° throughout the experiment. When all the bromine has been introduced, stop the addition of the alkali, remove the heavy layer of bromoform, wash it with water, and dry with anhydrous calcium chloride. (If desired, the dry bromoform may be shaken with concentrated sulphuric acid to remove impurities, but this is not always necessary.) Distil the crude bromoform, preferably in a current of carbon dioxide, and collect the fraction boiling at 148–149·5°; this has a m.p. of 7–8°. The yield is 68 g.

Pure bromoform is somewhat unstable and darkens on keeping; it may be stabilised by the addition of 4 per cent. of its weight of ethyl alcohol or of a small quantity of diphenylamine.

III,45. IODOFORM

Place a solution of 6 g. of potassium iodide in 100 ml. of water in a 500 ml. flask and add 2 ml. of acetone. Slowly add, with frequent shaking, a 5 per cent. solution of sodium hypochlorite (1) as long as any precipitate of iodoform is formed; about 65 ml. are required. Allow the mixture to stand for about 10 minutes, then filter at the pump, wash the crystals two or three times with water, and drain the crystals thoroughly. Recrystallise the crude iodoform from methylated spirit (or rectified spirit) in the following manner. Place the crude material in a 100 or 150 ml. round-bottomed flask fitted with a reflux water condenser; add a small volume of methylated spirit and heat to boiling on a water bath. Continue the addition of the methylated spirit, in small quantities down the condenser, until all the iodoform has dissolved; about 50 ml. are used. Filter the hot solution through a fluted filter paper into a conical flask or small beaker, and cool thoroughly. The iodoform crystallises rapidly. Filter at the pump, drain thoroughly, and allow the crystals to dry. Pure iodoform melts at 119°. The yield is 3·5 g.

Note.

(1) The commercial 10–14 per cent. sodium hypochlorite solution should be diluted with an equal volume of water.

III,46. METHYLENE BROMIDE

Methylene bromide (CH_2Br_2) and methylene iodide (CH_2I_2) are easily prepared by the reduction of bromoform or iodoform respectively with sodium arsenite in alkaline solution:

$$CHX_3 + Na_3AsO_3 + NaOH \longrightarrow CH_2X_2 + NaX + Na_3AsO_4 \ (X = Br \text{ or } I)$$

Methylene chloride CH_2Cl_2, b.p. 41°, is obtained as a by-product in the commercial preparation of chloroform by the reduction of carbon tetrachloride with moist iron and also as one of the products in the chlorination of methane; it is a useful extraction solvent completely immiscible with water.

In a 1-litre three-necked flask, mounted on a steam bath and provided respectively with a separatory funnel, mechanical stirrer and double surface condenser, place 165 g. of bromoform (96 per cent.). Add 10 ml. of a solution of sodium arsenite made by dissolving 77 g. of A.R. arsenious oxide and 148 g. of A.R. sodium hydroxide in 475 ml. of water. Warm the mixture gently to start the reaction, and introduce the remainder of the sodium arsenite solution during 30–45 minutes at such a rate that the mixture refluxes gently. Subsequently heat the flask on the steam bath for 3–4 hours. Steam distil the reaction mixture (Fig. *II*, *41*, 1) and separate the lower layer of methylene bromide (79 g.). Extract the aqueous layer with about 100 ml. of ether; a further 3 g. of methylene bromide is obtained. Dry with 3–4 g. of anhydrous calcium chloride, and distil from a Claisen flask with fractionating side arm. The methylene bromide boils constantly at 96–97° and is almost colourless.

III,47. METHYLENE IODIDE

In a 1-litre three-necked flask, fitted with a mechanical stirrer, reflux condenser and a thermometer, place 200 g. of iodoform and half of a sodium arsenite solution, prepared from 54·5 g. of A.R. arsenious oxide, 107 g. of A.R. sodium hydroxide and 520 ml. of water. Start the stirrer and heat the flask until the thermometer reads 60–65°; maintain the mixture at this temperature during the whole reaction (1). Run in the remainder of the sodium arsenite solution during the course of 15 minutes, and keep the reaction mixture at 60–65° for 1 hour in order to complete the reaction. Allow to cool to about 40–45° (2) and filter with suction from the small amount of solid impurities. Separate the lower layer from the filtrate, dry it with anhydrous calcium chloride, and distil the crude methylene iodide (131 g.; this crude product is satisfactory for most purposes) under diminished pressure. Practically all passes over as a light straw-coloured (sometimes brown) liquid at 80°/25 mm.; it melts at 6°. Some of the colour may be removed by shaking with silver powder. The small dark residue in the flask solidifies on cooling.

Notes.

(1) If the temperature is allowed to rise, the yield is slightly diminished owing to the formation of a little methyl iodide.

(2) If the temperature falls below 40°, a precipitate of sodium arsenate will gradually separate and this will tend to produce an emulsion of the methylene iodide, thus rendering filtration and separation difficult.

III,48. 1 : 2 : 3-TRIBROMOPROPANE

Provide a 1-litre three-necked flask with a dropping funnel carrying a cotton wool (or calcium chloride) guard tube, a mechanical stirrer, and a thermometer reaching almost to the bottom of the flask, and cool the flask in a mixture of ice and salt. Place in the flask 182 g. (132 ml.) of allyl bromide (1) and 250 ml. of dry carbon tetrachloride (2), and introduce 255 g. (80 ml.) of dry A.R. bromine (3) into the dropping funnel. Set the stirrer in motion and when the temperature has fallen to — 5°, drop the bromine in slowly at such a rate that the temperature does not rise above 0° (about 90 minutes). Allow the orange-coloured solution (the colour is due to a slight excess of bromine) to warm to room temperature with constant stirring (about 30 minutes) and then transfer it to a large separatory funnel. Arrange a 500 ml. Claisen flask, heated in an oilbath at 120°, for distilling the solvent (as in Fig. *II*, *13*, 4), and drop in the solution from the funnel at such a rate that the flask is never more than two-thirds full. When all the solution has been transferred to the flask, raise the temperature of the bath to 150° in order to remove as much solvent as possible. Distil the residue under reduced pressure (Fig. *II*, *20*, 1); the residual carbon tetrachloride passes over first, followed by 1 : 2 : 3-tribromopropane at 92–93°/10 mm. (or 100–103°/18 mm.) as an almost colourless liquid. The yield is 400 g.

$$CH_2BrCH{=}CH_2 + Br_2 \longrightarrow CH_2BrCHBrCH_2Br$$

Notes.

(1) The allyl bromide (Section III,35) should be dried over anhydrous calcium chloride and redistilled; the fraction b.p. 69–72° is collected for use in this preparation.

(2) Commercial carbon tetrachloride is dried by distilling and rejecting the first 10 per cent. of the distillate.

(3) Bromine is dried by shaking once with an equal volume of concentrated sulphuric acid.

ESTERS OF INORGANIC ACIDS

Strictly speaking the alkyl halides are esters of the halogen acids, but since they enter into many reactions (*e.g.*, formation of Grignard reagents, reaction with potassium cyanide to yield nitriles, etc.) which cannot be brought about by the other esters, the alkyl halides are usually distinguished from the esters of the other inorganic acids. The preparation of a number of these is described below.

Alkyl sulphites. From the alcohol and thionyl chloride, for example:

$$2C_4H_9^{\alpha}OH + SOCl_2 \longrightarrow \underset{\text{Di-}n\text{-butyl sulphite}}{(C_4H_9^{\alpha})_2SO_3} + 2HCl$$

Alkyl phosphates. From phosphorus oxychloride and the alcohol in the presence of pyridine, for example:

$$3C_4H_9^{\alpha}OH + POCl_3 + 3C_5H_5N \longrightarrow \underset{\text{Tri-}n\text{-butyl phosphate}}{PO(OC_4H_9^{\alpha})_3} + 3C_5H_5N,HCl$$

Alkyl borates. By heating boric acid with excess of the alcohol; the water formed in the reaction is removed by fractional distillation as an azeotropic mixture with the alcohol, for example:

$$B(OH)_3 + 3C_4H_9^{\alpha}OH \longrightarrow \underset{\text{Tri-}n\text{-butyl borate}}{B(OC_4H_9^{\alpha})_3} + 3H_2O$$

Alkyl thiocyanates. From potassium or sodium thiocyanate and the alkyl halide in alcoholic solution, for example:

$$KSCN + C_3H_7^{\alpha}Br \longrightarrow \underset{n\text{-Propyl thiocyanate}}{C_3H_7^{\alpha}SCN} + KBr$$

Alkyl nitrites. By the interaction at 0° of the alcohol with sodium nitrite in the presence of excess of concentrated sulphuric acid, for example:

$$C_5H_{11}^{\alpha}OH + HONO \xrightarrow{H_2SO_4} \underset{n\text{-Amyl nitrite}}{C_5H_{11}^{\alpha}ONO} + H_2O$$

Aliphatic nitro compounds. These are isomeric with the alkyl nitrites and may be prepared from the alkyl halide and silver nitrite, for example:

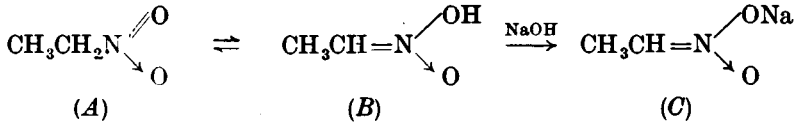
$$C_4H_9^{\alpha}Br + AgNO_2 \longrightarrow \underset{\text{1-Nitro-}n\text{-butane}}{C_4H_9^{\alpha}NO_2} + AgBr$$

Nitromethane is more easily prepared by heating together equimolecular amounts of sodium monochloroacetate and sodium nitrite in aqueous solution; sodium nitroacetate is intermediately formed and is decomposed to nitromethane and sodium bicarbonate. The latter yields sodium carbonate and carbon dioxide at the temperature of the reaction.

$$ClCH_2COONa + NaNO_2 \longrightarrow NO_2CH_2COONa + NaCl$$
$$NO_2CH_2COONa + H_2O \longrightarrow CH_3NO_2 + NaHCO_3$$

Nitroethane may be similarly obtained from sodium α-chloropropionate. This is a general reaction for α-chloro-carboxylic acids, but in practice only monochloroacetic acid and α-chloropropionic acid are readily available.

The nitroparaffins in which the nitro group is attached to a primary or secondary carbon atom exist in tautomeric forms, for example:



(*A*) (*B*) (*C*)

The normal form *A* can pass by tautomeric change under the influence of alkali into the acidic hydroxy form *B*, which in turn can yield the sodium salt *C*. Nitroparaffins are therefore pseudo-acids, and are soluble in alkaline solution.

The simpler nitroparaffins (nitromethane, nitroethane, 1- and 2-nitropropane) are now cheap commercial products. They are obtained by the vapour phase nitration of the hydrocarbons: a gaseous mixture of two mols of hydrocarbon and 1 mol of nitric acid vapour is passed through a narrow reaction tube at 420–475°. Thus with methane at 475° a 13 per cent. conversion into nitromethane is obtained; ethane at 420° gives a 9 : 1 mixture of nitroethane (b.p. 114°) and nitromethane (b.p. 102°); propane at 420° affords a 21 per cent. yield of a complex mixture of 1- (b.p. 130·5°) and 2-nitropropane (b.p. 120°), nitroethane and nitromethane, which are separated by fractional distillation.

Alkyl sulphates. The dimethyl and diethyl esters may be prepared *inter alia* by the interaction of chlorosulphonic acid with the anhydrous alcohol, followed by distillation of the resulting alkyl sulphuric acid under diminished pressure, for example:

$$CH_3OH + ClSO_3H \longrightarrow CH_3OSO_3H + HCl$$
$$2CH_3OSO_3H \longrightarrow CH_3OSO_2OCH_3 + H_2SO_4$$

The preparation of these compounds in the laboratory is not recommended and is rarely worth while because of the cheapness of the commercial products. **Dimethyl sulphate** is a heavy liquid, boiling at 188·5°, and is practically without odour. *The vapour is highly poisonous and the substance should only be used in a fume cupboard with a good draught. The liquid itself is readily absorbed through the skin, with toxic results.*

Dimethyl sulphate is of particular value for the methylation of phenols and sugars. The phenol is dissolved in a slight excess of sodium hydroxide solution, the theoretical quantity of dimethyl sulphate is added, and the mixture is heated on a water bath and shaken or stirred mechanically (compare Section IV,104). Under these conditions only one of the methyl groups is utilised; the methyl hydrogen sulphate formed in the reaction reacts with the alkali present:

$$ROH + (CH_3)_2SO_4 + NaOH \longrightarrow ROCH_3 + CH_3NaSO_4 + H_2O$$

Diethyl sulphate, b.p. 210° (decomp.), does not ordinarily react so vigorously as dimethyl sulphate, but is nevertheless of great value for ethylations. It is somewhat less poisonous than the methyl analogue, but the same precautions should be taken. Both sulphates should be stored in glass-stoppered bottles sealed with paraffin wax, for they attack cork.

III,49. *n*-BUTYL SULPHITE

Fit up the apparatus shown in Fig. *III, 31*, 1; the capacity of the Claisen flask should be 100 ml. Place 40 g. (24·5 ml.) of redistilled thionyl chloride in the flask and 50 g. (62 ml.) of dry *n*-butyl alcohol (b.p. 116–117°) in the dropping funnel. Cool the flask in ice and add the *n*-butyl alcohol, with frequent shaking, over 1 hour (1). Reflux the mixture gently for 1 hour to complete the reaction and to remove the residual hydrogen chloride. Arrange the apparatus for distillation, and distil under normal pressure until the temperature rises to 120°; then distil under diminished pressure (Fig. *II, 20*, 1) and collect the di-*n*-butyl sulphite at 116–118°/20 mm. The yield is 55 g.

Note.

(1) For preparations on a larger scale, a three-necked flask should be used and mechanical stirring substituted for hand shaking.

COGNATE PREPARATIONS

Methyl sulphite. From 22 g. (28 ml.) of anhydrous methyl alcohol and 40 g. (24·5 ml.) of thionyl chloride. B.p. 126°. Yield : 31 g.

Ethyl sulphite. From 40 g. (51 ml.) of absolute ethyl alcohol and 52 g. (32 ml.) of thionyl chloride. B.p. 156–157°. Yield : 40 g.

***n*-Amyl sulphite.** From 55 g. (67·5 ml.) of *n*-amyl alcohol and 40 g. (24·5 ml.) of thionyl chloride. B.p. 111·5°/5 mm. Yield : 53 g.

III,50. *n*-BUTYL PHOSPHATE

The apparatus required is a 1-litre three-necked flask, the three necks of which carry respectively a double surface condenser, a mercury-sealed stirrer, and a short-stemmed dropping funnel and a thermometer (passing through a two-holed cork). Calcium chloride (or cotton wool) guard tubes should be provided for the dropping funnel and the reflux condenser. Place 111 g. (137 ml.) of dry *n*-butyl alcohol, 130 g. (132·5 ml.) of dry pyridine and 140 ml. of dry benzene in the flask, set the stirrer in motion and cool the flask in an ice-salt mixture until the temperature falls to — 5°. Introduce 76·5 g. (40·5 ml.) of redistilled phosphorus oxychloride (b.p. 106–107°) dropwise from the funnel at such a rate that the temperature does not rise above 10°. Reflux gently for 2 hours, and then allow to cool to room temperature. Add 250 ml. of water to dissolve the pyridine hydrochloride, separate the benzene layer, wash it several times with water until the washings are neutral, and dry over 10 g. of anhydrous sodium or magnesium sulphate. Remove most of the benzene under normal pressure (Fig. *II*, *13*, 4 but with a Claisen flask replacing the distilling flask), and finally distil under diminished pressure. Collect the *n*-butyl phosphate at 160–162°/15 mm. (or 138–140°/6 mm.). The yield is 95 g.

The above is a general procedure for preparing trialkyl orthophosphates. Similar yields are obtained for **trimethyl phosphate**, b.p. 62°/5 mm.; **triethyl phosphate**, b.p. 75·5°/5 mm.; **tri-*n*-propyl phosphate**, b.p. 107·5°/5 mm.; **tri-*iso*-propyl phosphate**, b.p. 83·5°/5 mm.; **tri-*iso*-butyl phosphate**, b.p. 117°/5·5 mm.; and **tri-*n*-amyl phosphate**, b.p. 167·5°/5 mm. The alkyl phosphates are excellent alkylating agents for primary aromatic amines (see Section IV,41); they can also be used for alkylating phenols (compare Sections IV,104–105). Trimethyl phosphate also finds application as a methylating agent for aliphatic alcohols (compare Section III,58).

III,51. *n*-BUTYL BORATE

The apparatus required consists of a 1-litre bolt-head flask carrying a dropping funnel and a 30 cm. Hempel column filled with $\frac{1}{4}''$ glass rings or with $\frac{1}{8}''$ porcelain rings (Fig. *II*, *15*, 3 ; compare Fig. *III*, *61*, 1) or a 30 cm. all-glass Dufton column (Fig. *II*, *15*, 2) connected to an efficient double surface condenser or to a long (40–50 cm.) Liebig condenser. The fractionating column is fitted with a thermometer. Place 62 g. of A.R. boric acid, 333 g. (412 ml.) of *n*-butyl alcohol and a few chips of porous porcelain in the flask. Heat the reaction mixture (*e.g.*, in an air bath, Fig. *II*, *5*, 3) so that it boils gently, and adjust the rate of heating so

that 45–50 ml. of distillate are collected in 30 minutes. The temperature of the vapour at the top of the column remains at 91° over a period of about 2 hours whilst an azeotropic mixture of water and *n*-butyl alcohol distils ; the latter separates into two layers and contains about 72 per cent. of wet alcohol. After 1 hour separate the upper layer of *n*-butyl alcohol in the distillate, dry it with anhydrous potassium carbonate or anhydrous magnesium sulphate, and return it to the flask through the dropping funnel ; repeat this process after 90 minutes of heating. Subsequently the temperature at the top of the column rises slowly as most of the water is removed, and when the temperature has risen to 110–112° (after 2 hours or so) stop the heating. Transfer the reaction mixture as rapidly as possible (to minimise the hydrolysis of the *n*-butyl borate by moisture in the atmosphere) to a 1-litre Widmer flask (Fig. *II*, *24*, 3 : this should have a 25–30 cm. fractionating side arm and be well lagged) and distil under reduced pressure (Fig. *II*, *20*, 1). The unreacted *n*-butyl alcohol passes over first, and the temperature then rises sharply. The receiver is changed, and the *n*-butyl borate is collected at 114–115°/15 mm. (or 103–105°/8 mm.). The yield is 210 g.

COGNATE PREPARATION

***n*-Amyl Borate.** Use 62 g. of A.R. boric acid and 396 g. (490 ml.) of *n*-amyl alcohol. During the first hour the azeotropic mixture, containing approximately 44 per cent. of *n*-amyl alcohol and 56 per cent. of water, passes over at 95° : subsequently the temperature rises slowly to 136–137°. It is unnecessary to return the recovered *n*-amyl alcohol to the reaction mixture. The yield of *n*-amyl borate, b.p. 146–148°/16 mm., is 260 g.

III,52. *n*-PROPYL THIOCYANATE

Fit a 1-litre three-necked flask with a mercury-sealed stirrer, a reflux condenser and a 250 ml. separatory funnel. Place 133 g. of A.R. potassium thiocyanate and 310 ml. of rectified spirit in the flask, stir the mixture vigorously and heat to boiling. Run in from the separatory funnel 154 g. (113·5 ml.) of *n*-propyl bromide (Section **III,35**) during the course of 15–20 minutes ; potassium bromide separates. Reflux the mixture, with vigorous stirring, for 5 hours ; the stirring must be vigorous otherwise bumping occurs. Filter off the precipitated potassium bromide from the cold reaction mixture (1) and wash it with 75 ml. of rectified spirit. Distil off as much of the alcohol as possible on a water bath through a short column. Treat the residue in the flask with 125 ml. of water, and separate the upper layer of *n*-propyl thiocyanate. Extract the aqueous layer with two 50 ml. portions of ether. Combine the ether extracts with the crude thiocyanate, dry with anhydrous sodium or magnesium sulphate, and remove most of the ether on a water bath. Distil the residue through an efficient fractionating column (*e.g.*, a long all-glass Dufton column, Fig. *II*, *15*, 2 ; a Hempel column filled with $\frac{1}{8}''$ porcelain rings or with $\frac{1}{4}''$ glass rings, Fig. *II*, *15*, 3 : a modified Hempel column, Fig. *II*, *15*, 5) ; all these columns must be well lagged with asbestos cloth and preferably heated electrically. A little ether, ethyl alcohol and water pass over first (to 110°) ; the temperature then rises rapidly to

164–165° and the remainder distils constantly at 165°. The yield of *n*-propyl thiocyanate is 93 g.

Note.

(1) The evil-smelling residue in the reaction flask is best removed by the cautious addition of concentrated nitric acid.

COGNATE PREPARATION

***n*-Butyl thiocyanate.** Use 133 g. of A.R. potassium thiocyanate, 310 ml. of rectified spirit and 172 g. (135 ml.) of *n*-butyl bromide. The yield of *n*-butyl thiocyanate, b.p. 183–184°, is 126 g.

III,53. *n*-AMYL NITRITE

Equip a 1-litre three-necked flask with a powerful mechanical stirrer, a separatory funnel with stem extending to the bottom of the flask, and a thermometer. Cool the flask in a mixture of ice and salt. Place a solution of 95 g. of A.R. sodium nitrite in 375 ml. of water in the flask and stir. When the temperature has fallen to 0° (or slightly below) introduce slowly from the separatory funnel a mixture of 25 ml. of water, 62·5 g. (34 ml.) of concentrated sulphuric acid and 110 g. (135 ml.) of *n*-amyl alcohol, which has previously been cooled to 0°. The rate of addition must be controlled so that the temperature is maintained at ± 1°; the addition takes 45–60 minutes. Allow the mixture to stand for 1·5 hours and then filter from the precipitated sodium sulphate (1). Separate the upper yellow *n*-amyl nitrite layer, wash it with a solution containing 1 g. of sodium bicarbonate and 12·5 g. of sodium chloride in 50 ml. of water, and dry it with 5–7 g. of anhydrous magnesium sulphate. The resulting crude *n*-amyl nitrite (107 g.) is satisfactory for many purposes (2). Upon distillation, it passes over largely at 104° with negligible decomposition. The b.p. under reduced pressure is 29°/40 mm.

Notes.

(1) Care must be exercised in handling *n*-amyl and the other alkyl nitrites; inhalation of the vapour may cause severe headache and heart excitation. The preparation must therefore be conducted in an efficient fume cupboard.

(2) *n*-Amyl and other alkyl nitrites decompose slowly upon standing and should be kept in a cool place. They must be used within a few days or, at most within two weeks of their preparation. The decomposition products include water, oxides of nitrogen, the alcohol and polymerisation products of the aldehyde.

COGNATE PREPARATION

***n*-Hexyl nitrite.** Use 95 g. of A.R. sodium nitrite in 375 ml. of water; a mixture of 25 ml. of water, 62·5 g. (34 ml.) of concentrated sulphuric acid and 127·5 g. (156 ml.) of *n*-hexyl alcohol. The yield of crude product is 124 g. B.p. 129–130·5° or 52°/44 mm.

***n*-Butyl nitrite.** Use quantities as for n-*Hexyl nitrite*, but with 114·5 g. (141·5 ml.) of *n*-butyl alcohol replacing the *n*-hexyl alcohol. The yield of crude product is 110 g. *n*-Butyl nitrite boils at 76·5–77·5° at atmospheric pressure with slight decomposition, but distils unchanged at 27°/88 mm.

III,54. 1-NITRO-*n*-BUTANE (*$AgNO_2$ Method*)

In a 200 ml. distilling flask place 64 g. (50 ml.) of dry *n*-butyl bromide and 80 g. of dry silver nitrite (1). Insert a reflux condenser, carrying a cotton wool (or calcium chloride) guard tube, into the mouth of the flask and close the side arm with a small stopper. Allow the mixture to stand for 2 hours; heat on a steam bath for 4 hours (some brown fumes are evolved), followed by 8 hours in an oil bath at 110°. Distil the mixture and collect the fraction of b.p. 149–151° as pure 1-nitro-*n*-butane (18 g.). A further small quantity may be obtained by distilling the fractions of low boiling point from a Widmer flask.

Note.

(1) The silver nitrite may be prepared as described in Section II,50, *17*. The product supplied by Johnson, Matthey and Co. Ltd., of Hatton Garden, London, E.C. 1, is satisfactory; it should be washed with absolute methyl or ethyl alcohol, followed by sodium-dried ether, and dried in an electrically-heated oven at 100° for 30 minutes (longer heating results in darkening on the surface): the substance should be kept in a vacuum desiccator until required.

Cognate Preparation

1-Nitro-*n*-hexane. Use 41 g. of dry silver nitrite, 51 g. of *n*-hexyl iodide (35·5 ml.) and 100 ml. of sodium dried ether. Reflux on a water bath for 8 hours; decant the ethereal solution and wash the solid well with sodium-dried ether. Distil the residue, after the removal of the ether from the combined extracts, from 5 g. of dry silver nitrite, and collect the fraction of b.p. 190–192° (13 g.) as 1-nitro-*n*-hexane. The pure compound is obtained by distilling under diminished pressure: b.p. 81·5°/15 mm.

III,55. NITROMETHANE

To a mixture of 125 g. of chloroacetic acid (Section **III,125**) and 125 g. of crushed ice contained in a 1-litre distilling flask, add, with stirring or shaking, sufficient 40 per cent. sodium hydroxide solution * to render the solution faintly alkaline to phenolphthalein. About 90 m l. are required; the temperature should not be allowed to rise above 20°,or else sodium glycolate will form. Introduce a solution of 73 g. of pure sodium nitrite in 100 ml. of water into the flask; insert a thermometer dipping well into the liquid. Connect the distilling flask to an efficient (*e.g.*, double surface) condenser set for downward distillation; the receiver should preferably be cooled in ice water. Heat the mixture slowly until the first appearance of bubbles of carbon dioxide; this occurs when the temperature has reached 80–85°. Immediately remove the flame. The reaction (decomposition of the sodium nitroacetate) sets in with liberation of heat and the temperature rises to almost 100° without further application of external heat. If heat is applied after the temperature of the reaction mixture reaches 85°, much frothing will occur and serious loss of nitromethane will result. If the reaction becomes too vigorous, it may be checked somewhat by applying a wet cloth to the flask. During

* Alternatively, effect the neutralisation with about 75 g. of finely-powdered, anhydrous sodium carbonate added in small portions with frequent shaking.

the exothermic reaction about 30 ml. of nitromethane, accompanied by about 40 ml. of water, distil over. When the exothermic reaction apparently ceases (temperature below 90°), heat the mixture gently until the temperature rises to 110°. Transfer the distillate to a separatory funnel, allow to stand for at least 30 minutes to complete the separation of the two layers, and remove the lower layer of nitromethane. Dry it with anhydrous calcium chloride or anhydrous calcium sulphate and distil: 30 g. of nitromethane, b.p. 100–102°, are obtained. A further small quantity (3–4 g.) may be isolated by mixing the aqueous layer with one quarter of its weight of sodium chloride, distilling, and separating the nitromethane from the distillate.

(For a discussion of the *Reactions and Characterisation of Aliphatic Nitro Compounds*, see Section **IV,16B.**)

ALIPHATIC ETHERS

Diethyl ether may be prepared from ethyl alcohol by the "sulphuric acid process." A mixture of alcohol and sulphuric acid in equimolecular proportions is heated to about 140° and alcohol is run in at the rate at which the ether produced distils from the reaction mixture. Ethyl hydrogen sulphate (or ethyl sulphuric acid) is first formed and this yields ether either by reacting directly with a molecule of alcohol or by the formation and alcoholysis of diethyl sulphate (I):

1. $C_2H_5OH + HOSO_2OH \longrightarrow C_2H_5OSO_2OH + H_2O$

2. $C_2H_5OSO_2OH + HOC_2H_5 \xrightarrow{140°} C_2H_5OC_2H_5 + HOSO_2OH$

3. $C_2H_5OSO_2OH + HOC_2H_5 \longrightarrow C_2H_5OSO_2OC_2H_5\ (I) + H_2O$

4. $C_2H_5OSO_2OC_2H_5 + C_2H_5OH \xrightarrow{140°} C_2H_5OC_2H_5 + C_2H_5OSO_2OH$

If the temperature is allowed to rise to 170°, much of the ethyl hydrogen sulphate decomposes into ethylene:

5. $C_2H_5OSO_2OH \xrightarrow{170°} CH_2{=}CH_2 + HOSO_2OH$

The sulphuric acid and ethyl hydrogen sulphate required in reactions *1* and *3* respectively are regenerated in reactions *2* and *4*, but the water formed is retained in the acid mixture and ultimately results in such a dilution that the conversion into ether is no longer efficient. Furthermore, some ethylene is always formed; this partly polymerises to give materials capable of reacting with sulphuric acid and reducing it to sulphur dioxide. In industrial practice, one part of sulphuric acid is sufficient for the production of about 200 parts of ether.

The above simple process cannot be applied to the preparation of the homologues; a higher temperature is required (di-*n*-amyl ether, for example, boils at 169°) and, under these conditions, alkene formation predominates, leading ultimately to carbonisation and the production of sulphur dioxide. If, however, the water is largely removed by means of a special device (see Fig. *III*, *57*, 1) as soon as it is formed, good yields of ethers may be obtained from primary alcohols, for example:

$$\underset{n\text{-Butyl alcohol}}{2C_4H_9{}^{\alpha}OH} \xrightarrow{H_2SO_4} \underset{\text{Di-}n\text{-butyl ether}}{C_4H_9{}^{\alpha}OC_4H_9{}^{\alpha}} + H_2O$$

Mixed ethers may be prepared by the interaction of an alkyl halide and a sodium alkoxide (**Williamson's synthesis**), for example:

$$\underset{n\text{-Hexyl alcohol}}{2C_6H_{13}{}^{\alpha}OH} + 2Na \longrightarrow \underset{\text{Sodium } n\text{-hexyloxide}}{2C_6H_{13}{}^{\alpha}ONa} + H_2$$

$$C_6H_{13}{}^{\alpha}ONa + C_2H_5I \longrightarrow \underset{\text{Ethyl } n\text{-hexyl ether}}{C_6H_{13}{}^{\alpha}OC_2H_5} + NaI$$

Higher alcohols ($> C_3$) react comparatively slowly with sodium because of the slight solubility of the sodium alkoxide in the alcohol; a large excess (say, 8 mols) is therefore employed. The mixed ether is distilled off, and the process (formation of alkoxide and its reaction with the alkyl halide) may be repeated several times. The excess of alcohol can be recovered.

*cyclo*Aliphatic alcohols form sodio compounds with difficulty if small pieces

of sodium are employed; the best results are given by " molecular " (granulated) sodium (Section II,50,*6*), for example:

$$C_6H_{11}ONa + C_2H_5I \longrightarrow \underset{\textit{cyclo}\text{Hexyl ethyl ether}}{C_6H_{11}OC_2H_5} + NaI$$

The preparation of anhydrous diethyl ether (suitable for Grignard reactions, etc.) is described in Section II,47,*1*. The precautions required in handling ether are given in Section II,14.

III,56. DIETHYL ETHER *

Assemble the apparatus shown in Fig. *III*, *56*, 1. Fit the 500 ml. distilling flask with a two-holed cork carrying a thermometer reaching to

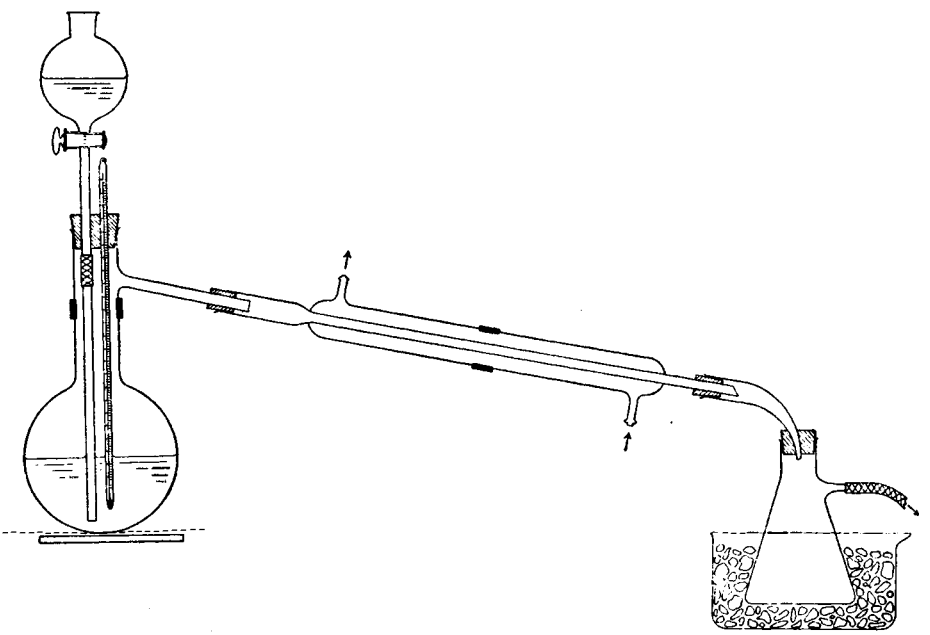


Fig. *III*, *56*, 1.

within 1 cm. of the bottom of the flask and a dropping funnel. Extend the stem of the dropping funnel by means of glass tubing of the same size as the stem of the funnel; make the connection (" glass to glass ") with rubber " pressure " tubing *above* the side arm of the flask. Pass the side arm of the distilling flask through a cork in the upper end of a long Liebig or preferably a double surface condenser; the lower end of the latter passes through an adapter into a filter flask cooled in crushed ice or ice water. Attach to the filter flask a length of rubber tubing leading below the level of the bench, so that any ether escaping condensation cannot return to the vicinity of the flame. Make sure that the stopcock of the separatory funnel is well greased and that all joints fit well.

* The preparation of diethyl ether is described here for the sake of completeness. It is an unsuitable exercise for beginners. Di-*n*-butyl ether (Section III,57) offers an excellent alternative.

Pour 75 ml. of rectified spirit into the flask and add cautiously, with frequent shaking to ensure thorough mixing, 75 ml. of concentrated sulphuric acid. Reassemble the apparatus and see that the extension of the dropping funnel and the thermometer are below the surface of the liquid. Place 150 ml. of rectified spirit in the dropping funnel. Heat the flask on a wire gauze until the thermometer records a temperature of 140°, and run in the alcohol at approximately the same rate as the liquid distils. The temperature must be kept constant between 140° and 150° throughout the addition of alcohol. When all the alcohol has been introduced into the flask (about 90 minutes), continue the heating and maintain the temperature at 140–145° for a few minutes, and then extinguish the flame beneath the flask. Transfer the distillate, composed of ether mixed with a little alcohol, water and sulphurous acid, to a separatory funnel; shake it with 30 ml. of 5 per cent. sodium hydroxide solution, allow the mixture to settle and draw off the alkali solution (lower layer). Repeat the process of shaking and drawing off the lower layer first with 25 ml. of water, and then with 30 ml. of 50 per cent. calcium chloride solution (to remove most of the alcohol). Pour the ether from the mouth of the funnel to a dry conical flask containing 10–15 g. of anhydrous calcium chloride (this will remove both the water and the residual alcohol) allow the ether to stand, with occasional shaking, in the stoppered flask for at least 30 minutes but preferably for several hours. Filter the ether through a fluted filter paper (Section **II,29**) directly into a 150 ml. distilling flask containing a few fragments of porous porcelain, and arrange the remainder of the apparatus exactly as in Fig. *III*, *56*, 1 except that the dropping funnel is omitted and the thermometer bulb is just below the level of the side arm. Heat the flask in a large beaker of water; the water should have previously been heated to 50–60° at some distance from the apparatus. Arrange the depth of the flask in the water bath so that the ether distils slowly. Collect the fraction boiling between 33° and 38°. The yield is 60–65 g. Pure ether boils at 34°.

Note.

The student should read Section **II,14** on the precautions attending the use of inflammable solvents before commencing the above preparation.

III,57. DI-*n*-BUTYL ETHER

The success of this preparation depends upon the use of the apparatus (1) depicted in Fig. *III*, *57*, 1, which permits of the automatic separation of the water produced in the reaction; this will be termed a water-separator tube. Convenient dimensions for students' preparations are indicated in the diagram. Determine the volume v of the tube up to the neck, *i.e.*, between A and B, by adding water from a burette. The quantity of water which should be eliminated, assuming a quantitative conversion of the alcohol into the ether, may be computed from the equation:

$$\underset{2 \times 74 \text{ g.}}{2C_4H_9^{\alpha}OH} - \underset{18 \text{ g.}}{H_2O} = \underset{130 \text{ g.}}{(C_4H_9^{\alpha})_2O}$$

Thus 50 g. of *n*-butyl alcohol should yield $50 \times 18/148 = 6{\cdot}1$ g. of water.

Assemble the apparatus illustrated in Fig. *III*, *57*, 2. *D* is a 200 ml. Pyrex bolt-head flask carrying the water-separator tube *C* and a thermometer, the bulb of which is about 1 cm. from the bottom of the flask: *E* is a small Liebig condenser. Place (v — 6·1 ml.) of water in the tube *AB* and 50 g. (62 ml.) of *n*-butyl alcohol together with 16 g. (9 ml.) of concentrated sulphuric acid in the flask *D*. Heat the flask gently on a wire gauze so that the liquid refluxes and is condensed by the condenser *E*. Water and *n*-butyl alcohol will first collect in *C*, and when the combined volumes exceed v ml., automatic separation of the two liquids will commence; the water will fall to the bottom of the tube *AB* and the lighter *n*-butyl alcohol will pass back into the flask. Continue the heating until the temperature inside the flask rises to 134–135° (after 30–40 minutes) and there is a smell of an unsaturated hydrocarbon (butylene) at the top of the condenser. At this stage 5–6 ml. of water will have collected in *AB* and the reaction may be regarded as complete. Further heating will merely result in considerable darkening of the mixture in the flask and the formation of the highly inflammable butylene. Allow the reaction mixture to cool or cool the flask under running water from the tap (2). Pour the contents of the flask and water-separator tube into a separatory funnel containing 100 ml. of water, shake well, and remove the upper layer containing the crude ether mixed with a little unchanged *n*-butyl alcohol. Shake the crude ether with 25 ml. of cold 50 per cent. sulphuric acid by weight (from 20 ml. of concentrated acid and 35 ml. of water) (3) for 2–3 minutes, separate the upper layer and repeat the extraction with another 25 ml. of the acid. Finally, wash twice with 25 ml. portions of water, dry with 2 g. of anhydrous calcium chloride. Filter through a fluted filter paper or a small cotton wool plug (supported in a small funnel) into a 50 ml. distilling flask, and distil. Collect the *n*-butyl ether at 139–142°. The yield is 15 g.

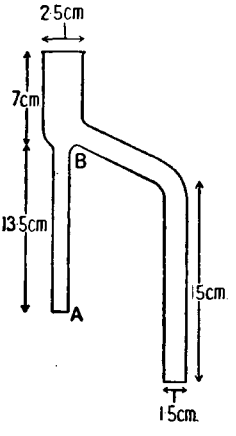


Fig. *III*, *57*, 1.

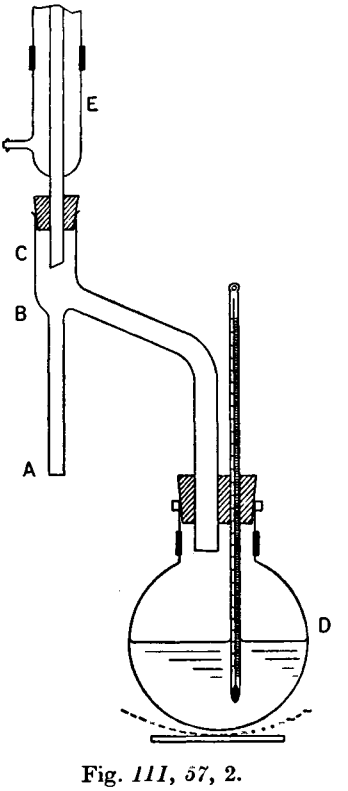


Fig. *III*, *57*, 2.

Notes.

(1) This is essentially a "Dean and Stark" tube (employed for determinations of moisture) but uncalibrated; the capacity of this receiver is 7·5–10 ml. A tube calibrated in 0·1 ml. may, of course, be employed, but for large classes the cheaper uncalibrated tube possesses obvious advantages.

(2) An alternative method for isolating the *n*-butyl ether utilises the fact that *n*-butyl alcohol is soluble in saturated calcium chloride solution whilst *n*-butyl ether is slightly soluble. Cool the reaction mixture in ice and transfer to a separatory funnel. Wash cautiously with 100 ml. of 2·5–3*N* sodium hydroxide solution; the washings should be alkaline to litmus. Then wash with 30 ml. of water, followed by 30 ml. of saturated calcium chloride solution. Dry with 2–3 g. of anhydrous calcium chloride, filter and distil. Collect the di-*n*-butyl ether at 139–142°. The yield is 20 g.

(3) This separation utilises the fact that *n*-butyl alcohol is soluble in 50 per cent. sulphuric acid by weight, whilst *n*-butyl ether is only slightly soluble.

Cognate Preparations

Di-*n*-amyl ether. Use 50 g. (61·5 ml.) of *n*-amyl alcohol (b.p. 136–137°) and 7 g. (4 ml.) of concentrated sulphuric acid. The calculated volume of water (5 ml.) is collected when the temperature inside the flask rises to 157° (after 90 minutes). Steam distil the reaction mixture, separate the upper layer of the distillate and dry it with anhydrous potassium carbonate. Distil from a 50 ml. Claisen flask and collect the fractions of boiling point (i) 145–175° (13 g.), (ii) 175–185° (8 g.) and (iii) 185–190° (largely 185–185·5°) (13 g.). Combine fractions (i) and (ii), reflux for 1 hour in a small flask with 3 g. of sodium, and distil from the sodium amyloxide and excess of sodium; this yields 9·5 g. of fairly pure *n*-amyl ether (iv). The total yield is therefore 22·5 g. A perfectly pure product, b.p. 184–185°, is obtained by further distillation from a little sodium.

Di-*iso*-amyl ether. Use 50 g. (62 ml.) of *iso*-amyl alcohol ("fermentation" alcohol, b.p. 131°). The calculated volume of water (5 ml.) is collected when the temperature inside the flask rises to 148–150° (after 90 minutes). Proceed as for n-*Amyl ether* and collect the fractions of b.p. 135–150° (14 g.), 150–168° (10 g.) and 168–174° (10 g.). After distillation over sodium the yield of *iso*-amyl ether, b.p. 170–171·5°, is 24 g.

Di-*n*-hexyl ether. Use 50 g. (61 ml.) of *n*-hexyl alcohol (b.p. 156–157°) and 6 g. (3·5 ml.) of concentrated sulphuric acid, and heat until the temperature rises to 180°. Pour the reaction mixture into water, separate the upper layer, wash it twice with 5 per cent. sodium hydroxide solution, then with water, and dry over anhydrous potassium carbonate. Distil from a 50 ml. Claisen flask, and collect the fractions of b.p. (i) 160–221° (17 g.), and (ii) 221–223° (17 g.). Reflux fraction (i) with 4 g. of sodium and distil from the excess of sodium: 9·5 g. of fairly pure *n*-hexyl ether, fraction (iii), are thus obtained. Combine fractions (ii) and (iii) and distil from a little sodium; collect the pure *n*-hexyl ether (19 g.) at 221·5–223°.

III,58. ETHYL *n*-HEXYL ETHER

Place 204 g. (249·5 ml.) (2 gram mols) of dry *n*-hexyl alcohol in a 350 ml. Claisen flask with fractionating side arm. Introduce 5·75 g. (0·25 gram atoms) of clean sodium in small pieces and warm under reflux (as in Fig. *III*, *58*, 1 but with dropping funnel omitted *) until all the sodium has reacted (*ca.* 2 hours). Introduce 39 g. (20 ml.) (0·25 gram

* Close the side arm of the flask with a small cork during the refluxing period.

mols) of ethyl iodide from the dropping funnel and reflux gently for 2 hours; sodium iodide gradually separates. Rearrange the apparatus for distillation and collect the crude ether at 143–148° (27 g.). When cold, fit up the apparatus as in Fig. *III*, *58*, 1, add a further 5·75 g. (0·25 gram atoms) of clean sodium and warm until all has reacted: alternatively, allow the reaction to proceed overnight, by which time all the sodium will have reacted. Introduce a further 39 g. (0·25 gram atoms) of ethyl iodide and reflux for 2 hours; distil off the crude ether and collect the fraction passing over at 143–148°. Combine the two distillates. Remove most of the *n*-hexyl alcohol still present in the crude ether by heating under reflux for 2 hours with a large excess of sodium: fit a bent tube (to act as a still head) to the flask and distil until no more liquid passes over. Distil the resulting liquid from a few grams of sodium contained in a Claisen flask with fractionating side arm and collect the ethyl *n*-hexyl ether at 140–143°. The yield is 30 g. If the sodium is appreciably attacked, indicating that all the alcohol has not been completely removed, repeat the distillation from a little fresh sodium.

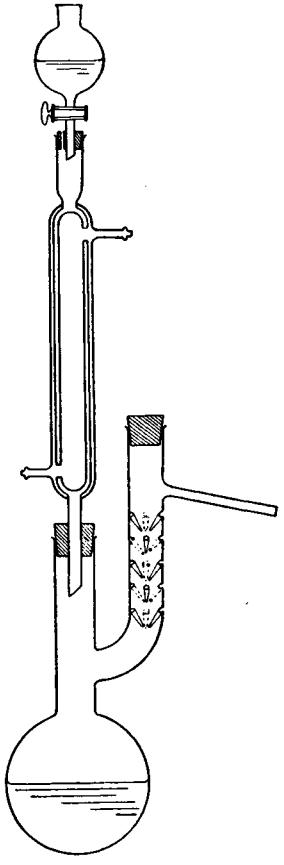


Fig. *III*, *58*, 1.

COGNATE PREPARATIONS

Methyl *n*-hexyl ether. Use 204 g. (249·5 ml.) of *n*-hexyl alcohol, 2 × 5·75 g. of clean sodium, and 2 × 35·5 g. (2 × 15·5 ml.) of methyl iodide. The yield of methyl *n*-hexyl ether, b.p. 125–126° is 42 g.

Methyl *n*-butyl ether. Use 148 g. (183 ml.) of *n*-butyl alcohol, 2 × 5·75 g. of clean sodium, and 2 × 35·5 g. (2 × 15·5 ml.) of methyl iodide. The yield of methyl *n*-butyl ether, b.p. 70–71°, is 31 g.

III,59. *cyclo*HEXYL ETHYL ETHER

Prepare 15·5 g. of "molecular" sodium (granulated sodium) under xylene (Section **II,50,6**) and replace the xylene completely by 100 ml. of sodium-dried ether. Attach a double surface condenser to the flask and introduce slowly, with frequent shaking, a solution of 66 g. of pure *cyclo*hexanol in 50 ml. of anhydrous ether. Allow the reaction mixture to stand overnight to complete the formation of the sodio compound. Add 108 g. (56 ml.) of ethyl iodide: shake the mixture when the ether will boil gently. Allow the reaction to proceed for 12–18 hours: a blue solid separates. Fit a bent tube (to act as a still head) and a condenser to the flask, and distil off the diethyl ether on a water bath; then replace the water bath by an air bath (Fig. *II*, *5*, 3) and distil as long as liquid passes over. Reflux the distillate (containing some unchanged *cyclo*-hexanol) with a large excess of sodium and distil again.

Finally distil from a well-lagged Widmer flask (compare Figs. *II*, *24*, 2–5) over a little sodium. Collect the *cyclo*-hexyl ethyl ether at 148–150°. The yield is 21 g. If the sodium is appreciably attacked, repeat the distillation from a fresh quantity of sodium.

III,60. REACTIONS AND CHARACTERISATION OF ALIPHATIC ETHERS

Chemically, the ethers are inert compounds. The important reactions are :—

(i) After being dried with anhydrous calcium chloride, they do not react with sodium (compare alcohols and esters).

(ii) They are not attacked by dilute acid or by alkali (compare esters).

(iii) They generally dissolve in concentrated sulphuric acid to give *clear* solutions, and are precipitated upon dilution with water. This test is carried out by adding 1 ml. of concentrated sulphuric acid to 1 ml. of the ether cooled in ice : observe whether the solution is clear and if a discolouration occurs. Add the solution to ice water ; the original ether should be precipitated and no sulphur dioxide should be apparent.

CAUTION. Ethers that have been stored for long periods, particularly in partly-filled bottles, frequently contain small quantities of highly explosive peroxides. The presence of peroxides may be detected either by the " perchromic acid " test of qualitative inorganic analysis (addition of an acidified solution of potassium dichromate) or by the liberation of iodine from acidified potassium iodide solution (compare Section II,47,*I*). The peroxides are non-volatile and may accumulate in the flask during the distillation of the ether ; the residue is explosive and may detonate, when distilled, with sufficient violence to shatter the apparatus and cause serious personal injury. If peroxides are found, they must first be removed by treatment with acidified ferrous sulphate solution (Section II,47,*I*) or with sodium sulphite solution or with stannous chloride solution (Section VI,12). The common extraction solvents diethyl ether and di-*iso*-propyl ether are particularly prone to the formation of peroxides.

Characterisation of Aliphatic Ethers

The low reactivity of aliphatic ethers renders the problem of the preparation of suitable crystalline derivatives a somewhat difficult one. Increased importance is therefore attached to the physical properties (boiling point, density and refractive index) as a means for providing preliminary information. There are, however, two reactions based upon the cleavage of the ethers which are useful for characterisation.

1. **Reaction with 3 : 5-dinitrobenzoyl chloride.** Ethers undergo cleavage with 3 : 5-dinitrobenzoyl chloride in the presence of zinc chloride :

$$ROR + (NO_2)_2C_6H_3COCl \xrightarrow{ZnCl_2} (NO_2)_2C_6H_3COOR + RCl$$

The resulting alkyl 3 : 5-dinitrobenzoate may be employed for the characterisation of the ether. The method is only applicable to symmetrical or simple ethers ; a mixed aliphatic ether ROR′ would yield a mixture of inseparable solid esters.

Add 1 ml. of the alcohol-free ether to 0·1–0·15 g. of finely-powdered anhydrous zinc chloride and 0·5 g. of pure 3 : 5-dinitrobenzoyl chloride (Section **III,27,***1*) contained in a test-tube ; attach a small water condenser and reflux gently for 1 hour. Treat the reaction product with 10 ml. of 1·5*N* sodium carbonate solution, heat and stir the mixture for 1 minute upon a boiling water bath, allow to cool, and filter at the pump. Wash the precipitate with 5 ml. of 1·5*N* sodium carbonate solution and twice with 5 ml. of ether. Dry on a porous tile or upon a pad of filter paper. Transfer the crude ester to a test-tube and boil it with 10 ml. of chloroform or carbon tetrachloride ; filter the hot solution, if necessary. If the ester does not separate on cooling, evaporate to dryness on a water bath, and recrystallise the residue from 2–3 ml. of either of the above solvents. Determine the melting point of the resulting 3 : 5-dinitrobenzoate (Section **III,27**).

2. **Cleavage of ethers with hydriodic acid.** Aliphatic ethers suffer fission when boiled with constant boiling point hydriodic acid :

$$ROR' + 2HI \longrightarrow RI + R'I + H_2O$$

If the ether is a simple one (R = R'), the identification of the resulting alkyl iodide presents no difficulties. If, however, it is a mixed aliphatic ether, the separation of the two alkyl iodides by fractional distillation is generally difficult unless R and R' differ considerably in molecular weight and sufficient material is available.

Reflux 1 ml. of the ether with 5 ml. of freshly distilled, constant boiling point hydriodic acid (Section **II,49,***2*), b.p. 126–128°, for 2–3 hours. Add 10 ml. of water, distil and collect about 7 ml. of liquid. Decolourise the distillate by the addition of a little sodium bisulphite, and separate the two layers by means of a dropper pipette (Fig. *II, 27,* 1). Determine the b.p. of the resulting iodide by the Siwoloboff method (Section **II,12**) and prepare a crystalline derivative (Section **III,42**).

The physical properties of a number of aliphatic ethers are collected in Table **III,60**. Some related heterocyclic compounds are included in the Table.

TABLE III,60. ALIPHATIC ETHERS

Ether	B.P.	$d_{4°}^{20°}$	$n_D^{20°}$
Chloromethyl methyl	59°	1·070	1·397
Diethyl	34	0·714	1·353
Chloromethyl ethyl	83 (d)	1·026	1·404
α-Chloroethyl methyl	73	0·991	1·400
β-Chloroethyl methyl	91	1·035	1·411
αα′-Dichlorodiethyl	114	1·111	1·423
ββ′-Dichlorodiethyl	178	1·210	1·457
Di-*n*-propyl	90	0·749	1·381
Di-*iso*-propyl	68	0·726	1·368
Di-*n*-butyl	141	0·770	1·399
Di-*n*-amyl	185	0·785	1·412
Di-*iso*-amyl	171	0·778	1·409
Di-*n*-hexyl	223	0·793	1·420
Di-*n*-heptyl	259	0·801	1·427
Di-*n*-octyl	288	0·806	1·433
Di-*n*-decyl	185°/5 mm.	0·815	1·441
Methyl *n*-butyl	70	0·774	1·374
Ethyl *n*-butyl	92	0·749	1·382
Methyl *n*-amyl	99	0·761	1·387
Ethyl *n*-amyl	118	0·762	1·393
Methyl *n*-hexyl	126	0·772	1·397
Ethyl *n*-hexyl	142	0·772	1·401
*cyclo*Pentyl methyl	105	0·862	1·420
*cyclo*Pentyl ethyl	122	0·853	1·423
*cyclo*Hexyl methyl	134	0·875	1·435
*cyclo*Hexyl ethyl	149	0·864	1·435
Epichlorohydrin	117	1·181	1·438
Cineole	176	0·923	1·458
Ethyleneglycol dimethyl	83	0·866	1·379
Ethyleneglycol diethyl	123	0·848	—
Diethyleneglycol diethyl	187	0·906	1·411
Tetraethyleneglycol dimethyl	266	1·009	1·432
Benzyl methyl	171	0·965	1·501
Benzyl ethyl	186	0·948	1·496
Dibenzyl	299 (d)	1·042	—
Furan	32	0·937	1·422
Tetrahydrofuran	65	0·889	1·407
Sylvan (2-methylfuran)	64	0·913	1·434
Tetrahydrosylvan	79	0·855	1·407
Dihydropyran	86	0·923	1·440
Tetrahydropyran	88	0·881	1·421
Dioxan	102	1·034	1·417

ALIPHATIC ALDEHYDES

Aliphatic aldehydes may be prepared:—

1. By the controlled oxidation of primary alcohols with a solution of potassium or sodium dichromate in dilute sulphuric acid. To avoid the further oxidation to the corresponding acid, the aldehyde is removed as rapidly as possible by distillation through a fractionating column, for example:

$$\underset{n\text{-Butyl alcohol (b.p. 117°)}}{CH_3CH_2CH_2CH_2OH} \xrightarrow[H_2SO_4,\,[O]]{K_2Cr_2O_7,\ \text{and}} \underset{n\text{-Butyraldehyde (b.p. 75°)}}{CH_3CH_2CH_2CHO} + H_2O$$

With higher alcohols appreciable quantities of esters (compare Section III,82) may be formed.

2. By passing the alcohol vapour over a "copper-chromium oxide" catalyst deposited on pumice and heated to 330°, for example:

$$\underset{n\text{-Hexyl alcohol}}{CH_3(CH_2)_4CH_2OH} \longrightarrow \underset{n\text{-Hexaldehyde}}{CH_3(CH_2)_4CHO} + H_2$$

Small quantities of esters (in the above example *n*-hexyl *n*-caproate $CH_3(CH_2)_4COO(CH_2)_5CH_3$) are simultaneously formed. This is an excellent method for the preparation of aldehydes.

It is interesting to note that under the influence of aluminium alkoxides (in alcohol or, better, in benzene solution) aldehydes produce the ester (**Tischenko reaction**):

$$RCHO + RCHO \longrightarrow RCOOCH_2R$$

3. From ethyl orthoformate and the Grignard reagent, for example:

$$\underset{n\text{-Amyl magnesium bromide}}{C_5H_{11}{}^{\alpha}MgBr} + \underset{\text{Ethyl orthoformate}}{CH(OC_2H_5)_3} \longrightarrow C_5H_{11}{}^{\alpha}CH(OC_2H_5)_2 + C_2H_5OMgBr$$

$$\underset{n\text{-Hexaldehyde acetal}}{C_5H_{11}{}^{\alpha}CH(OC_2H_5)_2} + H_2O \xrightarrow{(H_2SO_4)} \underset{n\text{-Hexaldehyde}}{C_5H_{11}{}^{\alpha}CHO} + 2C_2H_5OH$$

4. From nitriles by treatment with anhydrous stannous chloride dissolved in ether saturated with hydrogen chloride; the resulting crystalline aldimine stannichloride, $[(RCH{=}NH_2)_2]\,SnCl_6$ or $(RCH{=}NH,HCl)_2SnCl_4$, is hydrolysed by warm water, and the aldehyde is isolated by distillation with steam or by extraction with a solvent (**Stephen reaction**), for example, for R = $CH_3(CH_2)_4$, *i.e.*, *n*-amyl:

$$\underset{n\text{-Amyl cyanide (}n\text{-capronitrile)}}{CH_3(CH_2)_4CN} + HCl \longrightarrow CH_3(CH_2)_4CCl{=}NH$$

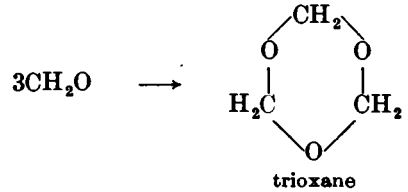
$$CH_3(CH_2)_4CCl{=}NH + SnCl_2 + 2HCl \longrightarrow CH_3(CH_2)_4CH{=}NH,HCl + SnCl_4$$

$$CH_3(CH_2)_4CH{=}NH,HCl + H_2O \longrightarrow \underset{n\text{-Hexaldehyde}}{CH_3(CH_2)_4CHO} + NH_4Cl$$

Formaldehyde is a gas, b.p. −21°, and is usually prepared by the dehydrogenation of methyl alcohol in the presence of heated copper or silver. By admitting air with the methyl alcohol vapour, part of the hydrogen is oxidised to give the heat necessary for the reaction:

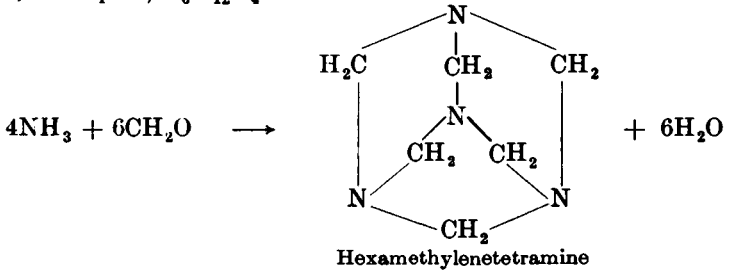
$$CH_3OH \xrightarrow[[O]]{Cu} HCHO + H_2O$$

It is marketed as a 35–40 per cent. solution in water (**formalin**). The reactions of formaldehyde are partly typical of aldehydes and partly peculiar to itself. By evaporating an aqueous solution **paraformaldehyde** or *paraform* $(CH_2O)_x$, an amorphous white solid is produced; it is insoluble in most solvents. When formaldehyde is distilled from a 60 per cent. solution containing 2 per cent. of sulphuric acid, it polymerises to a crystalline trimeride, **trioxane**, which can be extracted with methylene chloride; this is crystalline (m.p. 62°, b.p. 115°), readily soluble in water, alcohol and ether, and devoid of aldehydic properties:



trioxane

Upon heating the polymers, anhydrous gaseous formaldehyde is produced (compare Section III,17). By allowing a mixture of concentrated ammonia solution and formalin to evaporate, **hexamethylenetetramine** (also called *hexamine*, *urotropine*) $C_6H_{12}N_4$ is formed:



Hexamethylenetetramine

Much of the **acetaldehyde** of commerce is obtained by the hydration of acetylene in hot dilute sulphuric acid solution in the presence of mercuric sulphate as catalyst:

$$CH{\equiv}CH + HOH \longrightarrow [CH_2{=}CH{-}OH] \longrightarrow CH_3{-}CH{=}O$$

Acetaldehyde, b.p. 21°, undergoes rapid polymerisation under the influence of a little sulphuric acid as catalyst to give the trimeride **paraldehyde**, a liquid b.p. 124°, which is sparingly soluble in water. The reaction is reversible, but attains equilibrium when the conversion is about 95 per cent. complete; the unreacted acetaldehyde and the acid catalyst may be removed by washing with water:

$$\underset{\text{Acetaldehyde}}{3CH_3CHO} \overset{H_2SO_4}{\rightleftharpoons} \underset{\text{Paraldehyde}}{(CH_3CHO)_3}$$

Paraldehyde is inert to oxidising agents and exhibits none of the reactions of carbonyl compounds (compare Section III,74); its constitution is similar to that of trioxane, with CH_3CH replacing HCH. In view of the low boiling point of acetaldehyde (21°) its preparation (and storage) is not conveniently carried out directly from ethyl alcohol or acetylene. When acetaldehyde is required in the laboratory, paraldehyde can be readily depolymerised by adding a trace of sulphuric acid, which immediately gives the equilibrium mixture, and fractionating this to remove the acetaldehyde from the sphere of reaction: eventually all the paraldehyde is depolymerised. Another polymeride, **metaldehyde** $(CH_3CHO)_4$, a crystalline solid, is obtained by the action of hydrogen chloride below 0°, best in ethereal solution.

Aldehydes condense with alcohols in the presence of a catalyst (1–2·5 per

cent of an acid such as sulphuric, hydrochloric or *p*-toluene-sulphonic acid, or of calcium chloride) to yield acetals, for example:

$$CH_3CHO + 2C_2H_5OH \xrightarrow{CaCl_2} CH_3CH(OC_2H_5)_2 + H_2O$$
Diethyl acetal

$$CH_3CHO + 2C_4H_9{}^{\alpha}OH \xrightarrow[\text{sulphonic acid}]{p\text{-Toluene}} CH_3CH(OC_4H_9{}^{\alpha})_2 + H_2O$$
Di-*n*-butyl acetal

III,61. *n*-BUTYRALDEHYDE

Fit up the apparatus shown in Fig. *III*, *61*, 1. The bolt-head flask is of 500 ml. capacity and the Hempel column is filled with $\frac{1}{4}''$ glass rings

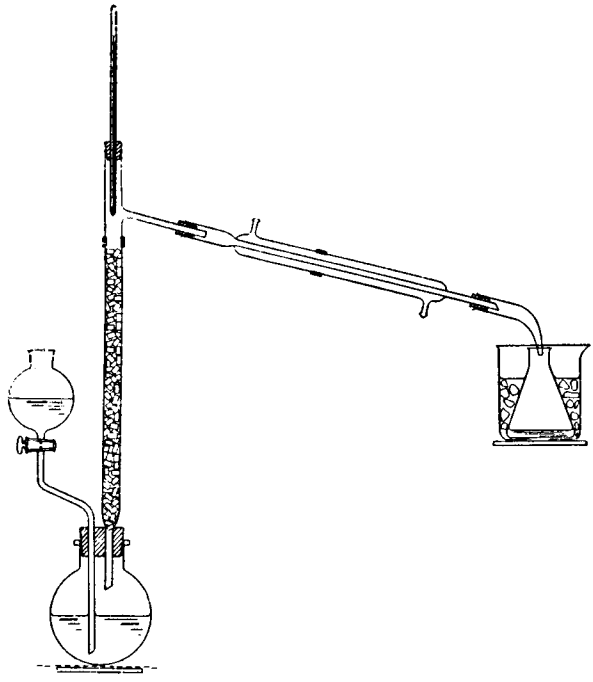


Fig. *III*, *61*, 1.

or with $\frac{1}{8}''$ porcelain rings (1); the receiver is cooled in crushed ice or in cold water. Dissolve 56 g. of sodium dichromate dihydrate in 300 ml. of water and add cautiously, with stirring, 40 ml. of concentrated sulphuric acid. Place 41 g. (51 ml.) of *n*-butyl alcohol together with a few small chips of porous porcelain in the flask, and the acidified dichromate solution in the separatory funnel. Heat the *n*-butyl alcohol to boiling so that the vapours reach the lowest rings in the fractionating column. Run in the dichromate solution during about 15 minutes and at such a rate that the temperature at the top of the column does not rise above 80–85°. The oxidation to *n*-butyraldehyde proceeds with the evolution of heat, but it may be necessary to heat the mixture with a *small* flame from time to time in order to prevent the temperature from falling below 75°. When all the oxidising agent has been added, continue heating the mixture

with a small flame for 15 minutes and collect all that passes over below 90°. Separate the small volume of water (*ca.* 2 ml.) from the distillate and dry the residue (29 g.) for 30–60 minutes with 3–4 g. of anhydrous magnesium sulphate. Meanwhile detach the fractionating column from the apparatus and dry the glass or porcelain rings by washing with acetone and blowing hot air through them. Fit the column into a 100 ml. bolt head flask and arrange for distillation as before. Distil the dried distillate slowly (1–2 drops per second) through the column and collect as *n*-butyraldehyde all that distils below 76°. The yield is 13 g. Pure *n*-butyraldehyde boils at 74·5°.

Note.

(1) The approximate dimensions of the packing are 25 cm. × 18–20 mm. Any other form of efficient fractionating column may be used.

COGNATE PREPARATION

Propionaldehyde. Use 34 g. (42·5 ml.) of *n*-propyl alcohol, and a solution containing 56 g. of sodium dichromate dihydrate, 300 ml. of water and 40 ml. of concentrated sulphuric acid. The experimental details are identical with those for *n*-butyraldehyde, except that the addition of the dichromate solution occupies 20 minutes, the temperature at the top of the column is not allowed to rise above 70–75°, and during the subsequent heating for 15 minutes the liquid passing over below 80° is collected; the receiver must be cooled in ice. The yield of propionaldehyde, b.p. 47–50°, is 12 g.

III,62. *n*-HEXALDEHYDE (*Catalyst Method*)

Preparation of catalyst ("copper-chromium oxide"). Dissolve 10·4 g. of A.R. barium nitrate in 280 ml. of water at about 80° and add to this hot solution 87 g. of A.R. cupric nitrate $\{Cu(NO_3)_2,3H_2O\}$; stir the mixture and heat until a homogeneous solution results. Prepare a solution of 50·4 g. of A.R. ammonium dichromate in a mixture of 200 ml. of water and 75 ml. of concentrated ammonia solution (sp. gr. 0·88). To the ammonium chromate solution at 25–30° add the hot (80°) nitrate solution in a thin stream with stirring. Allow the mixture to cool and filter off the yellowish-brown precipitate with suction; press with a glass stopper and suck as dry as possible. Transfer the precipitate of copper barium ammonium chromate to a large evaporating dish, add sufficient water to form a moderately thick paste, and introduce pumice (4–8 mesh) with stirring until most of the paste has been transferred to the pumice: about 300 g. of pumice are required. Heat on an electric hot plate until the particles of pumice no longer adhere one to another. Remove some of the impregnated pumice (yellowish-brown) to a small evaporating dish and heat, by means of a Bunsen flame, with stirring until the colour changes through brown to a uniform black. The catalyst is now ready for use; it is essentially barium-promoted copper-chromium oxide, together with a little cupric oxide, and will be termed the "copper-chromium oxide" catalyst * deposited upon pumice.

* It differs from the "copper-chromium oxide" catalyst described in Section VI,6 in that it has not been extracted with 10 per cent. acetic acid—a process which presumably removes some copper oxide.

Pack the catalyst into a Pyrex combustion tube about 90 cm. long and 15 mm. bore, and place plugs of glass wool at 25 cm. intervals; insert into a tube furnace and adjust to a temperature of 330°: full details of the complete apparatus are given in Section **III,72** and Fig. *III*, *72*, 1.

Dehydrogenation of *n*-hexyl alcohol. Place 100 g. (122 ml.) of *n*-hexyl alcohol in the dropping funnel (Fig. *III*, *72*, 1). Switch on the current for the furnace and, after 2 hours, allow the alcohol to pass into the tube at the rate of 1 drop every 3–4 seconds. The commencement of the dehydrogenation will be indicated by the production of white fumes at the point where the combustion tube enters the condenser and by the passage of gas (hydrogen) in the "bubbler" at the extreme end of the apparatus. Place 0·1 g. of hydroquinone in the receiver to act as a "stabiliser" for the aldehyde. When all the *n*-hexyl alcohol has passed through the catalyst tube, remove the aqueous layer from the distillate, dry the organic layer with a little anhydrous magnesium sulphate, and distil from a lagged Claisen flask with fractionating side arm (Figs. *II*, *24*, 2–5). Collect the fraction which passes over at 125–135° (30 g.) (1). Upon redistillation, 21 g. of *n*-hexaldehyde (2), b.p. 127–129°, are obtained.

Notes.

(1) If the high boiling residue is transferred to a small Claisen flask and distilled, some *n*-hexyl alcohol passes over first, followed by *n*-hexyl *n*-caproate (2 g.) at 240–250° (mainly 245°).

(2) About 0·1 per cent. of hydroquinone should be added as a "stabiliser" since *n*-hexaldehyde exhibits a great tendency to polymerise. To obtain *perfectly pure n-hexaldehyde*, treat the 21 g. of the product with a solution of 42 g. of sodium bisulphite in 125 ml. of water and shake; much bisulphite derivative will separate. Steam distil the suspension of the bisulphite compound until about 50 ml. of distillate have been collected; this will remove any non-aldehydic impurities together with a little aldehyde. Cool the residual aldehyde-bisulphite solution to 40–50°, and add slowly a solution of 32 g. of sodium bicarbonate in 80 ml. of water, and remove the free aldehyde by steam distillation. Separate the upper layer of *n*-hexaldehyde, wash it with a little water, dry with anhydrous magnesium sulphate and distil; the pure aldehyde passes over at 128–128·5°.

Cognate Preparations

***n*-Valeraldehyde.** Use 100 g. (123 ml.) of *n*-amyl alcohol, and fractionate the dried distillate. Collect the fraction of b.p. 98–110° (23 g.); upon redistillation, 20 g. of *n*-valeraldehyde, b.p. 101–105°, are obtained. From the high boiling point fractions 25 g. of *n*-amyl alcohol (b.p. 135–139°) may be recovered, together with 1·5 g. of *n*-amyl *n*-valerate (b.p. 205–210°).

***n*-Butyraldehyde.** Use 100 g. (123·5 ml.) of *n*-butyl alcohol. The yield of *n*-butyraldehyde, b.p. 70–75°, is 38 g., and of *n*-butyl *n*-butyrate, b.p. 165–170°, is 2 g.; 40 g. of *n*-butyl alcohol are recovered.

Propionaldehyde. Use 100 g. (124·5 ml.) of *n*-propyl alcohol and surround the receiver by a freezing mixture. The yield of propionaldehyde, b.p. 48–49·5° (mainly 49°), is 35 g., and of *n*-propyl propionate, b.p. 120–125°, is 1 g.; 30 g. of *n*-propyl alcohol are recovered.

III,63. *n*-HEXALDEHYDE (*Ethyl Orthoformate Method*)

The ethyl orthoformate required in this preparation may be prepared by the action of sodium upon a mixture of chloroform and dry alcohol:

$$2CHCl_3 + 6C_2H_5OH + 6Na \longrightarrow 2CH(OC_2H_5)_3 + 3H_2 + 6NaCl$$

Preparation of ethyl orthoformate. Fit a 1500 ml. round-bottomed flask with a long (60–80 cm.) reflux condenser. Make sure that the apparatus is thoroughly dry. Place 750 ml. of "super-dry" ethyl alcohol (Section **II,47,4**) and 123 g. (82 ml.) of dry chloroform in the flask. Add 52 g. of clean sodium, cut into small pieces, through the condenser in the course of 30 minutes; when the reaction becomes vigorous, cool the outside of the flask by running water from the condenser outlet. When all the sodium has reacted and the mixture has attained room temperature, filter off the sodium chloride through a sintered glass funnel. The filtration apparatus must be thoroughly dry, and a drying tube, filled with cotton wool, should be placed between the filter flask and the pump. Wash the solid on the filter with 50 ml. of absolute alcohol and allow the washings to run into the main filtrate. Distil the solution from a water bath through an efficient fractionating column in order to recover the excess of chloroform and most of the alcohol; collect the distillate (about 500 g.) (*A*) in a filter flask protected by a drying tube. Decant the liquid remaining in the flask from a little salt which has separated, and distil it either from a Claisen flask with fractionating side arm or through an all-glass Dufton (or Widmer) column. A fraction (*B*) of low boiling point passes over first, followed by the triethyl orthoformate (triethoxymethane) at 144–146°. The yield is 35 g., but depends somewhat upon the efficiency of the fractionation.

Carry out a second run with the recovered chloroform-alcohol mixture (*A*): add 100 g. of dry chloroform and sufficient "super-dry" ethyl alcohol (200–250 ml.) to give a total volume of 750 ml. Add 52 g. of sodium as before. Remove the excess of chloroform and alcohol as before on a water bath through a fractionating column, add the intermediate fraction (*B*) from the first run, and fractionate again. The yield of product b.p. 144–146°, is 45 g.

***n*-Hexaldehyde.** The apparatus required is a 1-litre three-necked flask, provided with a dropping funnel, a mercury-sealed stirrer and a double surface condenser (carrying a cotton wool or calcium chloride guard tube). Place 15 g. of dry magnesium turnings, 25 ml. of sodium-dried ether and a small crystal of iodine in the flask. Add 3 g. (2·5 ml.) of dry *n*-amyl bromide (Sections **III,35** and **III,37**) and set the stirrer in motion. As soon as the reaction commences, add 100 ml. of sodium-dried ether, followed by a solution of 91·5 g. (76 ml.) of dry *n*-amyl bromide in 100 ml. of anhydrous ether at such a rate that the ether refluxes steadily (about 20 minutes). If the reaction becomes too vigorous, cooling in ice water may be necessary. Reflux the solution for 30 minutes in order to complete the reaction. Remove the source of heat, cool the flask to about 5°, and add 74 g. (83 ml.) of ethyl orthoformate during about 10 minutes. Reflux the mixture for 6 hours; then arrange the condenser for distillation and remove the ether on a water

bath. Allow the reaction mixture to cool. Add 375 ml. of ice-cold 6 per cent. hydrochloric acid with stirring ; keep the contents of the flask cool by the occasional addition of a little crushed ice. When all the white solid has passed into solution, transfer to a separatory funnel and remove the upper layer of *n*-hexaldehyde diacetal. Hydrolyse the acetal by distilling it with a solution of 50 g. (27·5 ml.) of concentrated sulphuric acid in 350 ml. of water ; collect the aldehyde, which distils over as an oil, in a solution of 50 g. of sodium bisulphite in 150 ml. of water. Remove the oily layer (largely *n*-amyl alcohol) insoluble in the bisulphite solution and discard it. Steam distil the bisulphite solution until 100 ml. of the distillate have been collected : this will separate the remainder of the amyl alcohol and other impurities. Cool the residual bisulphite solution to about 45°, cautiously add a suspension of 40 g. of sodium bicarbonate in 100 ml. of water, and separate the resulting free aldehyde by steam distillation. Remove the upper layer (crude aldehyde) of the distillate, wash it with three 25 ml. portions of water, and dry it with 10 g. of anhydrous sodium or magnesium sulphate. Distil through a short column or from a Claisen flask with fractionating side arm, and collect the *n*-hexaldehyde (*n*-caproaldehyde) at 127–129°. The yield is 25 g.

III,64. *n*-HEXALDEHYDE (*from* n-*Amyl Cyanide*)

Into a 500 ml. three-necked flask, provided with a mechanical stirrer, a gas inlet tube and a reflux condenser, place 57 g. of anhydrous stannous chloride (Section **II,50,***11*) and 200 ml. of anhydrous ether. Pass in dry hydrogen chloride gas (Section **II,48,***l*) until the mixture is saturated and separates into two layers ; the lower viscous layer consists of stannous chloride dissolved in ethereal hydrogen chloride. Set the stirrer in motion and add 19·5 g. of *n*-amyl cyanide (Sections **III,112** and **III,113**) through the separatory funnel. Separation of the crystalline aldimine hydrochloride commences after a few minutes ; continue the stirring for 15 minutes. Filter off the crystalline solid, suspend it in about 50 ml. of water and heat under reflux until it is completely hydrolysed. Allow to cool and extract with ether ; dry the ethereal extract with anhydrous magnesium or calcium sulphate and remove the ether slowly (Fig. *II*, *13*, 4, but with the distilling flask replaced by a Claisen flask with fractionating side arm). Finally, distil the residue and collect the *n*-hexaldehyde at 127–129°. The yield is 19 g.

Cognate Preparation

***n*-Octaldehyde.** Use 25 g. of *n*-octonitrile, b.p. 87°/10 mm., 57 g. of anhydrous stannous chloride and 200 ml. of anhydrous ether. Isolate the aldehyde by steam distillation and ether extraction. An almost quantitative yield of *n*-octaldehyde, b.p. 65°/11 mm., is obtained.

III,65. ACETALDEHYDE (*from Paraldehyde*)

Assemble the simple fractional distillation apparatus shown in Fig. *II*, *16*, 1 : the round-bottomed flask should have a capacity of 200 or 250 ml. and the conical flask 100 ml. (Alternatively, a long all-glass

Dufton column may replace the Hempel column.) Place 50 ml. of paraldehyde in the flask together with 0·5 ml. of concentrated sulphuric acid (which acts as the depolymerising agent) (1) and a few small fragments of porous porcelain. Cool the receiver in crushed ice; place a *loose* plug of cotton wool between the adapter and the receiver to diminish losses due to evaporation. Warm the flask very gently on a wire gauze (or, better, in a water bath at 50–60°); do not allow the temperature at the head of the column to rise above 30–32°. The distillation must be conducted very slowly in order that the fractionation may be efficient, since acetaldehyde and paraldehyde form a constant boiling point mixture, b.p. 42° (53·4 and 46·6 mol per cent. respectively). In practice it is found that most of the acetaldehyde distils at 21–25°. Stop the distillation when 10 ml. of liquid remain in the flask: distillation to dryness may result in an explosion. The resulting acetaldehyde, produced in excellent yield, is sufficiently pure for many purposes, *e.g.*, for use in studying the reactions of acetaldehyde. If it is not required immediately, stopper the flask loosely with a cork and keep it in the ice chest or in a refrigerator until required.

To obtain pure acetaldehyde, the product must be redistilled. Clean and dry the 200–250 ml. flask first used, immerse it in cold or ice water pour in the crude acetaldehyde rapidly, attach the fractionating column, etc. Immerse the receiver in crushed ice. Heat the flask gently in a water bath and adjust the temperature so that the aldehyde distils slowly and at a uniform temperature. The temperature recorded at the top of the column may depend partly upon the temperature of the laboratory, if this is above 21°. Pure acetaldehyde boils at 21°.

Note.

(1) The sulphuric acid may be replaced by 1–2 g. of sulphamic acid (NH_2SO_3H) or by *p*-toluenesulphonic acid (*p*-$CH_3C_6H_4SO_3H$).

III,66. FORMALDEHYDE

Formaldehyde is a gas, b.p. — 21°, and cannot obviously be stored as such: moreover, it polymerises readily in the liquid and the gaseous state. The commercial preparation, *formalin*, is an aqueous solution containing 35–40 per cent. of formaldehyde and some methyl alcohol. The preparation of a solution of formaldehyde may be demonstrated by the following experiment.

Prepare a coil of copper wire by winding several turns around a glass tube. Heat the coil in the oxidising flame of a Bunsen burner for 1–2 minutes and plunge the spiral, whilst still red hot, into a test-tube containing a solution of 1 ml. of methyl alcohol and 5 ml. of water. Stopper the test-tube loosely, cool, remove the wire, and repeat the process two or three times. Observe the odour of the solution and use it (or formalin diluted with water) to carry out the following tests.

(i) **Resorcinol test.** Mix 1 drop of a 0·5 per cent. aqueous solution of resorcinol with 1–2 ml. of a dilute solution of formaldehyde (about 1 in 500) and pour this mixture carefully down the side of an inclined test-tube containing 2–3 ml. of concentrated sulphuric acid. A reddish-violet ring forms at the common surface of the two liquids. After a time, if

the solution is not too dilute, a white ring (consisting of a light flocculent precipitate), changing to red violet, forms in the aqueous liquid above the ring.

(ii) **Action of sodium hydroxide solution.** Boil a few drops of formalin solution diluted with a little water with 5 ml. of 10 per cent. sodium hydroxide solution for 5 minutes. Observe that no resin formation occurs (compare acetaldehyde and other aldehydes). Devise tests to prove that the reaction proceeds in accordance with the equation :

$$2HCHO + NaOH = CH_3OH + HCOONa$$

(iii) **β-Naphthol test.** Mix 3 drops of formalin, 3 ml. of 50 per cent. alcohol, 0·05 g. of β-naphthol, 3–5 drops of concentrated hydrochloric acid, and boil gently. The liquid soon becomes filled with a crystalline precipitate. Filter, wash, and recrystallise from dilute alcohol. Determine the m.p. The condensation product is methylene di-β-naphthol, m.p. 188° (decomp.) :

$$HCHO + 2C_{10}H_7{}^{\beta}OH \longrightarrow CH_2(C_{10}H_6{}^{\beta}.OH)_2 + H_2O$$

(iv) **Dimedone test.** Treat a neutral or slightly acid solution of dilute formaldehyde with a small quantity of a 10 per cent. alcoholic solution of dimedone (5 : 5-dimethyl*cyclo*hexane-1 : 3-dione) and stir. Filter off the precipitate after 15–20 minutes, and recrystallise it from dilute alcohol. The condensation product has m.p. 189° (compare Section **III,70,2**).

III,67. HEXAMETHYLENETETRAMINE (HEXAMINE)

This preparation illustrates another point of difference between formaldehyde and other aliphatic aldehydes.

Mix 50 ml. of formalin, containing about 37 per cent. of formaldehyde, with 40 ml. of concentrated ammonia solution (sp. gr. 0·88) in a 200 ml. round-bottomed flask. Insert a two-holed cork or rubber stopper carrying a capillary tube drawn out at the lower end (as for " vacuum" distillation) and reaching almost to the bottom of the flask, and also a short outlet tube connected through a filter flask to a water pump. Evaporate the contents of the flask as far as possible on a water bath under reduced pressure. Add a further 40 ml. of concentrated ammonia solution and repeat the evaporation. Attach a reflux condenser to the flask, add sufficient absolute ethyl alcohol (about 100 ml.) in small portions to dissolve most of the residue, heat under reflux for a few minutes and filter the hot alcoholic extract, preferably through a hot water funnel (all flames in the vicinity must be extinguished). When cold, filter the hexamine, wash it with a little absolute alcohol, and dry in the air. The yield is 10 g. Treat the filtrate with an equal volume of dry ether and cool in ice. A further 2 g. of hexamine is obtained.

Hexamethylenetetramine sublimes at about 260° and is very soluble in water.

III,68. ACETAL (*Acetaldehyde Diethylacetal*)

Place 50 g. of anhydrous calcium chloride and 260 g. (323 ml.) of rectified spirit (95 per cent. ethyl alcohol) in a 1-litre narrow neck bottle, and cool the mixture to 8° or below by immersion in ice water. Introduce slowly 125 g. (155 ml.) of freshly distilled acetaldehyde, b.p. 20–22° (Section **III,65**) down the sides of the bottle so that it forms a layer on the alcoholic solution. Close the bottle with a tightly fitting cork and shake vigorously for 3–4 minutes: a considerable rise in temperature occurs so that the stopper must be held well down to prevent the volatilisation of the acetaldehyde. Allow the stoppered bottle to stand for 24–30 hours with intermittent shaking. (After 1–2 hours the mixture separates into two layers.) Separate the upper layer (*ca.* 320 g.) and wash it three times with 80 ml. portions of water. Dry for several hours over 6 g. of anhydrous potassium carbonate and fractionate with an efficient column (compare Section **II,17**). Collect the fraction, b.p. 101–104°, as pure acetal. The yield is 200 g.

Cognate Preparation

Di-*n*-butyl acetal (*Acetaldehyde di-*n*-butyl acetal*). Place 44 g, (44·5 ml.) of paraldehyde, 187·5 g. (232 ml.) of *n*-butyl alcohol and 5 g. of *p*-toluenesulphonic acid in a 500 or 750 ml. round-bottomed flask. attach a reflux condenser, and reflux the mixture for 12 hours. Remove the small aqueous layer (about 1 ml.), wash with a solution of 2·5 g. of anhydrous sodium carbonate (to remove the acid), then with a mixture of "20-volume" hydrogen peroxide and 10 ml. of 10 per cent. sodium carbonate solution at 40° (to remove the excess of aldehyde), and finally with water. Dry over anhydrous potassium carbonate and distil through an efficient fractionating column (*e.g.*, a Widmer column, a Hempel column filled with $\frac{1}{4}''$ glass rings, or a modified Hempel column—see Figs. *II*, *15*, 2–5). The fraction distilling to 120° (75 g.) consists largely of *n*-butyl alcohol, the temperature rises rapidly to 183°, and the di-*n*-butyl acetal is collected at 183–190° (largely at 188°); there is a small high boiling point residue. The yield is 110 g. Upon redistillation, the acetal boils at 186·5–187·5°.

III,69. REACTIONS AND CHARACTERISATION OF ACETALS

Acetals are usually liquid; they are almost unaffected by alkalis and are not attacked by metallic sodium nor by Fehling's solution. They are identified by reference to the alcohol and aldehyde (or ketone if a ketal) which they yield when hydrolysed in acid solution. Hydrolysis proceeds readily in dilute acid solution (*e.g.*, with 3–5 per cent. acid):

$$RCH(OR')_2 + H_2O \xrightarrow{H^+} RCHO + 2R'OH$$

The rate of hydrolysis depends upon the solubility of the acetal in the hydrolysis medium. Acetals of low molecular weight are completely hydrolysed by refluxing for 5–10 minutes; those of higher molecular weight, and therefore of small solubility, may require 30–60 minutes, but

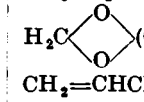
the rate of hydrolysis may be increased by the addition of dioxan which increases the solubility of the acetal.

CAUTION. Acetals, like ethers, may contain explosive peroxides which must be removed before distillation is attempted. The procedure to be adopted is similar to that described under *Ethers* (see Section **III,60**).

The experimental procedure to be followed depends upon the products of hydrolysis. If the alcohol and aldehyde are both soluble in water, the reaction product is divided into two parts. One portion is used for the characterisation of the aldehyde by the preparation of a suitable derivative (*e.g.*, the 2 : 4-dinitrophenylhydrazone, semicarbazone or dimedone compound—see Sections **III,70** and **III,74**). The other portion is employed for the preparation of a 3 : 5-dinitrobenzoate, etc. (see Section **III,27**) : it is advisable first to concentrate the alcohol by distillation or to attempt to salt out the alcohol by the addition of solid potassium carbonate. If one of the hydrolysis products is insoluble in the reaction mixture, it is separated and characterised. If both the aldehyde and the alcohol are insoluble, they are removed from the aqueous layer ; separation is generally most simply effected with sodium bisulphite solution (compare Section **III,74**),but fractional distillation may sometimes be employed.

The formulae and physical properties of a number of common acetals are collected in Table **III,69**.

TABLE III,69. ACETALS

Name	Formula	B.P.	$d_{4^\circ}^{20^\circ}$	$n_D^{20^\circ}$
Methylal . .	$CH_2(OCH_3)_2$	42°	0·859	1·353
Ethylal . .	$CH_2(OC_2H_5)_2$	87	0·831	1·373
n-Propylal . .	$CH_2(OC_3H_7{}^{\alpha})_2$	137	0·834	1·393
iso-Propylal .	$CH_2(OC_3H_7{}^{\beta})_2$	121	0·818	1·384
n-Butylal . .	$CH_2(OC_4H_9{}^{\alpha})_2$	181	0·835	1·406
iso-Butylal .	$CH_2(OC_4H_9{}^{\beta})_2$	164	0·824	1·400
n-Amylal .	$CH_2(OC_5H_{11}{}^{\alpha})_2$	219	0·838	1·416
n-Hexylal . .	$CH_2(OC_6H_{13}{}^{\alpha})_2$	255	0·841	1·423
Dimethylacetal .	$CH_3CH(OCH_3)_2$	64	0·852	1·366
Acetal . .	$CH_3CH(OC_2H_5)_2$	103	0·826	1·381
n-Propylacetal .	$CH_3CH(OC_3H_7{}^{\alpha})_2$	147	0·830	1·397
n-Butylacetal .	$CH_3CH(OC_4H_9{}^{\alpha})_2$	187	0·833	1·409
iso-Butylacetal .	$CH_3CH(OC_4H_9{}^{\beta})_2$	176	0·821	1·403
n-Amylacetal .	$CH_3CH(OC_5H_{11}{}^{\alpha})_2$	222	0·839	1·418
Ethylpropylal .	$CH_3CH_2CH(OC_2H_5)_2$	124	0·823	—
1 : 3-Dioxan .		105	1·034	1·420
Acrolein acetal .	$CH_2{=}CHCH(OC_2H_5)_2$	125	0·850	—

III,70. REACTIONS AND CHARACTERISATION OF ALIPHATIC ALDEHYDES

The following reactions are characteristic of aliphatic aldehydes: those which are shared by ketones, due to the presence of the carbonyl group, are given under *Aliphatic Ketones* (Section **III,74**).

Use the acetaldehyde prepared in Section **III,65** * for the following tests.

(i) **Reduction of ammoniacal silver nitrate solution.** Add a few drops of a dilute solution of the aldehyde to 2–3 ml. of an ammoniacal solution of silver nitrate {this contains the ion $[Ag(NH_3)_2]^+$} in a clean test-tube. A silver mirror is deposited on the walls of the tube either in the cold or upon warming in a beaker of boiling water.

$$CH_3CHO + 2[Ag(NH_3)_2]OH \longrightarrow CH_3COONH_4 + 2Ag + 3NH_3 + H_2O$$

Note.

Do not heat the silver solution or allow it to stand even for a few hours, since explosive silver fulminate may be formed. The ammoniacal solution of silver nitrate is prepared by treating 3 ml. of 0·1*N* silver nitrate solution with very dilute ammonia solution dropwise until the precipitate which is first formed just redissolves.

It is preferable to use Tollen's ammoniacal silver nitrate reagent, which is prepared as follows: Dissolve 3 g. of silver nitrate in 30 ml. of water (solution *A*) and 3 g. of sodium hydroxide in 30 ml. of water (solution *B*). When the reagent is required, mix equal volumes (say, 1 ml.) of solutions *A* and *B* in a *clean* test-tube, and add dilute ammonia solution drop by drop until the silver oxide is just dissolved. Great care must be taken in the preparation and use of this reagent, which must not be heated. Only a small volume should be prepared just before use, any residue washed down the sink with a large quantity of water, and the test-tubes rinsed with dilute nitric acid.

(ii) **Reduction of Fehling's solution.** Place 4 ml. of freshly prepared Fehling's solution [made by mixing equal volumes of Fehling's solution No. 1 (copper sulphate solution) and solution No. 2 (alkaline tartrate solution)] in a test-tube. Add 2–3 drops of acetaldehyde and boil the solution. A bright red precipitate of cuprous oxide is ultimately formed.

$$CH_3CHO + 2CuO \longrightarrow CH_3COOH + Cu_2O$$

Preparation of Fehling's solution. *Solution No. 1.* Dissolve 34·64 g. of A.R. copper sulphate crystals in water containing a few drops of dilute sulphuric acid, and dilute the solution to 500 ml.

Solution No. 2. Dissolve 60 g. of pure sodium hydroxide and 173 g. of pure Rochelle salt (sodium potassium tartrate) in water, filter if necessary through a sintered glass funnel, and make up the filtrate and washings to 500 ml.

Keep the two solutions separately in tightly stoppered bottles and mix exactly equal volumes immediately before use.

(iii) **Test with Schiff's reagent (fuchsin aldehyde reagent).** Add 1 drop of acetaldehyde to 2–3 ml. of water, and to this solution add 1 ml. of Schiff's reagent. Observe the production of a pink or bluish-red colouration.

Schiff's reagent is a dilute solution of fuchsin hydrochloride (*p*-rosaniline) that has been decolourised by sulphur dioxide. This decolourisation is the result of a

* If the temperature of the laboratory is above 20°, *n*-butyraldehyde (Section III,61) may be employed for all the tests with the exception of (vii).

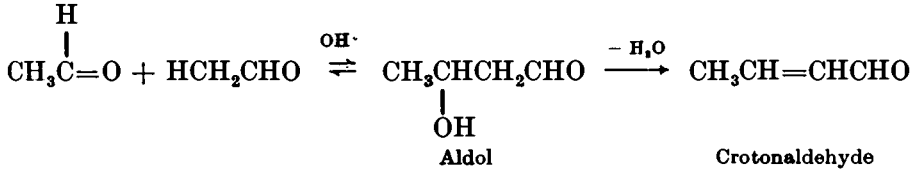
reaction between the *p*-rosaniline and sulphurcus acid that destroys the quinonoid structure of the dye and produces a colourless compound. The aldehyde, by combining with the sulphurous acid, restores the quinonoid structure and hence the colour.

By way of caution it should be noted that free alkali or the alkali salts of weak acids will redden the reagent like an aldehyde. It is also, of course, reddened by heat or when exposed in small quantities to the air for some time. Mineral acids greatly reduce the sensitivity of the test.

Preparation of Schiff's reagent. *Method 1.* Dissolve 0·2 g. of pure *p*-rosaniline hydrochloride in 20 ml. of a cold, freshly-prepared, saturated aqueous solution of sulphur dioxide; allow the solution to stand for a few hours until it becomes colourless or pale yellow. Dilute the solution to 200 ml. and keep it in a tightly-stoppered bottle. If the bottle is not adequately stoppered, the reagent will gradually lose sulphur dioxide and the colour will return. The solution keeps well if not unnecessarily exposed to light and air.

Method 2. Add 2 g. of sodium bisulphite to a solution of 0·2 g. of *p*-rosaniline hydrochloride and 2 ml. of concentrated hydrochloric acid in 200 ml. of water.

(iv) **Action of dilute sodium hydroxide solution.** Mix a few drops of acetaldehyde with 5 ml. of water and add 2–3 drops of 10 per cent. sodium hydroxide solution. Note that the solution acquires a yellow colour and that on boiling a characteristic pungent odour (due to crotonaldehyde produced by way of the aldol) is apparent.



Now warm 2–3 drops of acetaldehyde with 3–4 ml. of 10–20 per cent. sodium hydroxide solution, *i.e.*, with excess of concentrated alkali solution. Observe the formation of a yellow aldehyde resin and the attendant peculiar odour.

(v) **Polymerisation.** (*a*) Place 2 ml. of acetaldehyde in a test-tube which is immersed in a mixture of ice and salt. Insert a thermometer in the tube and observe the temperature; remove the thermometer and wipe it with a clean cloth. Add a drop of concentrated sulphuric acid on the end of the thermometer to the acetaldehyde, remove the test-tube from the freezing mixture, stir with the thermometer for about a minute. Note the rise in temperature. Add 3–4 ml. of water, and observe the formation of a liquid polymer (paraldehyde) which is insoluble in water.

(*b*) Dissolve 2 ml. of acetaldehyde in 5 ml. of dry ether, cool in a freezing mixture of ice and salt, and pass in dry hydrogen chloride gas for 30–60 seconds. The solid polymer, metaldehyde, may separate in a short time, otherwise cork the tube and allow it to stand for 10–15 minutes. Filter off the crystals.

(vi) **Sodium bisulphite test.** Aldehydes react with saturated sodium bisulphite solution to yield crystalline bisulphite - addition compounds:

$$RCHO + NaHSO_3 \rightleftharpoons RCH(OH)SO_3Na$$

A condition of equilibrium is reached (70–90 per cent. of bisulphite compound with equivalent quantities of the reagents in 1 hour), but by using a large excess of bisulphite almost complete conversion into the

addition compound results. Since the reaction is reversible, the aldehyde can be recovered by adding to an aqueous solution of the bisulphite compound sufficient sodium carbonate solution or hydrochloric acid to react with the free sodium bisulphite present in the equilibrium mixture. Bisulphite compounds may therefore be employed for the purification of aldehydes or for their separation from other organic substances.

The most satisfactory reagent is a saturated solution of sodium bisulphite containing some alcohol *; it must be prepared as required since it oxidises and decomposes on keeping. Frequently, a saturated aqueous solution is used without the addition of alcohol.

Prepare 10 ml. of saturated sodium bisulphite solution and add 4 ml. of the aldehyde: shake thoroughly and observe the rise in temperature. Filter the crystalline precipitate at the pump, wash it with a little alcohol, followed by ether, and allow it to dry.

Treat a small quantity of the bisulphite addition compound with 5 ml. of 10 per cent. sodium carbonate solution, and note the odour. Repeat the experiment with 5 ml. of dilute hydrochloric acid.

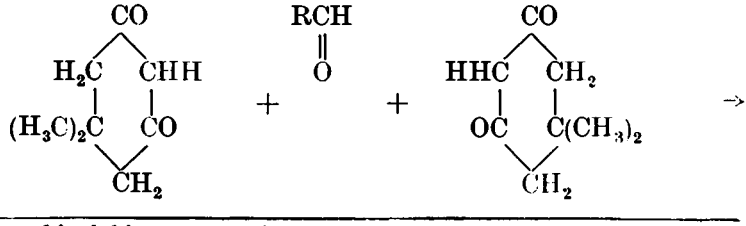
(vii) **β-Naphthol test.** Dissolve 0·2 g. of β-naphthol in 2 ml. of cold glacial acetic acid containing 2 drops of concentrated hydrochloric acid, add a drop of acetaldehyde, shake the mixture, then warm for 5 minutes at 60° and finally to boiling. Cool the mixture, shake vigorously to induce crystallisation, or add 1 drop of 50 per cent. ethyl alcohol and shake again. Recrystallise the white crystalline compound (ethylidene di-β-naphthol) from alcohol; it should have a m.p. of 172–173°.

$$CH_3CHO + 2C_{10}H_7OH \longrightarrow CH_3CH(C_{10}H_6OH)_2 + H_2O$$

Crystalline Derivatives of Aliphatic Aldehydes

1. **2 : 4-Dinitrophenylhydrazones.** Small quantities may be prepared with the class reagent described in Section **XI,7,***4*. A more satisfactory procedure is given under *Aliphatic Ketones*, Section **III,74,***1*.

2. **Dimedone derivatives.** Dimedone or 5 : 5-dimethyl*cyclo*hexane-1 : 3-dione † in saturated aqueous solution ‡ or in 10 per cent. alcoholic solution gives crystalline derivatives (**I**) with aldehydes, but not with ketones. The reaction is:

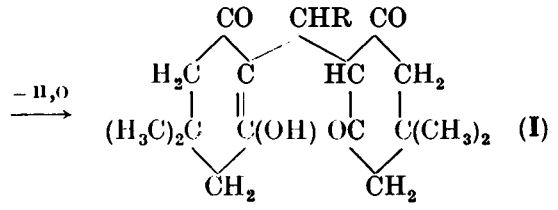


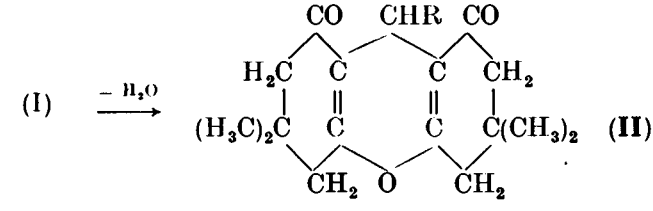
* This sodium bisulphite reagent is prepared by treating a saturated aqueous solution of sodium bisulphite with 70 per cent. of its volume of rectified (or methylated) spirit, and then adding just sufficient water to produce a clear solution.

The bisulphite solution obtained by passing sulphur dioxide into sodium carbonate solution is not recommended since the resulting yellow solution contains free sulphurous acid which dissolves some bisulphite compounds.

† Also termed dimethyldihydroresorcinol and methone. The derivatives (**I**) are conveniently termed formaldehyde *bis*-methone (R = H), etc.

‡ The solubilities in 100 ml. of water are:—19°, 0·40 g.; 25°, 0·42 g.; 50°, 1·19 g.; 80°, 3·20 g.; 90°, 3·84 g.





The condensation products are almost insoluble in water, but can be crystallised from *dilute* alcohol. Dimedone is therefore a good reagent for the detection and characterisation of aldehydes.

The alkylidene dimethone (dimedone) (**I**) upon boiling with glacial acetic acid, acetic anhydride, hydrochloric acid and other reagents frequently loses water and passes into a substituted octahydroxanthene or the " anhydride " (**II**), which often serves as another derivative. The derivatives (**I**) are soluble in dilute alkali and the resulting solutions give colourations with ferric chloride solution ; on the other hand, the " anhydrides " (**II**) are insoluble in dilute alkali and hence can easily be distinguished from the alkylidene dimedones (I).

Add 0·1 g. of the aldehyde in 5 ml. of 50 per cent. ethanol to 2 ml. of a 10 per cent. or saturated alcoholic solution of dimedone.* If a precipitate does not form immediately, warm for 5 mintues; if the solution is still clear at the end of this period, add hot water until the mixture is just cloudy and cool to about 5°. Collect the crystalline derivative and recrystallise it from methanol - water or ethanol - water.

To prepare the " anhydride ", boil a solution of 0·1 g. of the dimedone derivative (**I**) in 5 ml. of 80 per cent. ethanol to which 1 drop of concentrated hydrochloric acid has been added for 5 minutes, than add hot water until the mixture is just turbid, cool and collect the " anhydride " by filtration. Recrystallise it from dilute methanol.

3. **Semicarbazones.** For experimental details, see under *Aliphatic Ketones*, Section **III,74**,*2*.

For the preparation of oximes, phenylhydrazones and *p*-nitrophenylhydrazones (where applicable), see under *Aromatic Aldehydes*, Section **IV,135**,*4–6*.

The melting points of some crystalline derivatives of a number of selected aliphatic aldehydes are collected in Table **III,70**.

* The reagent is attacked by oxidising agents with the formation of formaldehyde, hence it cannot be used for the detection of the latter (or of other aldehydes) in the presence of oxidising agents.

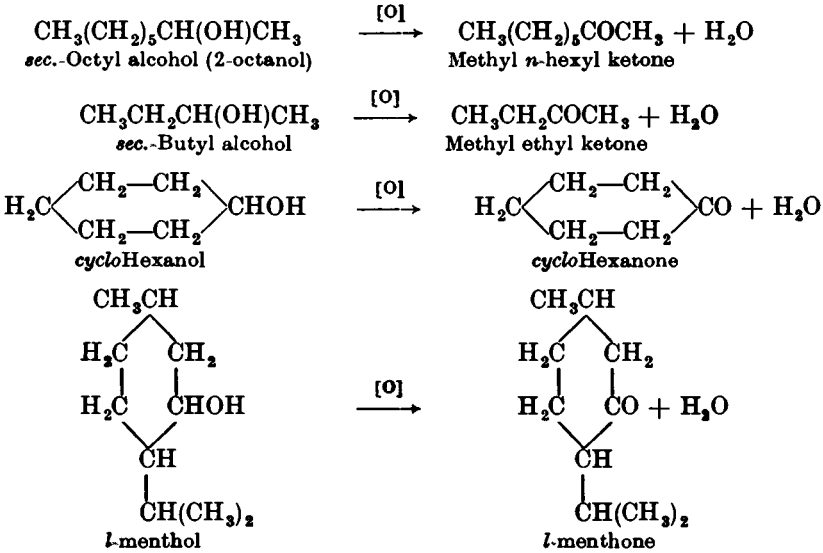
TABLE III,70. **ALIPHATIC ALDEHYDES**

Aldehyde	B.P.	Alkylidene Dimedone (I)	Dimedone "Anhydride" (II)	2 : 4-Dinitrophenylhydrazone	Semicarbazone	*p*-Nitrophenylhydrazone	Other Derivatives
Formaldehyde	− 21°	189°	171°	166°	169*d*	182°	Methylene di-β-naphthol, 190°
Acetaldehyde	20	141	174	168	163	129	Oxime, 47
Propionaldehyde	49	155	143	155	154 (89)	124	Oxime, 40
n-Butyraldehyde	75	142	141	123	106	87	—
iso-Butyraldehyde	64	154	144	187	126	131	—
Trimethylacetaldehyde	75	—	—	209	190	119	Oxime, 41
n-Valeraldehyde	104	105	113	98	—	—	Oxime, 52
iso-Valeraldehyde	92	155	173	123	132	110	Oxime, 48
n-Hexaldehyde	131	109	—	107	106	—	Oxime, 51
n-Heptaldehyde	155	103	112	108	109	73	Oxime, 57
n-Octaldehyde	170	90	101	106	101	80	Oxime, 60
n-Nonaldehyde	190	86	—	100	100	—	Oxime, 64
n-Decylaldehyde	208	92	—	104	102	—	Oxime, 69
α-Ethyl-*n*-butyraldehyde	117	102	—	134	96	—	—
α-Ethyl-*n*-hexaldehyde	163	—	—	120	254*d*	—	—
Crotonaldehyde	102	184	167	190	199	185	Phenylhydrazone, 56; oxime, 119
Diethylacetaldehyde	117	102	—	130	99	—	—
Furfural	161	162	164	230 (213)	203	154	Phenylhydrazone, 98
Tetrahydrofurfural	145	—	—	204	166	—	$d_{4°}^{20°}$ 1·107, $n_D^{20°}$ 1·436
Aldol	83°/20	147	126	—	110	—	—
Hexahydrobenzaldehyde	162	—	—	—	173	—	Oxime, 91
Acrolein	52	192	163	165	171	151	—
α-Citronellal	207	79	173	78	84	—	$d_{4°}^{20°}$ 0·855, $n_D^{20°}$ 1·449
Citral	229*d*	—	—	110	164	—	$d_{4°}^{20°}$ 0·887, $n_D^{20°}$ 1·488
Chloral (hydrate, m.p. 56°)	96	—	—	131	—	—	$d_{4°}^{20°}$ 1·512, $n_D^{20°}$ 1·457
Bromal	174	—	—	—	—	—	—
Paraldehyde	124	—	—	—	—	—	$d_{4°}^{20°}$ 0·994, $n_D^{20°}$ 1·420

ALIPHATIC KETONES

Aliphatic ketones may be prepared:

1. By the oxidation of secondary alcohols with potassium dichromate and dilute sulphuric acid, for example:



2. By passing the vapour of a monobasic acid through a tube containing manganous oxide deposited on pumice and heated to 300–350°, the metallic oxide acting as a catalyst, for example:

$$\underset{\text{Propionic acid}}{2CH_3CH_2COOH} \longrightarrow \underset{\text{Diethyl ketone}}{(CH_3CH_2)_2CO} + CO_2 + H_2O$$

If a mixture of monobasic acids is employed, the mixed ketone may be prepared, for example:

$$\underset{\text{Acetic acid}}{CH_3COOH} + \underset{n\text{-Butyric acid}}{CH_3CH_2CH_2COOH} \longrightarrow \underset{\text{Methyl } n\text{-propyl ketone}}{CH_3COCH_2CH_2CH_3} + CO_2 + H_2O$$

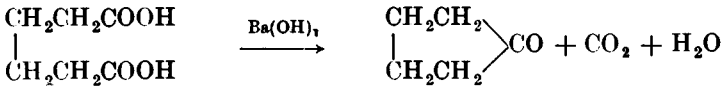
Small quantities of the symmetrical ketones $(CH_3)_2CO$ and $(CH_3CH_2CH_2)_2CO$ (di-*n*-propyl ketone) are formed as by-products: these can easily be removed by fractional distillation through an efficient column. An excess of the cheaper reagent, acetic acid, is employed; the resulting acetone is readily removed by washing with water and little di-*n*-propyl ketone is formed under these conditions.

3. By the ketonic hydrolysis of substituted acetoacetic esters; this is brought about by the action of dilute alkali in the cold, followed by acidification and boiling. The free substituted acetoacetic acid is produced, which readily undergoes decarboxylation (since it has a carboxyl and a carbonyl group on the same carbon atom) to give a ketone, for example:

$$CH_3COCHRCOOC_2H_5 \xrightarrow[\text{then } H_2SO_4]{\text{Dilute NaOH,}} [CH_3COCHRCOOH] \longrightarrow CH_3COCH_2R$$

Thus if R = *n*-propyl (ethyl *n*-propylacetoacetate), methyl *n*-butyl ketone is produced. The preparation of this ketone is described in Section III,152 under *Ethyl Acetoacetate*.

4. By pyrolysis of dibasic acids or their salts to yield cyclic ketones. The slow distillation of adipic acid with about 5 per cent. of baryta affords *cyclo*pentanone in good yield :



III,71. METHYL *n*-HEXYL KETONE

Assemble the apparatus shown in Fig. *II*, *13*, 9 using a 500 ml. flask. If a two-way adapter is not available, the apparatus illustrated in Fig. *III*, *71*, 1 may be employed : a dropping funnel with a long stem is bent so that it clears the condenser and may be supported in a ring, although this is not usually necessary for funnels of small capacity. Place a solution of 22·5 g. of sodium dichromate dihydrate in 150 ml. of water and 30 g. (16·5 ml.) of concentrated sulphuric acid in the flask, and add dropwise during about 30 minutes 30 g. (37 ml.) of *sec.*-octyl alcohol (capryl alcohol) (1) with frequent shaking to ensure thorough mixing (2). Heat under reflux on a boiling water bath for 2 hours, and steam distil the mixture (using the same flask, compare Fig. *II*, *40*, 1) until oily drops cease to come over. Separate the upper layer of ketone, wash it once with water, and dry over anhydrous potassium carbonate. Distil and collect the methyl *n*-hexyl ketone (2-octanone) at 171–174°. The yield is 20 g.

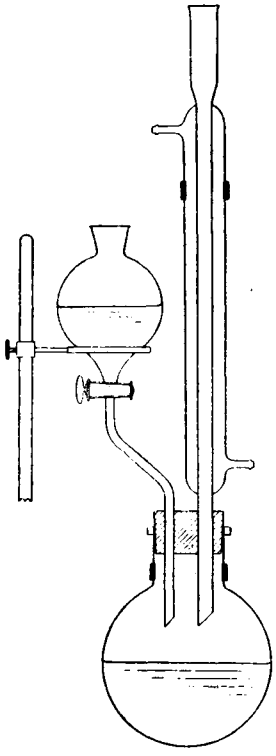


Fig. *III*, *71*, 1.

Notes.

(1) Commercial *sec.*-octyl alcohol may be employed. A slightly better product is obtained if the latter is redistilled : b.p. 177·5–180·5°. The distillation will remove the small proportion of ketonic impurity which is frequently present in the technical alcohol.

(2) Vigorous mechanical stirring is preferable, particularly for large-scale preparations ; a three-necked flask should be used. Thus for a preparation on four times the above scale, the addition of 120 g. (147 ml.) of *sec.*-octyl alcohol requires 1·5 hours and the yield is 110–115 g.

Cognate Preparations

Methyl ethyl ketone. Use the apparatus of Fig. *III*, *61*, 1 but with a 500 ml. round-bottomed flask. Place 40 g. (50 ml.) of *sec.*-butyl alcohol, 100 ml. of water and a few fragments of porous porcelain in the flask. Dissolve 100 g. of sodium dichromate dihydrate in 125 ml. of water in a beaker and add very slowly and with constant stirring 80 ml. of concentrated sulphuric acid ; allow to cool, and transfer the resulting solution to the dropping funnel. Heat the flask on a wire gauze or in an air bath until the alcohol mixture commences to boil. Remove the flame and run in the dichromate solution slowly and at such a rate that the temperature

at the top of the column does not rise above 90–92°. Shake the flask from time to time. When all the dichromate solution has been run in, heat the flask gently and collect all the liquid which passes over below 95°. Disconnect the flask, cool, and discard the contents. Clean the flask, transfer the distillate into it, and fractionate slowly. Collect the fraction, b.p. 78–82°, as methyl ethyl ketone. Pure methyl ethyl ketone has b.p. 80°.

***cyclo*Hexanone.** Dissolve 51 g. of sodium dichromate dihydrate in 250 ml. of water in a 600 ml. beaker and add carefully, with continuous stirring, 44 g. (24 ml.) of concentrated sulphuric acid. Allow the mixture to cool. Place 25 g. of *cyclo*hexanol in a 500 ml. conical or flat-bottomed flask, and add the dichromate solution to it in one portion. Shake the mixture to ensure thorough mixing and observe the temperature with a thermometer. Considerable heat is evolved in the oxidation. When the temperature rises to 55°, cool the flask in a vessel of cold water or under the tap; sufficient external cooling should be applied to keep the temperature between 55° and 60°, *i.e.*, the temperature must not be allowed to fall below 55° or rise above 60°. When the temperature of the mixture no longer rises above 60° upon the removal of the external cooling, allow the flask to stand with occasional shaking for 1 hour.

Pour the reaction mixture into a 1-litre round-bottomed flask, add 250 ml. of water, fit a still head and a condenser for downward distillation (Fig. *II*, *13*, 3, but without the thermometer). Distil the mixture until about 125 ml. of distillate (two layers) have been collected. Saturate with salt (about 30 g. are required), and separate the upper layer of *cyclo*hexanone: extract the aqueous layer with 25–30 ml. of ether and combine the ether extract with the *cyclo*hexanone layer. Dry with about 6 g. of anhydrous sodium or magnesium sulphate, filter the solution into a distilling flask of suitable size to which a condenser has previously been attached. Distil off the ether from a water bath—a beaker containing warm water is satisfactory. Distil the residual liquid from an air bath or a wire gauze, and collect the *cyclo*hexanone at 153–156°. The yield is 16 g.

***l*-Menthone.** Dissolve 60 g. of sodium dichromate dihydrate in 300 ml. of water in a 500 ml. bolt-head flask provided with a mechanical stirrer; add slowly, while stirring the solution, 50 g. (27 ml.) of concentrated sulphuric acid. Introduce 45 g. of menthol crystals, m.p. 42–43°, in four portions and continue stirring the mixture. Heat is evolved and the temperature of the mixture rises to about 55°; if this temperature is not attained, warm gently with a small flame to this temperature. A black spongy mass is first produced, which softens as the temperature rises and finally forms a dark brown oil on the surface. The temperature falls as soon as the oxidation is complete. Transfer the reaction mixture to a separatory funnel and extract with 100 ml. of ether. Wash the ethereal extract with 100 ml. portions of 5 per cent. sodium hydroxide solution until the colour changes from dark brown to light yellow: three or four washings are usually required. Wash once with 25 ml. of water, and dry with a few grams of anhydrous sodium or magnesium sulphate. Remove the ether on a water bath (Fig. *II*, *13*, 4 but with Claisen flask) and distil the residue under atmospheric pressure. Collect the *l*-menthone at

205–208° (38 g.). The distillation may also be conducted under reduced pressure : b.p. 98–100°/18 mm.

III,72. DIETHYL KETONE

The complete assembly for carrying out the catalytic decomposition of acids into ketones is shown in Fig. *III*, *72*, 1. The main part of the apparatus consists of a device for dropping the acid at constant rate into a combustion tube containing the catalyst (manganous oxide deposited upon pumice) and heated electrically to about 350° ; the reaction products are condensed by a double surface condenser and collected in a flask (which may be cooled in ice, if necessary) ; a glass " bubbler " at the end of the apparatus indicates the rate of decomposition (evolution of carbon dioxide). The furnace may be a commercial cylindrical furnace, about 70 cm. in length, but it is excellent practice, and certainly very much cheaper, to construct it from simple materials.

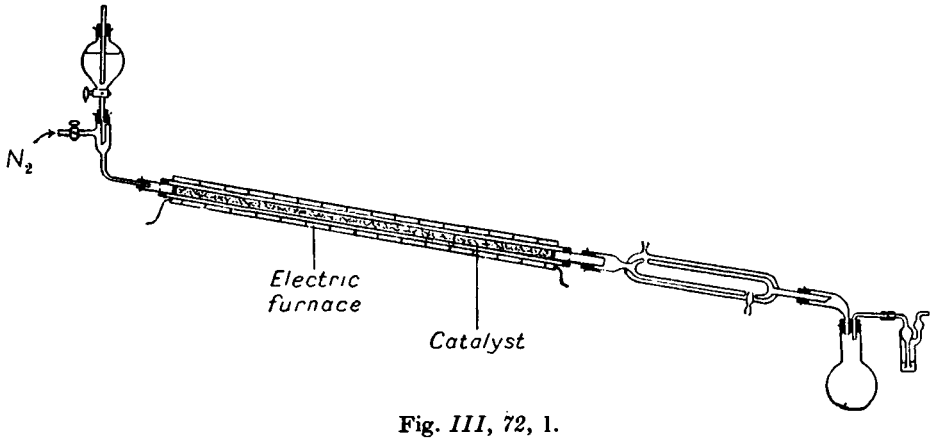


Fig. *III*, *72*, 1.

Construction of the electric tube furnace. Secure a thin-walled iron tube, 78 cm. long and 2·8 cm. in internal diameter, and securely wrap it with asbestos cloth (*ca.* 2 mm. thickness). Wind the central 70 cm. evenly with 10 metres of nichrome wire of No. 30 S.W.G., and cover it with two thicknesses of asbestos cloth held in position by copper wire ligatures. Complete the insulation by wrapping a further two thicknesses of the asbestos cloth round the tube. Attach the two ends of the nichrome wire to two insulated connectors and then to a power point (*e.g.*, 220 volt mains). The temperature inside a Pyrex glass tube placed close to the walls of the furnace is about 350° : some adjustment of temperature may be achieved by removing one of the outer coverings of asbestos cloth. It is, however, preferable to connect the two ends of the nichrome wire to the mains through a small variable resistance (*e.g.*, 25 ohms carrying 2·5 amperes) * or to a variable ratio transformer (*e.g.*, " variac," type 200–CMH †) or to a Sunvic energy control unit (type TYB).‡ The

* An ammeter, reading to 1·5–2·0 amperes, should be placed in the circuit.
† Supplied by Zenith Electric Ltd.
‡ Supplied by Sunvic Controls Ltd.

combustion tube may then be placed in the furnace, and the temperature determined in various positions in the tube either with a long nitrogen-filled thermometer or preferably with a thermo-couple ; the temperature will be found to be constant over the central 40–50 cm. of the tube. A graph may be constructed with temperatures as ordinates and instrument (ammeter, " variac " or energy regulator unit) readings as abscissae ; such a calibration is well worth while as it considerably extends the utility of the furnace.

Preparation of the catalyst. Fill a hard glass (*e.g.*, Pyrex) tube, 100 cm. long and 1·5 cm. internal diameter, with pumice (4–8 mesh). Transfer the pumice into a thick suspension of about 40 g. of freshly precipitated manganous carbonate contained in a beaker. (The manganous carbonate is prepared by adding a solution of 38 g. A.R. anhydrous sodium carbonate to a solution of 70 g. of A.R. crystallised manganous chloride, and filtering). Heat the beaker on a hot plate with vigorous stirring with a glass rod until most of the water is expelled, then transfer the solid to a shallow porcelain basin and continue the heating, with stirring, until the lumps no longer cling together ; take great care to avoid local overheating. It is important to adjust the volume of water used in preparing the suspension of manganous carbonate so that most of the latter is absorbed by the pumice ; if much water has to be evaporated, the manganous carbonate does not adhere satisfactorily. When many preparations are to be carried out, it is advisable to prepare a larger quantity of the catalyst in one operation.

Description of apparatus and method of use. Pack the catalyst into a hard glass or Pyrex tube, 100 cm. long and 1·5 cm. in internal diameter, and hold it in position by means of plugs of purified glass wool (Section **II, 47,4**). Insert the glass tube in the electric furnace and fix it centrally with the aid of asbestos pulp inserted in the annular space between the two ends. Fit up the apparatus as shown in Fig. *III, 72,* 1 : note the constant pressure device in the dropping funnel (500 or 1000 ml. capacity) which permits the dropping of the liquid in the funnel at constant rate without the need of adjustment during the addition. Heat the pumice in a gentle stream of nitrogen for 8 hours at 360–400° in order to convert the manganous carbonate into manganous oxide, and then allow to cool in a stream of this gas. Place 740 g. (746 ml.) of redistilled propionic acid, b.p. 139–141°, in the dropping funnel, the tap of which has been previously lubricated with a " hard grease." Heat the furnace to about 350° whilst a slow stream of nitrogen is passed through the catalyst tube. After 2–3 hours adjust the stopcock so that not more than 30 drops of liquid per minute fall from the funnel into the adapter ; stop the stream of nitrogen during the addition of the acid. The apparatus requires very little attention, and the circulation of the acid over the catalyst occupies 48–72 hours. The distillate consists of two layers. Separate the lower aqueous layer, salt out the ketone with solid potassium carbonate, and add it to the main ketonic layer. Treat the combined liquids with small quantities of anhydrous potassium carbonate (1) until effervescence ceases (this both removes the excess of acid and dries the ketone), filter, and distil through a short column. Collect the diethyl ketone at 101–103°. The yield is 252 g. An improved yield may be

obtained by recirculating the distillate over the catalyst, but in practice this is rarely worth while. It must be remembered that on each occasion that the catalyst is allowed to cool, a slow stream of nitrogen must be passed through the apparatus to prevent the oxidation of the manganous oxide catalyst.

Note.

(1) An alternative method of working up the distillate, which has its advantages when dealing with volatile ketones or when it is suspected that conversion into the ketone is incomplete, is to treat the combined ketones with sodium hydroxide pellets until the mixture is alkaline. Should solids separate, these may be dissolved by the addition of a little water. The ketone is then separated, dried over anhydrous potassium carbonate, and fractionated.

COGNATE PREPARATIONS

Di-*n*-propyl ketone. Use 880 g. (920 ml.) of *n*-butyric acid, b.p. 162–164°. The yield of ketone, b.p. 142–143°, is 285 g.*

Methyl *n*-propyl ketone. Use 360 g. of glacial acetic acid and 176 g. (184 ml.) of *n*-butyric acid. The yield of methyl *n*-propyl ketone, b.p. 102–104°, is 75 g.; 75 g. of acetone, b.p. 56–57°,† are also obtained.

Ethyl *n*-propyl ketone. Use 296 g. (298 ml.) of propionic acid and 352 g. (368 ml.) of butyric acid. The yield is 214 g. of ethyl *n*-propyl ketone, b.p. 122–124°; the by-products are 98 g. of diethyl ketone, b.p. 100–102° and 66 g. of di-*n*-propyl ketone, b.p. 144–146°.

Di-*n*-amyl ketone. Use 400 g. (428 ml.) of *n*-caproic acid, b.p. 204–206°. The yield of ketone, b.p. 222–226°, is 225 g.

For the preparation of *methyl* n-*butyl ketone* and *methyl* n-*amyl ketone* by another method, see Section **III,152.**

III,73. *cyclo*PENTANONE

Mix 200 g. of adipic acid intimately with 10 g. of finely-powdered, crystallised barium hydroxide. Place the mixture in a 1-litre distilling flask, fitted with a thermometer reaching to within 5 mm. of the bottom; connect the flask with a condenser and receiver. Heat the mixture gradually in an air bath (1) to 285–295° during about 90 minutes and maintain it at this temperature until only a small amount of dry residue remains in the flask; this requires a further 2 hours. The temperature must not be allowed to rise above 300°, since at this temperature the adipic acid distils quite rapidly; the best working temperature is 290°. The *cyclo*pentanone distils slowly accompanied by a little adipic acid. Separate the ketone from the water in the distillate, and dry it with anhydrous potassium carbonate; this treatment simultaneously removes the traces of adipic acid present. Finally distil from a flask of suitable size and collect the *cyclo*pentanone at 128–131°. The yield is 92 g.

* All the yields given refer to one circulation of the acid (or acids) over the catalyst, but can be improved by recirculating the product, from which the water layer has been removed, over the catalyst. With the higher ketones, the second circulation may result in carbonisation of the catalyst, thus rendering it inefficient.

† The symmetrical ketones, produced as by-products in the preparation of mixed ketones, are separated by distillation through an efficient fractionating column. If acetone is a by-product (as in the preparation of methyl *n*-propyl ketone), some is lost in the washing process.

Note.

(1) An iron saucepan with a layer of sand at the bottom is quite satisfactory: the distilling flask is immersed in the bath to within 2 cm. of the side arm, and two asbestos boards, cut to fit the neck of the flask, rest on top of the bath (as in Fig. *II*, 5, 3). Somewhat better results are obtained if the bath is filled with nickel shot.

III,74. REACTIONS AND CHARACTERISATION OF ALIPHATIC KETONES

Ketones, unlike aldehydes (Section **III,70**), do not (*a*) reduce ammoniacal solutions of silver salts, (*b*) reduce Fehling's solution, (*c*) react with Schiff's reagent, (*d*) yield resins with strong sodium hydroxide solution, and (*e*) react with the dimedone reagent. Most ketones which contain the $-COCH_3$ grouping (*e.g.*, acetone) {excluding those possessing the phenyl C_6H_5 grouping} or those which contain the $>CO$ grouping as part of the ring (*e.g.*, *cyclo*hexanone) react with sodium bisulphite solution to an appreciable extent. Aldehydes and those ketones which combine appreciably with sodium bisulphite react with hydrogen cyanide to form **cyanohydrins**:

$$>C=O + HCN \longrightarrow >C(OH)CN$$

The carbonyl compound may be mixed with an aqueous solution of sodium or potassium cyanide and mineral acid is added, or the bisulphite compound may be treated with an equivalent quantity of sodium cyanide, for example:

$$CH_3COCH_3 \xrightarrow{NaHSO_4} (CH_3)_2C(OH)SO_3Na \xrightarrow{NaCN} \underset{\text{Acetone cyanohydrin}}{(CH_3)_2C(OH)CN}$$

Most of the characteristic reactions of ketones (RR'CO) depend upon condensation with substituted amines. The reactions occur between the carbonyl group and the $-NH_2$ group of the substituted amine, and hence are also shared by aldehydes RHCO:

$$>C=O + H_2N- \longrightarrow >C=N- + H_2O$$

Many of these are crystalline compounds of sharp m.p. and are therefore useful for identification and characterisation. These include the condensation products with:

(i) **Hydroxylamine** (NH_2OH). The substance formed is termed an **oxime**, for example:

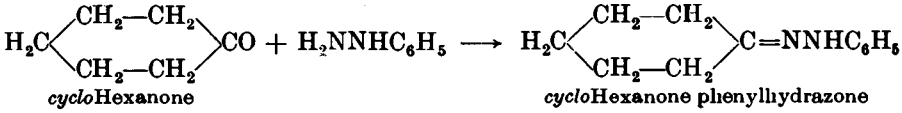
$$(CH_3)_2CO + H_2NOH \longrightarrow \underset{\text{Acetoxime}}{(CH_3)_2C=NOH} + H_2O$$

(ii) **Hydrazine** (NH_2NH_2). The product formed is called a **hydrazone**, but since this derivative possesses a free amino group it can condense with another molecule of the carbonyl compound to yield an **azine**:

$$RCHO + H_2NNH_2 \longrightarrow \underset{\text{Hydrazone}}{RCH=NNH_2} \xrightarrow{RCHO} \underset{\text{Azine}}{RCH=NN=CHR}$$

This double condensation is prevented by the use of substituted hydrazines.

(iii) **Phenylhydrazine** ($C_6H_5NHNH_2$). Carbonyl compounds react with phenylhydrazine to give **phenylhydrazones**. These derivatives are largely oils (or possess low melting points) for many aliphatic aldehydes and ketones, but are generally crystalline for aromatic carbonyl compounds and also for *cyclo*aliphatic and heterocyclic aldehydes and ketones, for example :



*cyclo*Hexanone — *cyclo*Hexanone phenylhydrazone

(iv) **2:4-Dinitrophenylhydrazine** (O_2N-C$_6$H$_3$(NO$_2$)-$NHNH_2$). The **2:4-dinitrophenylhydrazones** (see Section **XI,7,4**) formed with this reagent are generally highly crystalline and almost insoluble in water (because of their high molecular weight) and are therefore eminently suitable for the detection and characterisation of carbonyl compounds.

(v) **Semicarbazide hydrochloride** ($NH_2CONHNH_2,HCl$). This is one of the best reagents for the characterisation of carbonyl compounds since the derivatives, known as **semicarbazones**, are readily formed, are highly crystalline, possess sharp melting points, and are easily crystallised (*e.g.*, from alcohol or acetone) :

$$R_1R_2C{=}O + H_2NNHCONH_2 \longrightarrow \underset{\text{Semicarbazone}}{R_1R_2C{=}NNHCONH_2} + H_2O$$

The reagent is, however, more expensive than 2 : 4-dinitrophenylhydrazine.

In order to obtain practice in the preparation of the above derivatives, experimental details for a few typical examples will be given.

A. Purification of commercial *cyclo*hexanone through the bisulphite compound

Prepare a saturated solution of sodium bisulphite at the laboratory temperature from 40 g. of finely powdered sodium bisulphite : about 70 ml. of water are required. Measure the volume of the resulting solution and treat it with 70 per cent. of its volume of rectified spirit (or methylated spirit) ; add sufficient water (about 45 ml.) to just dissolve the precipitate which separates. Introduce 20 g. of commercial *cyclo*hexanone into the aqueous-alcoholic bisulphite solution with stirring and allow the mixture to stand for 30 minutes ; stir or shake occasionally. Filter off the crystalline bisulphite compound at the pump, and wash it with a little methylated spirit.

Transfer the bisulphite compound to a separatory funnel and decompose it with 80 ml. of 10 per cent. sodium hydroxide solution. Remove the liberated *cyclo*hexanone, saturate the aqueous layer with salt and extract

it with 30 ml. of ether. Combine the ether extract with the ketone layer and dry with 5 g. of anhydrous magnesium or sodium sulphate. Filter the dried ethereal solution into a 50 ml. distilling flask (1), attach a condenser, add a few fragments of porous porcelain, and distil off the ether from a water bath ; take the usual precautions against fire. Distil the residual *cyclo*hexanone using an air bath or an asbestos-centred wire gauze, and collect the fraction, b.p. 153–155°. The yield of pure *cyclo*hexanone is 15–18 g., depending upon the purity of the sample of ketone employed.

Note.

(1) Alternatively—and this procedure is recommended—remove the ether with the apparatus shown in Fig. *II*, *13*, 4. A slightly improved yield is obtained if a short fractionating column is used.

B. Acetoxime

Dissolve 5 g. of hydroxylamine hydrochloride in 10 ml. of water in a small conical flask and add a solution of 3 g. of sodium hydroxide in 10 ml. of water. Cool the solution in cold or ice water, and add 6 g. (7·6 ml.) of acetone slowly. Cool the flask, shake well, and leave overnight, during which time the oxime may crystallise out. If no crystals appear, cork the flask and shake vigorously when the acetoxime usually separates as colourless crystals. Filter the crystals at the pump, dry rapidly between filter paper (yield : 2·6 g.) and determine the m.p. (59°). Extract the filtrate with two 20 ml. portions of ether, and remove the solvent : a further 0·5 g. of acetoxime (m.p. 60°) is obtained. Recrystallise from light petroleum, b.p. 40–60° (*CAUTION :* inflammable) to obtain the pure acetoxime, m.p. 60°. Acetoxime sublimes when left exposed to the air.

B'. *cyclo*Hexanone Oxime

Dissolve 2·5 g. of hydroxylamine hydrochloride and 4 g. of crystallised sodium acetate in 10 ml. of water in a small flask or in a test-tube. Warm the solution to about 40° and add 2·5 g. of *cyclo*hexanone. Stopper the vessel securely with a cork and shake vigorously for a few minutes : the oxime soon separates as a crystalline solid. Cool in ice, filter the crystals at the pump, and wash with a little cold water. Recrystallise from light petroleum, b.p. 60–80°, and dry the crystals upon filter paper in the air. The yield of pure *cyclo*hexanone oxime, m.p. 90°, is 2·5 g.

C. *cyclo*Hexanone Phenylhydrazone

Prepare a solution of phenylhydrazine by dissolving 1·0 g. of phenylhydrazine hydrochloride and 1·5 g. of crystallised sodium acetate in 10 ml. of water ; * if the resulting solution is turbid, filter. Add a solution of 0·5 ml. of *cyclo*hexanone in 8 ml. of water to the reagent

* The reagent may also be prepared by dissolving 1 ml. of phenylhydrazine in a solution of 1 ml. of glacial acetic acid and 10 ml. of water. This procedure is not so convenient as that from the solid hydrochloride because of the poisonous character of phenylhydrazine (both liquid and vapour). If the liquid is accidentally spilled on the skin, wash it at once with dilute acetic acid, followed by soap and water.

contained in a test-tube, cork the tube, and shake vigorously until the phenylhydrazone has crystallised. Filter the crystals at the pump and wash well with water. Recrystallise from dilute alcohol. M.p. 77°.

D. Acetone Semicarbazone

Prepare a solution of 1·0 g. of semicarbazide hydrochloride ($NH_2CONHNH_2$,HCl) and 1·5 g. of crystallised sodium acetate in 10 ml. of water in a test-tube. Add 1 ml. of acetone, close the tube with a cork and shake vigorously. Allow the mixture to stand, with occasional vigorous shaking, for 10 minutes: it is advantageous to cool in ice. Filter the crystals, wash with a little cold water, and recrystallise from water or dilute alcohol. The m.p. of acetone semicarbazone is 187°.

CRYSTALLINE DERIVATIVES OF ALIPHATIC ALDEHYDES AND KETONES

1. **2 : 4-Dinitrophenylhydrazones.** Small quantities may be prepared with the class reagent described in Section **XI,7,***4*. The following procedure is generally more satisfactory.

Suspend 0·25 g. of 2 : 4-dinitrophenylhydrazine in 5 ml. of methanol and add 0·4–0·5 ml. of concentrated sulphuric acid cautiously. Filter the warm solution and add a solution of 0·1–0·2 g. of the carbonyl compound in a small volume of methanol or of ether. If no solid separates within 10 minutes, dilute the solution carefully with 2*N* sulphuric acid. Collect the solid by suction filtration and wash it with a little methanol. Recrystallise the derivative from alcohol, dilute alcohol, alcohol with ethyl acetate or chloroform or acetone, acetic acid, dioxan, nitromethane, nitrobenzene or xylene.

The following reagent, a **0·25M solution of 2 : 4-dinitrophenylhydrazine,** may be used for the preparation of derivatives of keto compounds. Dissolve 25 g. of 2 : 4-dinitrophenylhydrazine in 300 ml. of 85 per cent. phosphoric acid in a 600 ml. beaker on a steam bath, dilute the solution with 200 ml. of 95 per cent. ethanol, allow to stand, and filter through a sintered glass funnel. It must be emphasised that *this reagent is not suitable for the routine detection of carbonyl compounds* since it also gives a precipitate in the cold with certain amines, esters and other compounds: if, however, a dilute solution of the ketonic compound in ethanol is treated with a few drops of the reagent and the mixture diluted with water and heated, the precipitate produced with non-ketonic compounds generally dissolves.

For the preparation of 2 : 4-dinitrophenylhydrazones, dissolve the carbonyl compound (say, 0·5 g.) in 5 ml. of ethanol and add the calculated volume of the reagent. If a precipitate does not form immediately, dilute with a little water. Collect the derivative and recrystallise it as above.

2. **Semicarbazones.** Dissolve 1 g. of semicarbazide hydrochloride and 1·5 g. of crystallised sodium acetate in 8–10 ml. of water add 0·5–1 g. of the aldehyde or ketone and shake. If the mixture is turbid, add alcohol (acetone-free) or water until a clear solution is obtained; shake the mixture for a few minutes and allow to stand. Usually the semicarbazone crystallises from the cold solution on standing, the time varying from a few minutes to several hours. The reaction may be accelerated,

if necessary, by warming the mixture on a water bath for a few minutes and then cooling in ice water. Filter off the crystals, wash with a little cold water, and recrystallise from water or from methyl or ethyl alcohol either alone or diluted with water.

Note.

When semicarbazide is heated in the absence of a carbonyl compound for long periods, condensation to **biurea**, $NH_2CONHNHCONH_2$, m.p. 247–250° (decomp.), may result; occasionally this substance may be produced in the normal preparation of a semicarbazone that forms slowly. Biurea is sparingly soluble in alcohol and soluble in hot water, whereas semicarbazones with melting points in the same range are insoluble in water: this enables it to be readily distinguished from a semicarbazone.

3. **Oximes.** The method given for semicarbazones (see *2*) may be employed: use 1 g. of hydroxylamine hydrochloride, 2 g. of crystallised sodium acetate and 0·5 g. of the aldehyde or ketone. It is usually advisable to warm on a water bath for 10 minutes.

For water-insoluble aldehydes or ketones, the following alternative procedure may be used. Reflux a mixture of 0·5 g. of the aldehyde or ketone, 0·5 g. of hydroxylamine hydrochloride, 5 ml. of ethanol and 0·5 ml. of pyridine on a water bath for 15–60 minutes. Remove the alcohol either by distillation (water bath) or by evaporation of the hot solution in a stream of air (water pump). Add 5 ml. of water to the cooled residue, cool in an ice bath and stir until the oxime crystallises Filter off the solid, wash it with a little water and dry. Recrystallise from alcohol (95 per cent. or more dilute), benzene, or benzene - light petroleum (b.p. 60–80°).

4. **Benzylidene derivatives.** Compounds containing the ketomethylene group (—CH_2CO) react with benzaldehyde to yield benzylidene derivatives:

$$RCOCH_2R' + C_6H_5CHO \longrightarrow RCOC(=CHC_6H_5)R' + H_2O$$

$$RCH_2COCH_2R' + 2C_6H_5CHO \longrightarrow RC(=CHC_6H_5)COC(=CHC_6H_5)R' + 2H_2O$$

Cyclic ketones yield dibenzylidene derivatives.

Dissolve 1 g. of the ketomethylene compound and 1·1 g. or 2·2 g. of pure benzaldehyde (according as to whether the compound may be regarded as $RCOCH_2R'$ or as RCH_2COCH_2R') in about 10 ml. of rectified (or methylated) spirit, add 0·5 ml. of 5*N*-sodium hydroxide solution, shake and allow the mixture to stand for about an hour at room temperature. The benzylidene derivative usually crystallises out or will do so upon "scratching" the walls of the vessel with a glass rod. Filter off the solid, wash it with a little cold alcohol, and recrystallise it from absolute alcohol (or absolute industrial spirit).

Experimental details for the preparation of oximes, phenylhydrazones and *p*-nitrophenylhydrazones will be found under *Aromatic Aldehydes*, Section **IV,135**,*4–6*.

Table **III,74** lists the melting points of derivatives of some selected aliphatic and *cyclo*aliphatic ketones.

TABLE III, 74. **ALIPHATIC KETONES**

Ketone	B.P.	M.P.	2 : 4-Dinitrophenylhydrazone	Semicarbazone	Benzal Derivative	Phenylhydrazone	*p*-Nitrophenylhydrazone	Other Derivatives
Acetone	56°	—	128°	190°	112°	42°	149°	Oxime, 59°
Diethyl ketone	102	—	156	139	—	—	144	Oxime, 69
Di-*n*-propyl ketone	144	—	75	133	—	—	—	—
Di-*iso*-propyl ketone	124	—	88	160	—	—	—	Oxime, 34
Di-*n*-butyl ketone	188	—	—	90	—	—	—	—
Di-*iso*-butyl ketone	168	—	92	122	—	—	—	—
Di-*n*-amyl ketone	223	14°	—	—	—	—	—	$d_{4°}^{20°}$ 0·825, $n_D^{20°}$ 1·429
Di-*n*-hexyl ketone	255	33	—	—	—	—	97	—
Methyl ethyl ketone	80	—	115	146	—	—	129	—
Methyl *n*-propyl ketone	102	—	144	112	—	—	117	Oxime, 58
Methyl *iso*-propyl ketone	94	—	120	114	—	—	109	—
Methyl *n*-butyl ketone	128	—	107	125	—	—	88	Oxime, 49
Methyl *iso*-butyl ketone	117	—	95	132	—	—	79	Oxime, 58
Methyl *n*-amyl ketone	151	—	89	123	—	—	—	—
Methyl *n*-hexyl ketone	173	—	58	123	—	—	93	—
Chloroacetone	119	—	125	150	—	—	—	Oxime, 71
Acetol (hydroxyacetone)	146	—	129	196	—	103	—	—
Acetoin (methylacetylcarbinol)	145	—	318	185	—	—	—	—
*cyclo*Pentanone	131	—	146	210	190	55	154	Oxime, 57
*cyclo*Hexanone	156	—	162	167	118	81	147	Oxime, 91
*cyclo*Heptanone	180	—	148	162	108	—	—	—
2-Methyl*cyclo*pentanone	139	—	—	184	—	—	—	—
2-Methyl*cyclo*hexanone	165	—	137	197	—	—	132	Oxime, 43
3-Methyl*cyclo*hexanone	170	—	155	191	122	94	119	
4-Methyl*cyclo*hexanone	171	—	134	203	99	110	128	Oxime, 39

TABLE III,74. ALIPHATIC KETONES—*continued*

Ketone	B.P.	M.P.	2 : 4 Dinitrophenylhydrazone	Semicarbazone	Benzal Derivative	Phenylhydrazone	*p*-Nitrophenylhydrazone	Other Derivatives
Diacetone alcohol	166°	—	203°	—	—	—	209°	Oxime, 58°
Mesityl oxide	130	—	203	164°	—	142°	134	Oxime, 49
Pinacolone	106	—	125	158	41°	—	—	Oxime, 78
Phorone	199	28°	118	221	—	—	—	Oxime, 48
Iso-phorone	215	—	130	199	77	68	—	Oxime, 79
Acetylacetone	139	—	209	—	—	—	—	Oxime, 149
Diacetyl	88	—	315 (Di)	279 (Di)	53	243 (Di)	230	Dioxime, 234
Acetonyl acetone	194	—	257 (Di)	220	—	120 (Di)	—	Dioxime, 137
Methyl acetoacetate	170	—	—	152	—	—	—	$d_{4°}^{20°}$ 1·077, $n_D^{20°}$ 1·420
Ethyl acetoacetate	181	—	93	133	—	—	—	$d_{4°}^{20°}$ 1·025, $n_D^{20°}$ 1·420
Methyl laevulinate	196	—	142	143	—	96	—	$d_{4°}^{20°}$ 1·050, $n_D^{20°}$ 1·423
Ethyl laevulinate	206	—	102	148	—	104	—	$d_{4°}^{20°}$ 1·011, $n_D^{20°}$ 1·423
Furoin	—	135	217	—	—	81	—	Oxime, 161
Furil	—	165				184	199	Dioxime, 100
d-Camphor	209	179	177	238	98	233	217	Oxime, 119
d-Carvone	230	—	191	163	—	110	175	Oxime, 73
Pulegone	224	—	147	174	—	—	—	Oxime, 119
β-Thujone	202	—	114	174	—	—	—	Oxime, 55
l-Menthone	209	—	146	189	—	53	—	Oxime, 59
d-Fenchone	193	—	140	184	—	—	—	Oxime, 167
α-Ionone	130°/13	—	151	143(108)	—	—	113	Oxime, 90
β-Ionone	139°/18	—	128	149	—	—	173	—

III,75. ACETONE CYANOHYDRIN

Equip a 1-litre three-necked flask with a mechanical stirrer, a separatory funnel and a thermometer. Place a solution of 47 g. of sodium cyanide (or 62 g. of potassium cyanide) in 200 ml. of water in the flask, and introduce 58 g. (73·5 ml.) of pure acetone. Add slowly from the separatory funnel, with constant stirring, 334 g. (275 ml.) of 30 per cent. sulphuric acid by weight. Do not allow the temperature to rise above 15–20°; add crushed ice, if necessary, to the mixture by momentarily removing the thermometer. After all the acid has been added continue the stirring for 15 minutes. Extract the reaction mixture with three 50 ml. portions of ether, dry the ethereal extracts with anhydrous sodium or magnesium sulphate, remove most of the ether on a water bath and distil the residue rapidly under diminished pressure. The acetone cyanohydrin passes over at 80–82°/15 mm. The yield is 62 g.

III,76. *n*-HEPTALDOXIME

Fit a 1-litre three-necked flask with an efficient mechanical stirrer, a double surface condenser and a thermometer. Place 115 g. (141 ml.) of *n*-heptaldehyde (1) and a solution of 87 g. of hydroxylamine hydrochloride in 150 ml. of water in the flask, and stir the mixture vigorously (2). Introduce, through a separatory funnel fitted into the top of the reflux condenser by means of a grooved cork, a solution of 67 g. of anhydrous sodium carbonate in 250 ml. of water at such a rate that the temperature of the reaction mixture does not rise above 45°. Continue the stirring for 1 hour at room temperature. Separate the upper layer and wash the oil with two 25 ml. portions of water; dry with anhydrous sodium or magnesium sulphate. Distil from a Claisen flask with fractionating side arm (Figs. *II*, *24*, 2–5) using an oil bath. A small fraction of low boiling point (containing *n*-heptonitrile and *n*-heptaldoxime) passes over first, and as soon as the temperature is constant the *n*-heptaldoxime is collected (*e.g.*, at 103–107°/6 mm.); the temperature of the oil bath is maintained at about 30° above the boiling point of the liquid. The yield is about 110 g., and the liquid slowly solidifies on cooling and melts at 44–46°; it is sufficiently pure for conversion into *n*-heptylamine (Section **III,121**). If required pure, the heptaldoxime may be recrystallised from 60 per cent. ethyl alcohol (25 g. of solid to 70 ml. of solvent) and then melts at 53–55° (the m.p. depends somewhat upon the rate of heating).

$$2CH_3(CH_2)_5CHO + 2NH_2OH,HCl + Na_2CO_3 \longrightarrow 2CH_3(CH_2)_5CH{=}NOH + CO_2 + 2NaCl + 3H_2O$$

Notes.

(1) The oenanthol should be dried and redistilled: b.p. 150–156° or 54–59°/16 mm.

(2) The solution may be rendered homogeneous by the addition of ethyl alcohol, but the yield appears to be slightly diminished and more high boiling point material is produced.

Cognate Preparation

Methyl *n*-hexyl ketoxime. From methyl *n*-hexyl ketone (Section **III,71**) in 90 per cent. yield. B.p. 106–108°/12 mm.

III,77. PINACOL AND PINACOLONE

Acetone is reduced by amalgamated magnesium largely to a bimolecular reduction product, tetramethylethylene glycol or **pinacol** $(CH_3)_2C(OH)C(OH)(CH_3)_2$; some *isopropyl* alcohol is also formed:

$$2(CH_3)_2CO + Mg(Hg) \longrightarrow \underset{\text{Magnesium pinacolate}}{(CH_3)_2C(O)\cdots Mg\cdots O(CH_3)_2C} \xrightarrow{H_2O} \underset{\text{Pinacol}}{(CH_3)_2C(OH)\text{—}(CH_3)_2C(OH)}$$

Pinacol possesses the unusual property of forming a crystalline hexahydrate, m.p. 45°, and the pinacol is separated in this form from the unreacted acetone and the *iso*propyl alcohol. The magnesium is conveniently amalgamated by dissolving mercuric chloride in a portion of the acetone; mercury is then liberated by the reaction:

$$HgCl_2 + Mg \longrightarrow Hg + MgCl_2$$

The anhydrous compound, pinacol, is a liquid; it may be prepared from the hydrate by azeotropic distillation with benzene.

Pinacol upon dehydration with acid catalysts (*e.g.*, by distillation from 6*N* sulphuric acid or upon refluxing for 3–4 hours with 50 per cent. phosphoric acid or hydrated oxalic acid) is transformed into methyl *tert.*-butyl ketone or **pinacolone**:

$$\underset{\text{Pinacol}}{(CH_3)_2C(OH)\text{—}C(OH)(CH_3)_2} \xrightarrow{H^+} \underset{\text{Pinacolone}}{(CH_3)_2C(CH_3)\text{—}CO\text{—}CH_3} + H_2O$$

This arrangement, known as the **pinacol - pinacolone rearrangement,** is general for 1 : 2-glycols $RR'C(OH)\cdot C(OH)R''R'''$. The striking feature of the change is the shifting of a methyl group from one of the glycol carbon atoms to the other. This interesting transformation is believed to proceed as follows. The glycol reacts with a proton to give the oxonium ion (I); elimination of water affords the carbonium ion (II); the carbonium ion may undergo a rearrangement involving a 1 : 2 shift of the methyl group with its electron pair (carbanion) to give the new carbonium ion (III); the latter loses a proton to give the product of the rearrangement, pinacolone (IV).

$$\underset{}{CH_3\text{—}C(OH)(CH_3)\text{—}C(OH)(CH_3)\text{—}CH_3} \xrightarrow{H^+} \underset{\text{(I)}}{CH_3\text{—}C(OH)(CH_3)\text{—}C(OH_2^+)(CH_3)\text{—}CH_3} \xrightarrow{-H_2O} \underset{\text{(II)}}{CH_3\text{—}C(CH_3)(OH)\text{—}C^+(CH_3)\text{—}CH_3}$$

$$\xrightarrow[\text{shift}]{1:2} \underset{\text{(III)}}{CH_3\text{—}C^+(OH)\text{—}C(CH_3)_2\text{—}CH_3} \xrightarrow{-H^+} \underset{\text{(IV)}}{CH_3\text{—}C(=O)\text{—}C(CH_3)_2\text{—}CH_3}$$

It must be pointed out that transformations of this type do not take place stepwise, as indicated above; the ultimate change is equivalent to the simultaneous separation of the hydroxyl group and attachment of the migrating

alkyl anion to the rear of the carbon atom from which the hydroxyl group is removed, this carbon atom undergoing a Walden inversion.

The pinacolone may be employed for the preparation of **trimethylacetic acid (pivalic acid)** by oxidation with sodium hypobromite solution :

$$(CH_3)_3C—COCH_3 \xrightarrow[H_2SO_4]{3NaOBr;} (CH_3)_3C—COOH + CHBr_3$$

Pinacol hydrate. Place into a dry 1-litre round-bottomed flask, fitted with a separatory funnel and an efficient double surface condenser (Fig. *III*, *71*, 1) and carrying cotton wool (or calcium chloride) guard tubes 20 g. of dry magnesium turnings and 200 ml. of anhydrous benzene. Place a solution of 22·5 g. of mercuric chloride in 100 g. (127 ml.) of dry A.R. acetone in the separatory funnel and run in about one quarter of this solution ; if the reaction does not commence in a few minutes, as indicated by a vigorous ebullition, warm the flask on a water bath and be ready to cool the flask in running water to moderate the reaction. Once the reaction has started, no further heating is required. Add the remainder of the solution at such a rate that the reaction is as vigorous as possible and yet under control. When all the mercuric chloride solution has been run in and whilst the mixture is still refluxing, add a mixture of 50 g. (63·5 ml.) of dry A.R. acetone and 50 ml. of dry benzene. When the reaction slows down, warm the flask on a water bath for 1–2 hours. During this period the magnesium pinacolate swells up and nearly fills the flask. Cool slightly, disconnect the flask from the condenser and shake until the solid mass is well broken up : it may be necessary to use a stirrer. Attach the condenser and reflux for about 1 hour, or until the magnesium has disappeared.

Now add 50 ml. of water through the separatory funnel and heat again on the water bath for 1 hour with occasional shaking. This converts the magnesium pinacolate into pinacol (soluble in benzene) and a precipitate of magnesium hydroxide. Allow the reaction mixture to cool to 50° and filter at the pump. Return the solid to the flask and reflux with a fresh 125 ml. portion of benzene for 10 minutes in order to extract any remaining pinacol ; filter and combine with the first filtrate. Distil the combined extracts to one half the original volume in order to remove the acetone : treat the residual benzene solution with 60 ml. of water and cool in an ice bath, or to at least 10–15°, with good stirring. After 30–60 minutes, filter the pinacol hydrate which has separated at the pump and wash it with benzene to remove small quantities of mercury compound present as impurities : alternatively, centrifuge the mixture in a basket centrifuge. Dry the pinacol hydrate by exposure to air at the laboratory temperature. The yield is 90 g. ; m.p. 46–57°. This product is sufficiently pure for most purposes. The crude pinacol hydrate may be purified by dissolving it in an equal weight of boiling water, treating with a little decolourising carbon if necessary, filtering the hot solution and cooling in ice ; the recovery is over 95 per cent.

Pinacol (*tetramethylethyleneglycol*). Pinacol hydrate may be dehydrated in the following manner (compare Section **II,39**). Mix 100 g. of pinacol hydrate with 200 ml. of benzene and distil ; a mixture of water and benzene passes over. Separate the lower layer and return the upper layer

of benzene to the distilling flask. Repeat the process until the benzene distillate is clear. Finally distil the anhydrous pinacol and collect the fraction boiling at 169–173° (50 g.). The pure pinacol has m.p. 43°, but on exposure to moist air the m.p. gradually falls to 29–30° and then rises to 45–46° when hydration to the hexahydrate is complete.

Pinacolone. In a 500 ml. round-bottomed flask carrying a dropping funnel and a connection to a condenser set for distillation, place 50 g. of pinacol hydrate and 130 ml. of 6*N* sulphuric acid. Distil the mixture until the upper layer of the distillate no longer increases in volume (15–20 minutes). Separate the pinacolone layer from the water and return the latter to the reaction flask. Then add 12 ml. of concentrated sulphuric acid to the water, followed by a second 50 g. portion of pinacol hydrate. Repeat the distillation. Repeat the process twice more until 200 g. of pinacol hydrate have been used.

Dry the combined pinacolone fractions over anhydrous magnesium sulphate and distil. Collect the pinacolone at 103–107°. The yield is 62 g.

Trimethylacetic acid. In a 2·5 litre three-necked flask, fitted with a thermometer, a mechanical stirrer and dropping funnel, place a solution of 165 g. of sodium hydroxide in 1400 ml. of water. Cool to 0° in an ice-salt bath. Add 240 g. (77 ml.) of bromine with vigorous stirring at such a rate as to keep the temperature below 10° (15–20 minutes). Cool again to 0°, introduce 50 g. of pinacolone, keeping the temperature below 10°. After the solution is decolourised (*ca.* 1 hour), continue the stirring for 3 hours at room temperature. Replace the thermometer by a " knee " tube connected to a condenser for distillation ; separate the bromoform and carbon tetrabromide (if present) by steam distillation ; heat the flask with a powerful (*e.g.*, a Fisher) burner. Remove the burner, cool the reaction mixture to 50°, and add 200 ml. of concentrated sulphuric acid cautiously through the dropping funnel. Heat the flask again ; the trimethylacetic acid passes over with about 200 ml. of water. When all the trimethylacetic acid (35–40 ml.) has distilled, a liquid heavier than water (possibly brominated pinacolone) begins to pass over. Stop the distillation at this point, separate the trimethylacetic acid from the aqueous layer, and dry it by distillation with 25 ml. of benzene (the latter carries over all the water) or with anhydrous calcium sulphate. Distil under reduced pressure and collect the trimethylacetic acid 75°–80°/20 mm. The yield is 33 g., m.p. 34–35°.

III,78. DIACETONE ALCOHOL

Acetaldehyde (and other aldehydes containing at least one hydrogen atom in the α-position) when treated with a small quantity of dilute sodium hydroxide solution or other basic catalyst gives a good yield of aldol (β-hydroxy-*n*-butyraldehyde) (I), which readily loses water, either by heating the isolated aldol alone or with a trace of mineral acid, to form crotonaldehyde (II) :

$$CH_3CHO + HCH_2CHO \overset{OH^-}{\rightleftharpoons} \underset{(I)}{CH_3CH(OH)CH_2CHO} \xrightarrow{-H_2O} \underset{(II)}{CH_3CH{=}CHCHO}$$

With concentrated alkali, a resin is formed from repeated aldol condensations between aldol, crotonaldehyde and acetaldehyde. A similar condensation occurs with acetone (b.p. 56°), but the equilibrium mixture contains only a few per cent. of diacetone alcohol (III), b.p. 166°:

$$(CH_3)_2CO + HCH_2COCH_3 \overset{Ba(OH)_2}{\rightleftharpoons} (CH_3)_2C(OH)CH_2COCH_3 \text{ (III)}$$

However, by using a special technique (boiling flask, containing acetone, attached to a Soxhlet apparatus filled with barium hydroxide, surmounted by a double surface condenser) and taking advantage of the fact that the dissociation of the diacetone alcohol to acetone proceeds extremely slowly in the absence of barium hydroxide, it is possible to prepare compound (III) satisfactorily. Solid barium hydroxide acts as a catalyst in the reaction; its solubility in acetone is very small. The liquid returning to the flask, heated on a water bath, contains the alcohol in small concentration; this remains in the boiling flask and only the much more volatile acetone passes into the Soxhlet apparatus and is recycled. After about 4 days the concentration of (III) in the boiling flask is 70–80 per cent., and can be easily separated from the acetone by fractional distillation.

Fit a 1-litre round-bottomed flask with a rubber stopper carrying a large Soxhlet extractor (Fig. *II*, *44*, 4), and attach an efficient double surface condenser to the latter. Place 595 g. (750 ml.) of commercial acetone, preferably dried over anhydrous potassium carbonate, and a few fragments of porous porcelain in the flask. Insert two large paper thimbles in the Soxhlet apparatus, one above the other; fill each about three-quarters full with barium hydroxide and fill the remainder of the space with glass wool (1). Heat the flask on a water bath or steam bath so that the acetone refluxes back into the extractor rather rapidly. Continue the heating until the acetone no longer refluxes when the flask is almost completely immersed in the boiling water bath (72–120 hours). The refluxing may be interrupted at any time for as long as desired without influencing the preparation. Equip the flask with a fractionating column attached to an efficient double surface condenser set for downward distillation. Immerse the flask in an oil bath and raise the temperature gradually to 125°; maintain this temperature as long as acetone distils over. The recovery of acetone is complete when the temperature at the top of the column is about 70°. Distil the residue (2) from a Claisen flask under diminished pressure (3); a little acetone passes over first, followed by the diacetone alcohol at 71–74°/23 mm. (or 62–64°/13 mm.). The yield is 450 g.

Notes.

(1) If the outlet of the siphon tube at the bottom of the Soxhlet apparatus is well plugged with cotton wool so that no finely-divided barium hydroxide can pass into the flask, the barium hydroxide may be placed directly into the extractor until the latter is three-quarters full; the remaining space is filled with glass wool.

If crystallised barium hydroxide ($Ba(OH)_2,8H_2O$) is employed, this becomes dehydrated after one run; the anhydrous compound is just as satisfactory and may be used repeatedly.

(2) The residual liquid contains about 95 per cent. of diacetone alcohol and is satisfactory for the preparation of mesityl oxide (Section III,79).

(3) Diacetone alcohol partially decomposes when distilled under normal pressure.

III,79. MESITYL OXIDE

Diacetone alcohol is readily dehydrated by adding a very small quantity of iodine as catalyst and distilling slowly:

$$(CH_3)_2C(OH)CH_2COCH_3 \xrightarrow{I_2} (CH_3)_2C{=}CHCOCH_3 + H_2O$$

The product, an αβ-unsaturated ketone, is known as mesityl oxide.

Fit a 750 ml. round-bottomed flask with a fractionating column attached to a condenser set for downward distillation. Place 500 g. of diacetone alcohol (the crude product is quite satisfactory), 0·1 g. of iodine and a few fragments of porous porcelain in the flask. Distil slowly with a small free flame (best in an air bath) and collect the following fractions: (*a*) 56–80° (acetone and a little mesityl oxide); (*b*) 80–126° (two layers, water and mesityl oxide); and (*c*) 126–131° (mesityl oxide). Whilst fraction (*c*) is distilling, separate the water from fraction (*b*), dry with anhydrous potassium carbonate or anhydrous magnesium sulphate, and fractionate from a small flask; collect the mesityl oxide at 126–131°. The yield is about 400 g.

SATURATED ALIPHATIC MONOBASIC ACIDS

Saturated aliphatic acids may be prepared :—

1. By oxidation of primary alcohols with alkaline potassium permanganate solution or with a dichromate and dilute sulphuric acid, for example :

$$\underset{\textit{iso}\text{-Butyl alcohol}}{(CH_3)_2CHCH_2OH} \xrightarrow[[O]]{KMnO_4} \underset{\textit{iso}\text{-Butyric acid}}{(CH_3)_2CHCOOH} + H_2O$$

$$\underset{\textit{iso}\text{Amyl alcohol}}{(CH_3)_2CHCH_2CH_2OH} \xrightarrow[\text{dil. } H_2SO_4]{Na_2Cr_2O_7} \underset{\textit{iso}\text{Valeric acid}}{(CH_3)_2CHCH_2COOH}$$

$$(+ \underset{\textit{iso}\text{Amyl } \textit{iso}\text{valerate}}{(CH_3)_2CHCH_2COOCH_2CH_2CH(CH_3)_2})$$

The oxidation with excess of dichromate and dilute sulphuric acid is not always satisfactory for alcohols higher than *n*-propyl because of the attendant production of appreciable amounts of esters : indeed by using a fairly high concentration of sulphuric acid, good yields of esters are obtained since esterification takes place at once, even in the cold, as long as an excess of alcohol is present, for example :

$$\underset{n\text{-Butyl alcohol}}{6C_4H_9{}^{\alpha}OH} + 2Na_2Cr_2O_7 + 8H_2SO_4 \longrightarrow \underset{n\text{-Butyl-}n\text{-butyrate}}{3C_3H_7{}^{\alpha}COOC_4H_9{}^{\alpha}} + 2Cr_2(SO_4)_3 + 2Na_2SO_4 + 14H_2O$$

2. By oxidation of aldehydes with potassium permanganate solution, for example :

$$\underset{n\text{-Heptaldehyde}}{3C_6H_{13}{}^{\alpha}CHO} + 2KMnO_4 + H_2SO_4 \longrightarrow \underset{n\text{-Heptoic acid}}{3C_6H_{13}{}^{\alpha}COOH} + K_2SO_4 + 2MnO_2 + H_2O$$

3. By hydrolysis of alkyl cyanides (or nitriles) * with alkali hydroxide solutions, for example :

$$\underset{n\text{-Butyl cyanide}}{C_4H_9{}^{\alpha}CN} + 2H_2O \xrightarrow{OH^-} \underset{n\text{-Valeric acid}}{C_4H_9{}^{\alpha}COOH} + NH_3$$

4. By the action of carbon dioxide upon a suitable Grignard reagent, for example :

$$\underset{\textit{sec.}\text{-Butyl chloride}}{C_2H_5CHClCH_3} + Mg \longrightarrow C_2H_5CH(MgCl)CH_3 \xrightarrow[H_2O]{CO_2,\ \text{then}} \underset{\textit{dl}\text{-Methylethylacetic acid}}{C_2H_5CH(COOH)CH_3}$$

5. By hydrolysis of substituted malonic esters with 50 per cent. potassium hydroxide, followed by decarboxylation of the resulting malonic acid by heating above the m.p. or, better, by rendering the aqueous solution of the potassium salt of the dibasic acid strongly acid and refluxing the mixture, for example :

$$C_4H_9{}^{\alpha}Br + CH_2(COOC_2H_5)_2 \xrightarrow{NaOC_2H_5} \underset{\text{Diethyl } n\text{-butylmalonate}}{C_4H_9{}^{\alpha}CH(COOC_2H_5)_2} \xrightarrow{50\%\ KOH}$$

$$\underset{n\text{-Butylmalonic acid}}{C_4H_9{}^{\alpha}CH(COOH)_2\ (\text{as salt})} \xrightarrow[\text{and heat}]{H_2SO_4} \underset{n\text{-Caproic acid}}{C_4H_9{}^{\alpha}CH_2COOH}$$

* These are readily available from the interaction of alkyl halides with sodium or potassium cyanide in aqueous-alcoholic solution (compare Section III,113).

III,80. *iso*BUTYRIC ACID

Place a mixture of 50 g. of *iso*butyl alcohol and a solution of 15 g. of sodium carbonate in 150 ml. of water in a 4-litre round-bottomed flask. Add a solution of 140 g. of potassium permanganate in 2750 ml. of water, with vigorous stirring, during 3–4 hours. Continue the stirring and cool the mixture to 4–5° by immersion in a bath of ice water. Allow the reaction mixture to attain room temperature gradually. After 12 hours, filter off (or, preferably, centrifuge) the precipitated manganese dioxide, evaporate the filtrate on a water bath to about 150 ml., and then cool. Cover the solution with a layer of ether and acidify with dilute sulphuric acid. Separate the ether layer and extract the aqueous layer two or three times with 50 ml. portions of ether. Dry the combined ethereal extracts over anhydrous sodium or magnesium sulphate, remove the ether on a water bath, and fractionate the residual liquid. Collect the *iso*-butyric acid at 153–155°. The yield is 45 g.

***n*-Valeric acid** may be similarly prepared utilising the following quantities: 75 g. *n*-amyl alcohol (Eastman Kodak product, redistilled), 19 g. of sodium carbonate in 190 ml. of water, 220 g. of potassium permanganate in 4,500 ml. of water. Use a 5- or 6-litre flask. Concentrate the filtered aqueous solution either by evaporation on a water bath or by distillation under reduced pressure. Isolate the *n*-valeric acid as detailed above for *iso*butyric acid. The yield is 55 g., b.p. 182–185°.

Cognate Preparations

***iso*Valeric acid.** Prepare dilute sulphuric acid by adding 140 ml. of concentrated sulphuric acid cautiously and with stirring to 85 ml. of water; cool and add 80 g. (99 ml.) of redistilled *iso*amyl alcohol. Place a solution of 200 g. of crystallised sodium dichromate in 400 ml. of water in a 1-litre (or 1·5 litre) round-bottomed flask and attach an efficient reflux condenser. Add the sulphuric acid solution of the *iso*amyl alcohol in *small* portions through the top of the condenser; * shake the apparatus vigorously after each addition. No heating is required as the heat of the reaction will suffice to keep the mixture hot. It is important to shake the flask well immediately after each addition and not to add a further portion of alcohol until the previous one has reacted; if the reaction should become violent, immerse the flask momentarily in ice water. The addition occupies 2–2·5 hours. When all the *iso*amyl alcohol has been introduced, reflux the mixture gently for 30 minutes, and then allow to cool. Arrange the flask for distillation (compare Fig. *II*, *13*, 3, but with the thermometer omitted) and collect about 350 ml. of distillate. The latter consists of a mixture of water, *iso*valeric acid and *iso*amyl *iso*valerate. Add 30 g. of potassium (*not* sodium) hydroxide pellets to the distillate and shake until dissolved. Transfer to a separatory funnel and remove the upper layer of ester (16 g.). Treat the aqueous layer contained in a beaker with 30 ml. of dilute sulphuric acid (1 : 1 by volume) and extract the liberated *iso*valeric acid with two

* If preferred, a 1·5 litre three-necked flask, equipped with a dropping funnel, mechanical stirrer and reflux condenser, may be used and the obvious modifications of technique introduced. This procedure is recommended.

50 ml. portions of carbon tetrachloride. Keep the carbon tetrachloride extract (*A*).

To obtain a maximum yield of the acid it is necessary to hydrolyse the by-product, *iso*amyl *iso*valerate : this is most economically effected with methyl alcoholic sodium hydroxide. Place a mixture of 20 g. of sodium hydroxide pellets, 25 ml. of water and 225 ml. of methyl alcohol in a 500 ml. round-bottomed flask fitted with a reflux (double surface) condenser, warm until the sodium hydroxide dissolves, add the ester layer and reflux the mixture for a period of 15 minutes. Rearrange the flask for distillation (Fig. *II*, *13*, 3) and distil off the methyl alcohol until the residue becomes pasty. Then add about 200 ml. of water and continue the distillation until the temperature reaches 98–100°. Pour the residue in the flask, consisting of an aqueous solution of sodium *iso*valerate, into a 600 ml. beaker and add sufficient water to dissolve any solid which separates. Add slowly, with stirring, a solution of 15 ml. of concentrated sulphuric acid in 50 ml. of water, and extract the liberated acid with 25 ml. of carbon tetrachloride. Combine this extract with extract (*A*), dry with a little anhydrous magnesium or calcium sulphate, and distil off the carbon tetrachloride (Fig. *II*, *13*, 4 ; 150 ml. distilling or Claisen flask), and then distil the residue. Collect the *iso*valeric acid 172–176°. The yield is 56 g.

***iso*Butyric acid.** This acid may also be prepared, although in smaller yield, by the oxidation of *iso*butyl alcohol with acidified dichromate solution. Place a solution of 200 g. of crystallised sodium dichromate in 400 ml. of water in a 1·5-litre three-necked flask equipped with a dropping funnel, mechanical stirrer and reflux condenser. Dissolve 67·5 g. (84 ml.) of redistilled *iso*butyl alcohol in cold dilute sulphuric acid prepared from 140 ml. of concentrated sulphuric acid and 85 ml. of water ; pour the solution into the dropping funnel. Add the sulphuric acid solution of the *iso*butyl alcohol to the stirred sodium dichromate solution at such a rate that the exothermic reaction is under control (1·5–2 hours). Reflux the mixture for 30 minutes and then distil ; collect about 400 ml. of distillate. Saturate the distillate with salt, and extract it with three 75 ml. portions of ether. Shake the combined ethereal extracts with 10 per cent. sodium hydroxide solution until the aqueous solution remains alkaline. Acidify the aqueous extract with dilute sulphuric acid, saturate with salt, and extract with three 50 ml. portions of ether. Dry the combined ethereal solutions resulting from the last extraction with anhydrous magnesium sulphate, remove the ether, and distil the residue (air bath). The yield of pure *iso*butyric acid, b.p. 154°, is 30 g.

III,81. *n*-HEPTOIC ACID *

Place 700 ml. of water and 161 g. (87·5 ml.) of concentrated sulphuric acid in a 1500 ml. flask. Introduce a mechanical stirrer into the flask and cool the latter in an ice bath. When the temperature is below 15°, add 85·5 g. (105 ml.) of redistilled *n*-heptaldehyde (b.p. 151–156° or

* Also termed *n*-heptanoic acid, *n*-heptylic acid, and oenanthic acid.

40–42°/10 mm.), followed by 85 g. of potassium permanganate in 10–15 g. portions. Add the permanganate at such a rate that the temperature does not rise above 20° (*ca.* 1 hour). Pass sulphur dioxide into the solution (or add sodium bisulphite) until the precipitated manganese dioxide *just* dissolves and the solution is clear. Separate the oily layer, wash it with water, and then dry with anhydrous sodium or magnesium sulphate. Distil through a short well-lagged fractionating column, and collect the crude *n*-heptoic acid at 215–224° (75 g.). Purify the crude acid by dissolving it in a solution of 35 g. of sodium hydroxide in 175 ml. of water, and steam distil from a 500 ml. flask until a test portion is free from oil. Cool the solution remaining in the flask to room temperature and acidify cautiously with 96 ml. of concentrated hydrochloric acid. Separate the liberated oenanthic acid, dry with anhydrous sodium or magnesium sulphate, and fractionate as before. Collect the pure *n*-heptoic acid (65 g.) at 218–222°.

III,82. *n*-BUTYL *n*-BUTYRATE

Fit a 1-litre three-necked flask with a mechanical stirrer, a thermometer and a separatory funnel. Place a cold solution of 120 ml. of concentrated sulphuric acid in 120 ml. of water, together with 120 g. (148 ml.) of *n*-butyl alcohol, in the flask and cool in a freezing mixture of ice and salt. Add a solution of 120 g. of crystallised sodium dichromate (or 175 g. of the moist technical hydrated salt) in 200 ml. of water from the separatory funnel to the vigorously stirred mixture at such a rate that the temperature does not rise above 20°. When most of the dichromate solution has been added, the reaction mixture becomes viscous and the stirring is rendered inefficient: allow the temperature to rise to 35° to accelerate the oxidation (above this temperature *n*-butyraldehyde, b.p. 74°, may be lost). Dilute the green, syrupy emulsion with an equal volume of water, and allow the mixture to stand in order that the separation of the oil may be as complete as possible (about 110 ml. containing the ester plus unchanged butyl alcohol, a little butyraldehyde and a little butyric acid). Wash the oil three times with water, dry it with anhydrous sodium or magnesium sulphate and distil slowly through an efficient, adequately-lagged fractionating column. Collect the fraction boiling at 150–170° (*ca.* 85 ml.) and wash it with five 7·5 ml. portions of 60 per cent. sulphuric acid (sp. gr. 1·5) (1), then with dilute sodium hydroxide solution until free from acid, and finally with water until neutral. Dry as before and fractionate. Collect the *n*-butyl *n*-butyrate at 163–167°. The yield is 50 g.

Note.

(1) *n*-Butyl alcohol is miscible with 60 per cent. sulphuric acid, but not with the ester.

III,83. *n*-VALERIC ACID (*Hydrolysis of* n-*Butyl Cyanide*)

Place 100 g. (105 ml.) of *n*-butyl cyanide (Section **III,113**) and a solution of 92 g. of pure sodium hydroxide in 260 ml. of water in a 1500 ml. round-bottomed flask, attach a double surface condenser, and reflux

over a wire gauze until the butyl cyanide layer disappears (5–10 hours). Add through the condenser 100 ml. of water, then slowly, and with external cooling, 125 ml. of 50 per cent. (by volume) sulphuric acid. Separate the upper layer of *n*-valeric acid (it may be necessary to filter first from any solid present), and dry it with anhydrous magnesium or calcium sulphate. Distil from a Claisen flask and collect the *n*-valeric acid at 183–185° (mainly 184°). The yield is 82 g. A further 5 g. of acid may be obtained by extracting the strongly acidified aqueous layer with ether (or benzene), combining the ethereal extracts with the low and high boiling point fractions of the previous distillation, removing the ether on a water bath, and distilling from a small flask.

III,84. *dl*-METHYLETHYLACETIC ACID

(Carbonation of a Grignard Reagent)

Fit a 1-litre three-necked flask with a mechanical stirrer, a double surface condenser and a separatory funnel (Fig. *II*, 7, 11, *a*), and provide both the condenser and funnel with cotton wool (or calcium chloride) guard tubes. Place 13·4 g. of dry magnesium turnings, 50 ml. of sodium-dried ether and a crystal of iodine in the flask : introduce 3 g. (3·5 ml.) of dry *sec.*-butyl chloride (Section **III,29**) (1). Warm the flask on a water bath or electric hot plate to start the reaction, and then allow it to proceed by its own heat for 20 minutes. Add a further 75 ml. of anhydrous ether, followed by a solution of 43 g. (49 ml.) of dry *sec.*-butyl chloride in 275 ml. of anhydrous ether over a period of 20–25 minutes. If the reaction becomes too vigorous, cool the flask momentarily with cold water. The refluxing will continue for about 20 minutes after the addition of the halide solution owing to the heat of the reaction. When this subsides, reflux the mixture for 1 hour. Cool the flask in a mixture of ice and salt to −12° (2) and add a further 100 ml. of anhydrous ether. Replace the separatory funnel by a tube 10 mm. in diameter with side tube (as in Fig. *II*, 7, 12, *b*) : insert a thermometer, held in position by a rubber sleeve, into the upper end. Arrange the thermometer to dip into the reaction mixture and the lower end of the wide tube to be about 6 cm. *above* the level of the liquid (this avoids the troublesome clogging of the tube with solid at a later stage) ; attach the side tube to a cylinder of carbon dioxide (3). Pass carbon dioxide into the flask at such a rate that the temperature does not rise above −5° when the mixture is rapidly stirred. After 2–2·5 hours, the temperature does not rise upon increasing the flow of carbon dioxide, but falls to about −12°. This drop in temperature (it is assumed, of course, that the freezing mixture is maintained) indicates the end point of the carbonation.

Immediately the reaction is complete, introduce through the condenser 250 ml. of 50 per cent. sulphuric acid (by weight) whilst cooling the mixture in ice and water and stirring vigorously. Transfer the mixture to a separatory funnel, remove the ether layer, and extract the aqueous layer with three 50 ml. portions of ether. Cool the combined ether extracts by the addition of ice, and add cautiously 100 ml. of 25 per cent. sodium hydroxide solution ; run off the aqueous layer and repeat the

extraction with a further 50 ml. of alkali solution of the same strength. The organic acid is thus converted into the sodium salt and passes into the aqueous layer : test the extracts with phenolphthalein to make certain that all the acid has been removed. Distil the alkaline extract until its volume is reduced by about 10 per cent. ; this removes ether and other volatile impurities. Allow to cool, and cautiously acidify with concentrated hydrochloric acid ; it is advisable to stir the mixture during the acidification process. Separate the upper layer of acid. Distil the water layer from a 1-litre flask until no more oily drops pass over ; saturate the distillate with salt, remove the acid layer, and combine it with the main product. Dry the combined acids with anhydrous magnesium or calcium sulphate, and distil. Collect the *dl*-methylethylacetic acid at 173–174°. The yield is 40 g.

Notes.

(1) *sec.*-Butyl chloride is employed in preference to the bromide because it is cheaper and the yield of acid is slightly higher.

(2) Some of the Grignard reagent may be oxidised by the air which is drawn in when the flask is cooled : this may be avoided by passing in dry nitrogen (the gas from a cylinder is passed through two wash bottles containing concentrated sulphuric acid) until the temperature has reached −12°. A T-piece is provided in the gas circuit, and the nitrogen or carbon dioxide is admitted to the flask through the same wide tube. The effect upon the yield is, however, quite small.

(3) The gas is dried by passage through wash bottles containing concentrated sulphuric acid. Alternatively and more simply, the technique (described below for *n*-valeric acid) utilising solid carbon dioxide (Dry Ice or Drikold) may be employed.

Cognate Preparation

***n*-Valeric acid** (*carbonation of the Grignard reagent*). The method detailed above, utilising gaseous carbon dioxide with the Grignard reagent from *n*-butyl chloride or bromide, may be used. The experimental details which follow describe the technique with solid carbon dioxide (Dry Ice or Drikold) as the carbonating agent.

Prepare a Grignard reagent from 12·2 g. of magnesium, a crystal of iodine, 69 g. (54 ml.) of *n*-butyl bromide (1) and 250 ml. of anhydrous ether in a 1-litre three-necked flask, following the method of Section **III,23** or the slightly modified procedure of Section **III,18**. Weigh out (rough balance) 125 g. of Dry Ice (2) on a piece of stiff paper : wrap the paper round the Dry Ice and, by means of a pestle, break it into small lumps, but keep the paper tightly round it. Empty the Dry Ice into a dry 1500 ml. beaker and at once pour in the Grignard reagent in a slow steady stream ; any unreacted magnesium will adhere to the sides of the flask. A vigorous reaction occurs. Stir the mass well, and allow it to stand until all the Dry Ice has evaporated. Then add slowly a mixture of 300 g. of crushed ice and 75 ml. of concentrated hydrochloric acid. Stir until the gelatinous compound is decomposed and there is a clean separation into two layers. Pour the mixture into a separatory funnel ; rinse the beaker with 50 ml. of ether and transfer this to the funnel. Separate the upper layer and extract the aqueous layer with three 40 ml. portions of ether. Treat the combined ethereal extracts of the crude acid with 25 per cent. sodium hydroxide solution, etc., and proceed exactly as described above

for methylethylacetic acid. Collect the *n*-valeric acid at 182–185° (3). The yield is 25 g.

Notes.

(1) Alternatively, use the equivalent amount of *n*-butyl chloride and prepare the Grignard reagent as for *sec.*-butyl magnesium chloride.

(2) Dry Ice should be handled with gloves or with a dry towel; if Dry Ice is held for a long time in the hand, it may cause frost bite.

(3) A method of drying the acid, which avoids the use of a solid desiccant, consists in mixing the liquid with benzene (this solvent may be used for extracting the aqueous layer) and distilling. A mixture of benzene and water passes over first, then, when all the water has been removed, benzene distils at 80°, followed by a rapid rise in temperature to the boiling point of *n*-valeric acid (compare Section II, 39). This procedure may be applied to the drying of most liquid acids. Better results are usually obtained if the benzene solution is subjected to a preliminary drying with anhydrous magnesium or calcium sulphate.

III,85. REACTIONS AND CHARACTERISATION OF ALIPHATIC CARBOXYLIC ACIDS

(i) **Action upon sodium bicarbonate solution.** Place 1 ml. of 5 per cent. sodium bicarbonate solution upon a watch glass; introduce the pure acid (1 drop or a little of the finely-powdered solid). Evolution of carbon dioxide indicates the presence of an acid.

Test the solution so obtained for **unsaturation** by adding cold 1 per cent. potassium permanganate solution a drop at a time. The immediate disappearance of the purple colour and the formation of a brown turbidity indicates the presence of a double bond (*Baeyer's test*). It must be noted that many substances, not unsaturated, decolourise warm acid or neutral potassium permanganate solution.

Test a small quantity of the aqueous solution or extract of the carboxylic acid with litmus or with Universal indicator paper.

(ii) **Ester formation.** Warm a small amount of the acid with 2 parts of absolute ethyl alcohol and 1 part of concentrated sulphuric acid for 2 minutes. Cool, and pour cautiously into aqueous sodium carbonate solution contained in an evaporating dish, and smell immediately. An acid usually yields a sweet, fruity smell of an ester. (Acids of high molecular weight often give almost odourless esters.)

(iii) **Neutralisation equivalent.** It is recommended that the neutralisation equivalent (or the **equivalent weight**) of the acid be determined: this is the number expressing the weight in grams of the compound neutralised by one gram equivalent of alkali. Weigh out accurately about 0·2 g. of the acid (finely powdered if a solid), add about 30 ml. of water and, if necessary, sufficient alcohol to dissolve most of the acid, followed by two drops of phenolphthalein indicator. Titrate with accurately standardised 0·1*N* sodium or barium hydroxide solution.* Calculate the equivalent weight from the expression:

$$\text{Neutralisation equivalent} = \frac{\text{Grams of acid} \times 1000}{\text{Ml. of alkali} \times \text{Normality of alkali}}$$

* For further details as to the standardisation of the alkali and the storage of standard alkali solutions, see Vogel, *A Text Book of Quantitative Inorganic Analysis: Theory and Practice*, Second Edition, 1951, 233 *et seq.* (Longmans, Green and Co. Ltd.).

CRYSTALLINE DERIVATIVES OF ALIPHATIC CARBOXYLIC ACIDS

1. **Amides, anilides and *p*-toluidides.** The dry acid is first converted by excess of thionyl chloride into the acid chloride :

$$RCOOH + SOCl_2 \longrightarrow RCOCl + SO_2 + HCl$$

The by-products are both gaseous and the excess of thionyl chloride (b.p. 78°) may be readily removed by distillation. Interaction of the acid chloride with ammonia solution, aniline or *p*-toluidine yields the amide, anilide or *p*-toluidide respectively :

$$RCOCl + 2NH_3 \longrightarrow RCONH_2 + NH_4Cl$$
$$RCOCl + 2R'NH_2 \longrightarrow RCONHR' + R'NH_2,HCl$$

Stopper the side arm of a 25 or 50 ml. distilling flask and fit a vertical water condenser into the neck. Place 0·5–1·0 g. of the dry acid (finely powdered if it is a solid) into the flask, add 2·5–5·0 ml. of redistilled thionyl chloride and reflux gently for 30 minutes ; it is advisable to place a plug of cotton wool * in the top of the condenser to exclude moisture. Rearrange the condenser and distil off the excess of thionyl chloride † (b.p. 78°). The residue in the flask consists of the acid chloride and can be converted into any of the derivatives given below.

(*a*) **Amides.** Treat the acid chloride cautiously with about 20 parts of concentrated ammonia solution (sp. gr. 0·88) and warm for a few moments. If no solid separates on cooling, evaporate to dryness on a water bath. Recrystallise the crude amide from water or dilute alcohol.

Alternatively, dissolve or suspend the acid chloride in 5–10 ml. of dry ether or dry benzene, and pass in dry ammonia gas. If no solid separates, evaporate the solvent. Recrystallise the amide from water or dilute alcohol.

(*b*) **Anilides.** Dilute the acid chloride with 5 ml. of pure ether (or benzene), and add a solution of 2 g. of pure aniline in 15–20 ml. of the same solvent until the odour of the acid chloride has disappeared ; excess of aniline is not harmful. Shake with excess of dilute hydrochloric acid to remove aniline and its salts, wash the ethereal (or benzene) layer with 3–5 ml. of water, and evaporate the solvent [*CAUTION !*] Recrystallise the anilide from water, dilute alcohol or benzene - light petroleum (b.p. 60–80°).

***p*-Bromoanilides** are similarly prepared with *p*-bromoaniline.

(*c*) ***p*-Toluidides.** Proceed as under (*b*), but substitute *p*-toluidine for aniline.

Anilides and *p*-toluidides may also be *prepared directly from the acids* ‡ by heating them with aniline or *p*-toluidine respectively :

$$RCOOH + R'NH_2 \longrightarrow RCONHR' + H_2O$$

* This is more convenient than the conventional calcium chloride guard tube and possesses the advantage of cheapness and hence can easily be renewed for each experiment : it is, of course, removed during distillations.

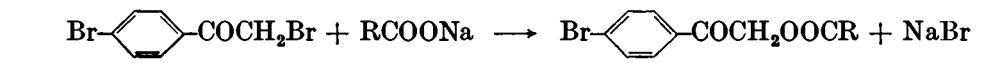
† If the boiling point of the acid chloride is too near that of thionyl chloride to render separation by distillation practicable, the excess of the reagent can be destroyed by the addition of pure formic acid :

$$HCOOH + SOCl_2 \longrightarrow CO + SO_2 + 2HCl$$

‡ Alternatively, the alkali metal salts of the acids may be heated with the hydrochloride of the appropriate base.

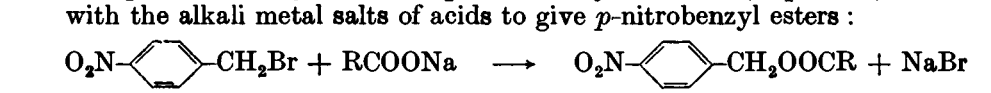
Place 1·0 g. of the monobasic acid and 2 g. of aniline or *p*-toluidine in a dry test-tube, attach a short air condenser and heat the mixture in an oil bath at 140–160° for 2 hours: do not reflux too vigorously an acid that boils below this temperature range and only allow steam to escape from the top of the condenser. For a sodium salt, use the proportions of 1 g. of salt to 1·5 g. of the base. If the acid is dibasic, employ double the quantity of amine and a reaction temperature of 180–200°: incidentally, the procedure is recommended for dibasic acids since the latter frequently give anhydrides with thionyl chloride. Powder the cold reaction mixture, triturate it with 20–30 ml. of 10 per cent. hydrochloric acid,* and recrystallise from dilute alcohol.

2. ***p*-Bromophenacyl esters.** *p*-Bromophenacyl bromide reacts with the alkali metal salts of acids to form crystalline *p*-bromophenacyl esters:



Dissolve or suspend 0·5 g. of the acid in 5 ml. of water in a small conical flask, add a drop or two of phenolphthalein indicator, and then 4–5 per cent. sodium hydroxide solution until the acid is just neutralised. Add a few drops of very dilute hydrochloric acid so that the final solution is *faintly* acid (litmus).† Introduce 0·5 g. of *p*-bromophenacyl bromide (m.p. 109°) dissolved in 5 ml. of rectified (or methylated) spirit, and heat the mixture under reflux for 1 hour: if the mixture is not homogeneous at the boiling point or a solid separates out, add just sufficient alcohol to produce homogeneity. [Di- and tri-basic acids require proportionately larger amounts of the reagent and longer refluxing periods.] Allow the solution to cool, filter the separated crystals at the pump, wash with a little alcohol and then with water. Recrystallise from dilute alcohol: dissolve the solid in hot alcohol, add hot water until a turbidity just results, clear the latter with a few drops of alcohol, and allow to cool. Acetone may sometimes be employed for recrystallisation.

3. ***p*-Nitrobenzyl esters.** *p*-Nitrobenzyl bromide (m.p. 100°) reacts with the alkali metal salts of acids to give *p*-nitrobenzyl esters:



It is important that the solution of the sodium salt be *faintly* acid in order that the formation of coloured by-products in the subsequent reaction may be prevented. If the molecular weight of the monobasic acid is known, it is desirable to employ a slight excess of the sodium salt, since excess of the latter is more easily removed than the unchanged reagent.

Use the procedure given under *2* for *p*-bromophenacyl esters. If the ester does not crystallise out on cooling, reheat the reaction mixture, and add small portions of hot water to the point of incipient cloudiness and allow to cool.

* When the derivative is appreciably soluble in ether, the following alternative procedure may be employed. Dissolve the cold reaction mixture in about 50 ml. of ether, wash it with 20–30 ml. of 10 per cent. hydrochloric acid (to remove the excess of base), followed by 20 ml. of 10 per cent. sodium hydroxide solution, separate the ether layer, and evaporate the solvent [*CAUTION!*]. Recrystallise the residue from dilute alcohol.

† If the sodium salt of the acid is available, dissolve 0·5 g. in 5 ml. of water, add a solution of 0·5 g. of the reagent in 5 ml. of alcohol, and proceed as detailed in the text after just acidifying (litmus) with dilute hydrochloric acid.

4. ***p*-Phenylphenacyl esters.** *p*-Phenylphenacyl bromide reacts with soluble salts of organic acids to yield crystalline *p*-phenylphenacyl esters:

$$p\text{-}C_6H_5C_6H_4COCH_2Br + NaOOCR \longrightarrow p\text{-}C_6H_5C_6H_4COCH_2OOCR + NaBr$$

The procedure is similar to that given under *2* and *3* above. Add a weighed amount of acid (0·005 mol) to 5 ml. of water in a small conical flask and neutralise it with *N* sodium carbonate or *N* sodium hydroxide. The final solution should be faintly acid to litmus (add more of the organic acid or a few drops of dilute hydrochloric acid); unless this precaution is taken, coloured by-products are formed which are very difficult to remove. [If the alkali metal salt is available, dissolve 0·005 mol* in 5 ml. of water, and render the solution just acid to litmus by the addition of dilute hydrochloric acid.] Introduce 10 ml. of alcohol, and if the salt of the organic acid is not thrown out of solution, add 0·005 mol of *p*-phenylphenacyl bromide: reflux the mixture for periods up to 1, 2 or 3 hours according to the basicity of the acid. If the salt of the organic acid is precipitated by the alcohol, add more water until the salt dissolves. Some of the esters are sparingly soluble in the reaction mixture and crystallise from the boiling solution; in most cases, however, crystal formation does not occur until the mixture is cooled. In some instances it may be necessary to concentrate the solution before crystallisation occurs. Recrystallise the crude *p*-phenylphenacyl ester from alcohol, dilute alcohol, acetone or benzene.

Certain dibasic acids, of which the sodium or potassium salts are sparingly osluble in dilute alcohol, cause difficulty; these should be neutralised with ethylamine solution.

5. **S-Benzyl-*iso*-thiuronium salts (S-Benzyl-*iso*-thiourea salts).** S-Benzyl-*iso*-thiuronium chloride (S-benzyl-*iso*-thiourea hydrochloride) reacts with the alkali metal salts of organic acids to produce crystalline S-benzyl-*iso*-thiuronium salts:

$$\left\{C_6H_5CH_2\text{—}S\text{—}\overset{\displaystyle NH_2}{\overset{\diagup}{C}}\text{—}NH_2\right\}^+ Cl^- + RCOONa \longrightarrow \left\{C_6H_5CH_2\text{—}S\text{—}\overset{\displaystyle NH_2}{\overset{\diagup}{C}}\text{—}NH_2\right\}^+ COOR^- + NaCl$$

It is important not to allow the reaction mixture to become appreciably alkaline, since the free base then decomposes rapidly yielding benzyl mercaptan, which has an unpleasant odour.

Dissolve (or suspend) 0·25 g. of the acid in 5 ml. of warm water, add a drop or two of phenolphthalein indicator and neutralise carefully with *ca. N* sodium hydroxide solution. Then add 2–3 drops of *ca.* 0·1*N* hydrochloric acid to ensure that the solution is almost neutral (*pale* pink colour). (Under alkaline conditions the reagent tends to decompose to produce the evil-smelling benzyl mercaptan.) If the sodium salt is available, dissolve 0·25 g. in 5 ml. of water, and add 2 drops of *ca.* 0·1*N* hydrochloric acid. Introduce a solution of 1 g. of S-benzyl-*iso*-thiuronium chloride in 5 ml. of water, and cool in ice until precipitation is

* Dibasic and tribasic acids will require 0·01 and 0·015 mol respectively.

complete. Recrystallise the crude derivative from dilute alcohol or from hot water.

With some acids (*e.g.*, succinic acid and sulphanilic acid) more satisfactory results are obtained by reversing the order of mixing, *i.e.*, by adding the solution of the sodium salt of the acid to the reagent. It should be pointed out that the melting points of the derivatives as determined on the electric hot plate (Fig. *II*, *11*, 1) may differ by 2–3° from those obtained by the capillary tube method. In view of the proximity of the melting points of the derivatives of many acids, the mixed m.p. test (Section **I,17**) should be applied.

The melting points of the derivatives of a number of selected aliphatic acids are collected in Table **III,85**.

Acid	B.P.	M.P.	Anilide	*p*-Toluidide	Amide	*p*-Bromphenacyl Ester	*p*-Nitrobenzyl Ester	*p*-Phenylphenacyl Ester	S-Benzyl-*iso*-thluronium Salt	*p*-Bromoanilide	Hydrazide*
MONOBASIC ACIDS											
Formic	101°	8°	50°	53°	3°	140°	31°	74°	151°	119°	54°
Acetic	118	16	114	153	82	86	78	111	136	166	77
Propionic	141	—	106	126	79	63	31	102	152	148	40
n-Butyric	163	—	96	75	116	63	35	82	149	111	44
iso-Butyric	154	—	105	109	129	77	—	89	149	151	104
n-Valeric	186	—	63	74	106	75	—	63	156	106	—
iso-Valeric	176	—	113	109	136	68	—	78	159	129	68
n-Hexoic (caproic)	205	—	95	74	100	72	—	70	157	105	—
n-Heptoic (oenanthic)	223	—	71	80	95	72	—	62	—	95	—
n-Octoic (caprylic)	239	16	57	70	110	67	—	67	157	102	—
n-Nonoic (pelargonic)	254	12	57	84	95	69	—	71	—	100	—
n-Decoic (capric)	269	31	70	78	100	67	—	—	—	102	—
n-Undecoic	164°/15	29	71	80	103	68	—	79	—	—	—
n-Dodecanoic (lauric)	225°/100	43	78	87	99	76	—	86	141	—	105
Myristic	250°/100	58	84	93	102	81	—	90	139	—	—
Palmitic	268°/100	63	91	98	106	86	43	94	141	—	111
Stearic	291°/100	70	94	102	109	90	—	97	143	—	—
Pivalic (trimethylacetic)	164	35	133	120	154	76	—	—	—	—	—
Diethylacetic	193	—	127	116	112	—	—	77	—	—	—
iso-Caproic (*iso*-butylacetic)	198	—	112	63	121	77	—	70	—	—	—
α-Ethyl-*n*-hexoic	228	—	—	—	101	—	—	54	—	—	—
10-Undecenoic	275	25	67	68	87	—	—	—	149	—	—
Cyanoacetic	—	66	198	—	120	—	—	—	—	—	—
Monochloroacetic	189	63	137	162	120	105	—	116	160	—	—
Dichloroacetic	194	10	119	153	97	99	—	—	178	—	—
Trichloroacetic	196	58	95	113	141	—	80	—	148	—	—
Monobromoacetic	208	50	130	91	91	—	—	—	—	—	—
Monoiodoacetic	—	83	144	—	95	—	—	—	—	—	—
α-Chloropropionic	186	—	92	124	80	—	—	—	—	—	—
α-Bromopropionic	206	25	99	125	123	—	—	—	—	—	—
Glycollic	—	79	97	143	120	138	107	—	146	—	—
Lactic	122°/15	18	59	107	79	113	—	145	153	—	—
Acrylic	140	13	105	141	85	—	—	—	—	—	—
Crotonic	189	72	118	132	160	95	67	—	172	—	—
Furoic (pyromucic)	—	134	124	108	142	139	134	86	211	—	80
Sorbic	—	134	153	—	—	129	—	—	—	—	—
Oleic	204°/5	14	41	42	76	46	—	60	—	—	—
Pyruvic	165 d	13	104	130	125	—	—	—	—	—	—
Laevulinic	246	33	102	109	108	84	61	—	—	—	—

TABLE III,85. **ALIPHATIC CARBOXYLIC ACIDS (*continued*)**

Acid	B.P.	M.P.	Anilide	*p*-Toluidide	Amide	*p*-Bromophenacyl Ester	*p*-Nitrobenzyl Ester	*p*-Phenylphenacyl Ester	S-Benzyl-*iso*-thiuronium Salt	*p*-Bromoanilide	Hydrazide*
MONOBASIC ACIDS (*continued*)											
Nicotinic	—	235°	85°	150°	128°	—	—	—	—	—	—
Methoxyacetic	203	—	58	—	96	—	—	—	—	—	—
Ethoxyacetic	207	—	—	—	82	104	—	—	—	—	—
Methylethylacetic	177	—	112	93	112	55	—	—	—	—	—
α-Furylacrylic	—	141	—	—	169	—	—	—	—	—	—
Hexahydrobenzoic	233	31	144	—	186	—	—	—	—	—	—
DIBASIC AND TRIBASIC ACIDS											
Oxalic (dihdrate)	—	101°	246°	268°	—	242°	204°	165° d	198°	—	243°
Malonic	—	135	225	253	170°	—	86	175	147	—	154
Succinic	—	185	229	255	260	211	88	208	154	—	168
Glutaric	—	98	224	218	175	137	69	152	161	—	176
Adipic	—	152	239	241	220	155	106	148	163	—	171
Pimelic	—	105	156	206	—	137	—	146 d	—	—	182
Suberic	—	142	187	219	217	144	85	151	—	—	—
Azelaic	—	106	187	202	172	131	44	141	—	—	—
Sebacic	—	134	202	201	208	147	73	140	155	—	—
Malic	—	101	197	207	157	179	124	106	124	—	178
Mucic	—	214	—	—	—	—	—	149	178	—	215
Fumaric	—	286	314	—	266	—	151	—	195	—	—
Maleic	—	135	187	142	181	168	89	168	163	—	—
Mesaconic	—	204	186	212	176	—	—	—	—	—	—
Citraconic	—	93	175	—	186	—	70	109	—	—	177
Itaconic	—	165	190	—	192	117	90	—	—	—	—
Camphoric	—	187	226	—	193	—	67	—	—	—	—
rac-Tartaric	—	206	—	—	226	—	147	—	—	—	—
meso-Tartaric	—	140	—	—	190	—	93	—	—	—	—
d-Tartaric	—	170	264	—	196	216	163	204	—	—	—
Citric (hydrated)	—	100	199	189	215	148	102	146	—	—	—
Aconitic	—	191	—	—	250	186	—	—	—	—	183 107

* See Section III,106 for details of the preparation of hydrazides.

ACID CHLORIDES OF ALIPHATIC CARBOXYLIC ACIDS

The conversion of aliphatic acids into their acid chlorides is usually accomplished with :—

1. **Phosphorus trichloride.** The reaction is not quite quantitative, for example :

$$\underset{\text{Acetic acid}}{3CH_3COOH} + \underset{\text{(B.p. 76°)}}{PCl_3} \longrightarrow \underset{\text{Acetyl chloride (b.p. 52°)}}{3CH_3COCl} + \underset{\text{(Dec. 200°)}}{H_3PO_3}$$

Some hydrogen chloride is evolved and small quantities of volatile phosphorus compounds are formed, due to such reactions as the following :

$$CH_3COOH + PCl_3 \longrightarrow CH_3COOPCl_2 + HCl$$
$$3CH_3COOH + PCl_3 \longrightarrow P(OCOCH_3)_3 + 3HCl$$

These may be largely removed by redistilling from a small quantity of glacial acetic acid.

Commercial preparations of acetyl chloride are best freed from volatile phosphorus compounds and dissolved hydrogen chloride by redistillation from 5–10 per cent. of the volume of pure dimethylaniline.

Very pure acid chlorides may be obtained by reaction between the anhydrous sodium salt of the acid and phosphorus oxychloride, for example :

$$3CH_3COONa + POCl_3 \longrightarrow 3CH_3COCl + Na_3PO_4$$

2. **Thionyl chloride.** This reagent (b.p. 76°) is generally used in excess of the theoretical quantity ; it cannot be employed for acetyl chloride (b.p. 52°) because of the difficulty of separation by fractional distillation. Excellent results are obtained, however, with butyric acid and acids of higher molecular weight, for example :

$$\underset{n\text{-Butyric acid}}{CH_3CH_2CH_2COOH} + SOCl_2 \longrightarrow \underset{n\text{-Butyryl chloride (b.p. 101°)}}{CH_3CH_2CH_2COCl} + SO_2 + HCl$$

The reason for using an excess of, say, 1 mol of thionyl chloride is to avoid anhydride formation :

$$RCOOH + RCOCl \rightleftharpoons RCO—O—OCR + HCl$$

The excess of thionyl chloride displaces the equilibrium to the left not only by removing the carboxylic acid ($RCOOH + SOCl_2 \longrightarrow RCOCl + SO_2 + HCl$) but also by thus keeping up a good supply of hydrogen chloride. The use of a larger excess than 1 mol (*i.e.*, more than 2 mols of $SOCl_2$ per mol of RCOOH) has little, if any, advantage, but reducing the quantity to 1·2 mols of $SOCl_2$ per mol of RCOOH usually lowers the yield of acid chloride by 10–20 per cent.

III,86. ACETYL CHLORIDE

Method 1. Use the apparatus depicted in Fig. *III*, *56*, 1, but omit the thermometer : also attach a cotton wool (or calcium chloride) tube to the side arm of the filter flask receiver * in order to prevent the entrance of moisture into the apparatus. Mount the reaction flask in a water bath (*e.g.*, a large beaker or other convenient vessel). It is important that all the apparatus be perfectly dry, since both phosphorus trichloride and acetyl chloride are decomposed by water. The set-up should be assembled in the fume cupboard.

Place 25 g. (24 ml.) of glacial acetic acid in the 100 or 125 ml. distilling flask and 20 g. (12·5 ml.) of phosphorus trichloride in the funnel ; fill

* A 100 ml. distilling flask may also be used.

the water bath with cold water. Add the phosphorus trichloride in small portions to the acetic acid, shaking the flask gently from time to time to ensure thorough mixing of the reagents. Allow the mixture to stand for 15 minutes, then heat the water bath at 40–50° for 30 minutes; by this time the evolution of hydrogen chloride will have ceased and the liquid in the flask will have separated into two layers. Heat the water bath to boiling so that the upper layer of crude acetyl chloride passes over; it is advantageous to cool the receiver in cold water during the distillation. Pour out the syrupy residue of phosphorous acid into a bottle provided for the purpose in the laboratory; clean and dry the flask.

Treat the distillate with 2 drops of glacial acetic acid (to destroy the phosphorus esters present) and redistil using the same apparatus as before except that the separatory funnel is replaced by a thermometer. Collect the liquid which passes over at 50–56°. Transfer the acetyl chloride to a weighed glass-stoppered bottle (since cork and rubber stoppers are attacked) and determine the weight. The yield is 22 g.

Method 2. Fit a reflux condenser into the mouth of a 250 ml. distilling flask (compare Fig. *III*, *28*, 1) and insert, by means of a grooved cork, a small separatory funnel into the top of the condenser; close the side arm of the distilling flask with a partially bored cork. Place 65 g. of anhydrous sodium acetate (Section **II,50,***9*) in the flask and 65 g. (39 ml.) of phosphorus oxychloride in the separatory funnel. Allow the phosphorus oxychloride to run in slowly on to the sodium acetate with frequent shaking; the addition should occupy about 30 minutes. Remove the separatory funnel, replace it by a cotton wool (or calcium chloride) guard tube, and allow the reaction mixture to stand for 10–12 hours. Arrange the distilling flask for distillation from a water bath (Fig. *II*, *13*, 1); continue the distillation as long as any liquid passes over (about 3 hours) (1). Redistil the resulting acetyl chloride (39 g.) from a 100 ml. distilling flask, and attach a cotton wool guard tube to the receiver (filter flask or distilling flask). It all distils at 51–52°.

Note.

(1) The solid residue in the flask dissolves readily in cold water.

III,87. *n*-BUTYRYL CHLORIDE

Fit a reflux condenser into the short neck of a 100 or 125 ml. Claisen flask, a separatory funnel into the long neck, and plug the side arm with a small cork (compare Fig. *III*, *31*, 1). Place 37·5 g. (22·5 ml.) of redistilled thionyl chloride in the flask and 22 g. (23 ml.) of *n*-butyric acid in the separatory funnel. Heat the flask gently on a water bath, and add the *n*-butyric acid during the course of 30–40 minutes; absorb the hydrogen chloride evolved in water using the device shown in Fig. *II*, *13*, 8 (compare Fig. *II*, *8*, 1). When all the acid has been introduced, heat on a water bath for 30 minutes. Rearrange the apparatus and distil: collect the crude acid chloride boiling between 70 and 110° in a distilling flask. Finally, redistil from a small Claisen flask with fractionating side arm (Fig. *II*, *24*, 2–5) or from a flask provided with a short fractionating column (*e.g.*, an all-glass Dufton column, Fig. *II*, *15*, 2): collect the *n*-butyryl chloride at 100–101°. The yield is 23 g.

III,88. REACTIONS AND CHARACTERISATION OF ACID CHLORIDES OF ALIPHATIC ACIDS

Carry out the following simple experiments with acetyl chloride (compare Section **III,86**).

(i) To a test-tube containing about 5 ml. of water add cautiously a few drops of acetyl chloride. Note that the acetyl chloride does not dissolve in the water, but on shaking reaction occurs with the evolution of heat and the formation of acetic acid.

$$CH_3COCl + H_2O \longrightarrow CH_3COOH + HCl$$

(ii) To 1 ml. of *absolute* ethyl alcohol in a dry test-tube add 1 ml. of acetyl chloride drop by drop (use a dropper pipette, Fig. *II*, *27*, 1); keep the mixture cold by holding the tube under the tap. Note whether any hydrogen chloride gas is evolved (blow across the mouth of the tube). Pour into 2 ml. of saturated salt solution and observe the formation of an upper layer of ester (ethyl acetate) and also note the odour of the ester; if this does not appear to have a fruit-like odour, add a little sodium carbonate to neutralise the acid and examine again.

$$CH_3COCl + C_2H_5OH \longrightarrow CH_3COOC_2H_5 + HCl$$

Repeat the test with 1 ml. of *n*-butyl alcohol.

(iii) Add 1 ml. of acetyl chloride, drop by drop, to 0·5–1 ml. of aniline. After the vigorous reaction is over, dilute the mixture with 5 ml. of water and observe the formation of a solid (acetanilide). Filter this off recrystallise from a little boiling water, and determine the m.p. after drying. Pure acetanilide melts at 114°.

$$CH_3COCl + 2C_6H_5NH_2 \longrightarrow C_6H_5NHCOCH_3 + C_6H_5NH_3Cl$$

The above simple experiments illustrate the more important properties of aliphatic acid chlorides. For **characterisation**, the general procedure is to hydrolyse the acid chloride by warming with dilute alkali solution, neutralise the resulting solution with dilute hydrochloric acid (phenolphthalein), and evaporate to dryness on a water bath. The mixture of the sodium salt of the acid and sodium chloride thus obtained may be employed for the preparation of solid esters as detailed under *Aliphatic Acids*, Section **III,85**. The anilide or *p*-toluidide may be prepared directly from the acid chloride (see (iii) above and Section **III,85,*l***).

The physical properties of a number of aliphatic acid chlorides are collected in Table **III,88**.

TABLE III,88. ACID CHLORIDES (ALIPHATIC)

Acyl Chloride	B.P.	M.P.	$d_{4^\circ}^{20^\circ}$	$n_{D}^{20^\circ}$
Acetyl . . .	52°	—	1.104	1·390
Propionyl . .	80	—	1·056	1·404
n-Butyryl . .	102	—	1·028	1·412
iso-Butyryl . .	92	—	1·017	1·408
n-Valeryl . .	127	—	1·000	1·420
iso-Valeryl . .	115	—	0·987	1·416
n-Caproyl (*n*-hexoyl)	152	—	0·975	1·426
iso-Caproyl (*iso*-butylacetyl)	144	—	0·973	—
n-Heptoyl . .	175	—	0·963	1·432
n-Octoyl . .	195	—	0·949	1·432
Chloroacetyl .	105	—	1·420	1·454
Dichloroacetyl .	108	—	—	—
Trichloroacetyl .	118	—	1·620	1·470
Oxalyl . .	63	—	1·479	1·432
Succinyl . .	192	17°	1·375	1·468
Glutaryl . .	218	—	1·324	1·473
Adipyl . .	125°/11	—	—	—

ACID ANHYDRIDES OF ALIPHATIC CARBOXYLIC ACIDS

Acid anhydrides of monobasic aliphatic acids may be prepared:—

1. By the reaction of the acid chloride with the corresponding sodium salt, for example:

$$\underset{\text{Acetyl chloride}}{CH_3COCl} + \underset{\text{Sodium acetate}}{CH_3COONa} \longrightarrow \underset{\text{Acetic anhydride}}{(CH_3CO)_2O} + NaCl$$

An equivalent result may be obtained by treating excess of sodium acetate with phosphorus oxychloride; acetyl chloride is an intermediate product and the final result is:

$$POCl_3 + 4CH_3COONa \longrightarrow NaPO_3 + 2(CH_3CO)_2O + 3NaCl$$

2. By the action of keten, CH_2CO, upon acids. Acetic anhydride is formed with acetic acid:

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

With higher aliphatic acids, RCOOH, keten yields first a mixed anhydride $CH_3COOCOR$, which can be distilled under reduced pressure; by slow distillation at atmospheric pressure the mixed anhydride undergoes rearrangement into the anhydride of the higher fatty acid and acetic acid, for example:

$$\underset{n\text{-Caproic acid}}{2CH_3(CH_2)_4COOH} + CH_2{=}C{=}O \longrightarrow \underset{n\text{-Caproic anhydride}}{[CH_3(CH_2)_4CO]_2O} + CH_3COOH$$

Keten itself can be prepared by the pyrolysis of acetone at 700°:

$$(CH_3)_2CO \xrightarrow{700°} CH_2{=}C{=}O + CH_4$$

Excellent results are obtained by passing acetone vapour over an electrically heated nichrome wire spiral: an apparatus, incorporating the latter, is described in the experimental section.

3. By the interaction in benzene solution of the acid chloride with the acid in the presence of pyridine, for example:

$$\underset{n\text{-Heptoyl chloride}}{CH_3(CH_2)_5COCl} + \underset{\text{Pyridine}}{C_5H_5N} + \underset{n\text{-Heptoic acid}}{CH_3(CH_2)_5COOH} \rightarrow$$

$$\underset{n\text{-Heptoic anhydride}}{CH_3(CH_2)_5CO{-}O{-}CO(CH_2)_5CH_3} + C_5H_5N,HCl$$

The presence of the base brings about the irreversible elimination of hydrogen chloride between the acid chloride and the acid; the resulting pyridine hydrochloride precipitates out as the reaction progresses.

Anhydrides of dibasic acids (succinic or glutaric acid type) **may be prepared:**

1. By dehydration with acetyl chloride, acetic anhydride or with phosphorus oxychloride, for example:

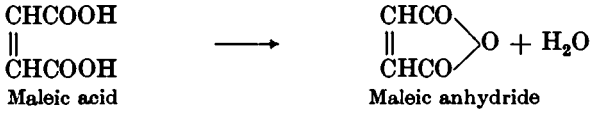
$$\underset{\text{Succinic acid}}{\begin{matrix}CH_2COOH\\|\\CH_2COOH\end{matrix}} + CH_3COCl \longrightarrow \underset{\text{Succinic anhydride}}{\begin{matrix}CH_2CO\\|\\CH_2CO\end{matrix}}O + CH_3COOH + HCl$$

$$\begin{matrix}CH_2COOH\\|\\CH_2COOH\end{matrix} + (CH_3CO)_2O \longrightarrow \begin{matrix}CH_2CO\\|\\CH_2CO\end{matrix}O + 2CH_3COOH$$

$$2(CH_2COOH)_2 + POCl_3 \longrightarrow 2(CH_2CO)_2O + HPO_3 + 3HCl$$

The acetic acid formed can often be used for the crystallisation of the anhydride.

2. By distilling the acid with an inert solvent of high boiling point, such as tetrachloroethane. The water passes over with the solvent and the anhydride remains, for example:



III,89. ACETIC ANHYDRIDE

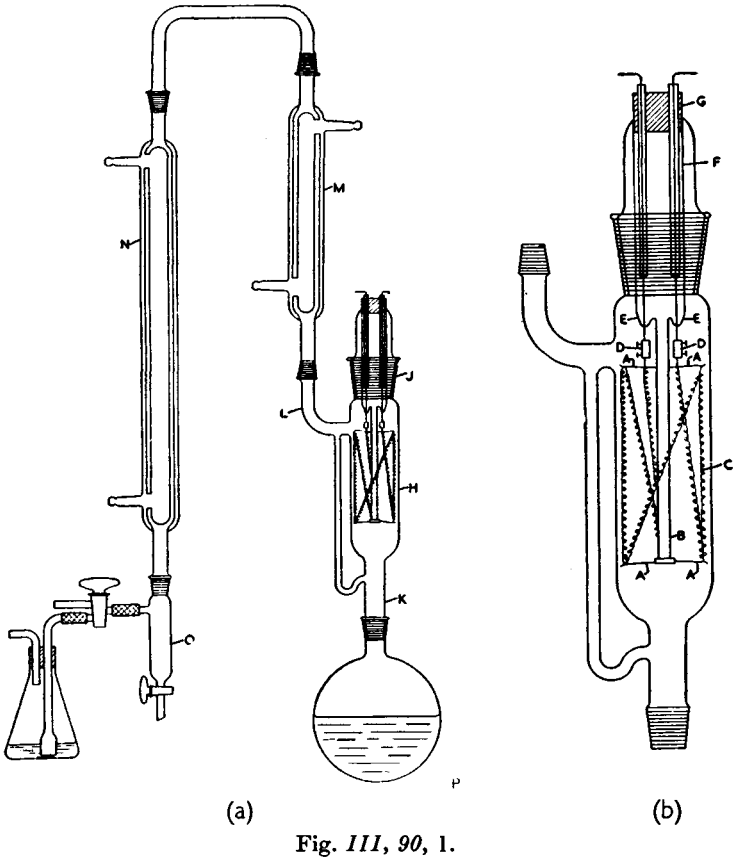
Assemble an apparatus consisting of a 100 or 125 ml. distilling flask carrying a dropping funnel, the stem of which passes below the side arm: attach the distilling flask to a condenser for downward distillation and use a 50 or 100 ml. distilling flask as receiver. Place 28 g. of finely powdered anhydrous sodium acetate (for preparation, see Section **II,50,9**) in the flask and 20 g. (18 ml.) of acetyl chloride in the dropping funnel. Disconnect the distilling flask from the condenser and immerse it in cold water or in ice water. Add about half of the acetyl chloride drop by drop; then remove the flask from the cooling bath and mix the contents thoroughly by cautious shaking and tapping of the flask against the palm of the hand. Return the flask to the cooling bath and run in the remainder of the acetyl chloride drop by drop. Do not allow the mixture to get so hot that it boils. When all the acetyl chloride has been added, remove the separatory funnel and replace it by a solid cork; thoroughly mix the contents of the flask as above. Attach the flask to the condenser and receiver. Clamp the flask at such a height that it can easily be heated by a Bunsen burner. Heat the flask by means of a luminous, smoky Bunsen flame, which is kept in constant motion round the base of the flask to ensure uniform heating and minimise the danger of cracking the flask. Continue the heating until no more liquid passes over. Add 2–3 g. of finely-powdered anhydrous sodium acetate to the distillate in order to convert any unchanged acetyl chloride into acetic anhydride, insert a cork carrying a thermometer into the flask, attach a condenser, and distil slowly. Collect the fraction which passes over at 135–140° as acetic anhydride. The yield is 20 g.

III,90. KETEN

An apparatus for the preparation of keten is illustrated in Fig. *III, 90,* 1; in it acetone vapour is passed over a nichrome filament heated at 700–750°, the yield of keten exceeding 90 per cent. The construction of the filament will be apparent from the enlarged figure (*b*). About 350 cm. of 24 gauge nichrome wire * is formed into a tight spiral by winding the wire around a glass rod 3 mm. in diameter and stretching the coil so formed to a length of 70 cm. The filament is held in position on 1·5 cm. long platinum hooks *A* sealed into the Pyrex glass rod *B* which supports them. The three platinum hooks at the bottom of the rod are placed 120° apart; two platinum hooks support the filament at a distance of 11 cm. above the lower end. The ends of the filament *C* are connected to tungsten leads by

* U.S.: B. and S. gauge 24 Chromel A wire, an alloy of 80% Ni and 20% Cr.

means of nickel or brass connectors *D*, 10 mm. in length and 3·5 mm. in internal diameter. The tungsten leads (24 gauge) are sealed into the glass at the points *E*; the leads are insulated by means of 6 mm. glass tubing *F*, which are held by a cork stopper *G*. If desired, the tungsten leads may be soldered immediately above the glass seal to copper wires (24 gauge) which are passed through the glass tubing *F*. The tungsten or copper wire leads are connected to the 220 volt a.c. mains through a variable transformer (Variac).



(a) (b)

Fig. *III*, *90*, 1.

All the glass in the apparatus is in Pyrex and connexions are made by means of standard glass joints of appropriate size. Chamber *H* is constructed from a 25 cm. length of glass tubing of 70 mm. internal diameter; the joint *J* is *B*55. The connecting tube *K* is in 12–15 mm. tubing, the side arm *L* is of 15 mm. tubing; the condensers *M* and *N* are efficient double surface condensers, 50 cm. and 90 cm. long respectively (the sizes are not critical); *O* is a liquid trap, constructed of 35 mm. tubing and is 120 mm. long, with side tube of 8 mm. diameter; the stopcock is for the removal of liquid from the trap.

To operate the apparatus, place acetone in the 2-litre round-bottomed flask *P* and heat the flask on a steam bath until the liquid refluxes gently

from the condenser *M*. After 5 minutes' refluxing to drive the air from the the chamber *H*, heat the filament *C* to a dull red glow (700–750°). Keten is formed almost immediately. The apparatus requires little attention, apart from occasionally removing the condensed liquid from the trap *O*. At the end of the run, the following operations must be carried out rapidly in this order: (i) remove the source of heat from the flask *P*, (ii) turn off the filament current, and (iii) open the stopcock on *O*.

The yield of keten may be determined by weighing the acetanilide produced by passing the gas stream through excess of aniline for a measured period of time. Attach two reaction flasks to both arms of the "three-way" stopcock, the first *Q* containing 25·0 g. and the second 5·0 g. of pure aniline; the second flask is introduced to prevent the escape of keten at the beginning and at the end of the determination. Cool the flasks in ice water. Pass the keten into the flask containing the larger amount of aniline for 30 minutes, then add an excess of dilute hydrochloric acid to remove the residual aniline, filter off the acetanilide, wash it with water, dry and weigh. Calculate the weight of keten produced per hour. This will be found to be of order of 0·45 mol of keten per hour.

$$C_6H_5NH_2 + CH_2{=}C{=}O \longrightarrow C_6H_5NHCOCH_3$$

III,91. *n*-CAPROIC ANHYDRIDE

Place 116 g. (126 ml.) of dry *n*-caproic acid in a 250 ml. gas wash bottle and cool in ice. Pass in 21–23 g. of keten (Section **III,90**) (1). Carefully distil the reaction mixture through a highly efficient fractionating column (*e.g.*, a well-lagged Widmer or all-glass Dufton column or from a modified Pyrex Hempel column—see Section II,17) (2), using an oil bath for heating. A fraction of low boiling point, containing acetone, keten, acetic acid and a little acetic anhydride, is thus removed at atmospheric pressure. Raise the temperature of the bath to 220° over a period of 1 hour and maintain it at this temperature for 3 hours from the time distillation commences: this time is necessary to ensure that the conversion of the mixed anhydride to caproic anhydride and acetic acid is complete and that the acetic acid is completely removed. Discontinue the distillation, allow to cool somewhat and distil the residue in the flask under reduced pressure (3–10 mm.). Discard the small fraction (20 g.) of low boiling point and collect the *n*-caproic anhydride at 118–121°/6 mm. (or 109–112°/3 mm.). The yield is 90 g.

Notes.

(1) Excess of keten over the calculated quantity does not increase the yield; it leads to more acetic anhydride being collected in the low boiling point fraction.

(2) The best results are obtained with a fractionating column surrounded by an electrically-heated jacket (compare Figs. *II*, *17*, 2, and *II*, *17*, 3), but this is not essential for *n*-caproic anhydride. For the preparation of propionic or *n*-butyric anhydride, a highly efficient fractionating column must be used in order to obtain satisfactory results.

Cognate Preparation

***n*-Heptoic anhydride** (1). In a 250 ml. round-bottomed three-necked flask, provided with a dropping funnel, stirrer and thermometer, place 15·8 g. (16·1 ml.) of dry pyridine (Section II,47, *22*) and 25 ml. of dry

benzene. Stir and add rapidly 14·8 g. (15·5 ml.) of *n*-heptoyl chloride (2): the temperature rises slightly and a pyridinium complex separates. Introduce 13·0 g. (14·1 ml.) of *n*-heptoic acid (Section **III,81**), with stirring, over a period of 5 minutes; the temperature rises to 60–65° and pyridine hydrochloride is formed. Continue the stirring for 10 minutes and collect the hygroscopic pyridine hydrochloride as rapidly as possible on a chilled Buchner or sintered glass funnel, and wash it with two 25 ml. portions of dry benzene. Remove the benzene from the filtrate under reduced pressure on a water bath, and distil the residue from a Claisen flask with fractionating side arm. Collect the *n*-heptoic anhydride at 170–173°/15 mm.; the yield is 20 g.

Notes.

(1) This is an example of the acid chloride - pyridine - acid method referred to in the theoretical section.

(2) Prepare *n*-heptoyl chloride from the acid by treatment with thionyl chloride as detailed for *n*-butyryl chloride (Section III,87); b.p. 173–175°.

III,92. SUCCINIC ANHYDRIDE

Method A. In a 500 ml. round-bottomed flask, fitted with a reflux condenser attached to a gas trap (Fig. *II*, *13*, 8), place 59 g. of succinic acid and 117·5 g. (107·5 ml.) of redistilled acetyl chloride. Reflux the mixture gently upon a water bath until all the acid dissolves (1–2 hours). Allow the solution to cool undisturbed and finally cool in ice. Collect the succinic anhydride, which separates in beautiful crystals, on a Buchner or sintered glass funnel, wash it with two 40 ml. portions of anhydrous ether, and dry in a vacuum desiccator. The yield of succinic anhydride, m.p. 118–119°, is 47 g.

Method B. In a 500 ml. round-bottomed flask, provided with a reflux condenser protected by a cotton wool (or calcium chloride) drying tube, place 59 g. of succinic acid and 102 g. (94·5 ml.) of redistilled acetic anhydride. Reflux the mixture gently on a water bath with occasional shaking until a clear solution is obtained (*ca.* 1 hour), and then for a further hour to ensure the completeness of the reaction. Remove the complete assembly from the water bath, allow it to cool (observe the formation of crystals), and finally cool in ice. Collect the succinic anhydride as in *Method A*. The yield is 45 g., m.p. 119–120°.

Method C. Place 59 g. of succinic acid in a 250 ml. Claisen flask. Fit a reflux condenser, attached to a gas trap (Fig. *II*, *8*, 1), into the short neck. Introduce 38 g. (23 ml.) of redistilled phosphorus oxychloride into the flask, and close the long neck and side arm with well-fitting corks. Heat the mixture slowly, cautiously at first with a smoky luminous flame, directing the flame so that all parts of the mixture are fairly evenly heated—there may be considerable frothing initially—and continue the heating until no more hydrogen chloride is evolved (20–30 minutes); after the initial frothing has subsided, the flask may be heated in an air bath (Fig. *II*, *5*, 3). Remove the condenser and arrange the flask for distillation; connect the side arm of the receiver to the sink in order to carry off the vapours (compare Fig. *II*, *13*, 4). After a few ml. of distillate have been collected, the temperature rises to 255°; change the receiver and collect the succinic anhydride at 255–260° (42 g.,

m.p. 118–120°) (1). Purify the distillate by dissolving it in 30 ml. of redistilled acetic anhydride and cool the hot solution in ice. Filter off the crystals at the pump, wash them with two 20 ml. portions of anhydrous ether, and dry in a vacuum desiccator or rapidly at 40°. The yield of pure succinic anhydride, m.p. 119–120°, is 36·5 g.

Note.

(1) The tarry residue in the flask may be removed by warm dilute sodium hydroxide solution.

III,93. MALEIC ANHYDRIDE

Mix 100 g. of maleic acid (Section **III,143**) and 100 ml. of tetrachloroethane in a 250 ml. Claisen or distilling flask provided with a thermometer, and attach a Pyrex Liebig condenser. Heat the flask in an air bath (Fig. *II*, *5*, 3) and collect the distillate in a measuring cylinder. When the temperature reaches 150°, 75 ml. of tetrachloroethane and 15–15·5 ml. of water are present in the receiver. Empty the water in the condenser and continue the distillation; change the receiver when the temperature reaches 190°. Collect the maleic anhydride at 195–197°. Recrystallise the crude anhydride from chloroform. The yield of pure maleic anhydride, m.p. 54°, is 70 g.

III,94. REACTIONS AND CHARACTERISATION OF ACID ANHYDRIDES (ALIPHATIC)

Carry out the following simple experiments with acetic anhydride (compare Section **III,89**).

(i) Mix 5 ml. of water in a test-tube with 0·5 ml. of acetic anhydride and shake. Observe that no apparent reaction occurs immediately. Upon warming, however, the acetic anhydride dissolves and acetic acid is formed:

$$(CH_3CO)_2O + H_2O \longrightarrow 2CH_3COOH$$

(ii) Mix 2 ml. of absolute ethyl alcohol with 1 ml. of acetic anhydride. No apparent reaction occurs in the cold. Heat the mixture gently for a few minutes: the anhydride slowly passes into solution. Treat with a little sodium carbonate solution; observe the characteristic odour of ethyl acetate. If the ester does not separate from the solution, add a little salt until saturated.

$$(CH_3CO)_2O + C_2H_5OH \longrightarrow CH_3COOC_2H_5 + CH_3COOH$$

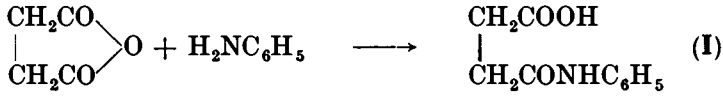
Repeat the experiment with 2 ml. of *n*-butyl alcohol.

(iii) Heat a mixture of 1 ml. of aniline and 1 ml. of acetic anhydride almost to the boiling point and cool. No solid separates. Add 4–5 ml. of water and rub the walls of the test-tube with a glass rod. Crystals of acetanilide are formed. Recrystallise from a little boiling water and determine the m.p. (114°).

$$(CH_3CO)_2O + C_6H_5NH_2 \longrightarrow C_6H_5NHCOCH_3 + CH_3COOH$$

Perform the following experiment with *succinic anhydride*. This illustrates the formation of an anilic acid, which is usually an excellent

derivative for the characterisation of an anhydride of a dibasic acid (particularly if it is a liquid) and indirectly for the dibasic acid itself. Dissolve 0·5 g. of succinic anhydride in 15 ml. of benzene by heating on a water bath, and add a solution of 0·5 ml. of aniline in 3 ml. of benzene. The anilic acid soon separates in a crystalline form.* Cool, filter off the crystals and wash with a little benzene. Recrystallise from dilute alcohol and determine the m.p. Pure succinanilic acid (**I**) melts at 150°



The above simple experiments illustrate the more important properties of the anhydrides of aliphatic acids. For their **characterisation,** the reaction with aniline or *p*-toluidine is frequently employed. Alternatively, the anhydride may be hydrolysed with dilute alkali as detailed under *Acid Chlorides*, Section **III,88,** and the resulting acid characterised as in Section **III,85.**

The physical properties of a number of acid anhydrides (aliphatic) are given in Table **III,94.**

* If the anhydride of an unknown acid is being used and the anilic acid does not crystallise after the mixture has been boiled for a short time, cool the solution, wash it with dilute hydrochloric acid to remove the excess of aniline, and evaporate the solvent; the anilic acid will then usually crystallise.

TABLE III,94. ACID ANHYDRIDES (ALIPHATIC)

Anhydride	B.P	M.P.	$d_{4^\circ}^{20^\circ}$	$n_D^{20^\circ}$
Acetic	140°	—	1·081	1·390
Propionic	166	—	1·022	1·404
n-Butyric	198	—	0·968	1·413
iso-Butyric	182	—	0·956	—
n-Valeric	218	—	0·925	—
iso-Valeric(β-Methyl-*n*-butyric)	215	—	0·933	1·404
n-Caproic (*n*-hexoic)	245	—	0·920	1·430
iso-Caproic (*iso*-butylacetic)	139°/19	—	—	—
n-Heptoic (oenanthic)	258	17°	0·917	1·433
n-Octoic (capric)	285	—	0·910	1·434
Crotonic	247	—	1·040	1·474
Succinic	261	120	—	—
Glutaric	150°/10	56	—	—
Maleic	198	56	—	—
Citraconic	213	7	—	—
Itaconic	139°/30	68	—	—
d-Camphoric	270	220	—	—
Monochloroacetic	109°/11	46	—	—
Dichloroacetic	101°/16	—	—	—
Trichloroacetic	223	—	—	—

ALIPHATIC ESTERS

Aliphatic esters may be prepared as follows:—

1. **From the acid.** The interaction between an acid and an alcohol is a reversible process and proceeds very slowly, for example:

$$\underset{\text{Acetic acid}}{CH_3COOH} + \underset{n\text{-Butyl alcohol}}{C_4H_9{}^{\alpha}OH} \rightleftharpoons \underset{n\text{-Butyl acetate}}{CH_3COOC_4H_9{}^{\alpha}} + H_2O$$

Equilibrium is only attained after refluxing for several days. If, however, about 3 per cent. (on the weight of the alcohol) of either concentrated sulphuric acid or of dry hydrogen chloride is added to the mixture, the same point of equilibrium can be reached in a few hours: the use of a mineral acid as a catalyst in the esterification was introduced by E. Fischer and Speier in 1895. When equimolecular quantities of acid and alcohol are employed, only about two-thirds of the theoretically possible yield of ester is obtained. According to the law of mass action, the equilibrium may be displaced in favour of the ester by the use of an excess of one of the components. It is frequently convenient to use an excess of the acid, but if the acid is expensive a large excess of the alcohol is more generally employed. This method of esterification, in general, gives good yields with primary alcohols, fairly good yields with secondary alcohols, and poor yields with tertiary alcohols: special methods must be adopted for the last-named (see below). Thus the order of reactivity in the esterification of acetic acid with the three isomeric butyl alcohols is primary > secondary $\gg$ tertiary, and this is the reverse of the order of reactivity of hydrogen chloride with the same alcohols (compare Sections **III,28,29,33**). The difference is due to the fact that the reactions are of different kinds:

$$(CH_3)_3COH + HOOCCH_3 \longrightarrow (CH_3)_3COOCCH_3 + H_2O$$
$$(CH_3)_3COH + HCl \longrightarrow (CH_3)_3CCl + H_2O$$

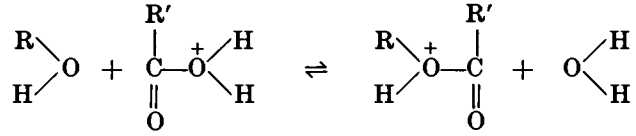
In the conversion of alcohols into alkyl halides, the *mechanism* is probably:

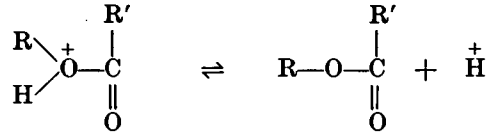
$$R{-}OH + HX \longrightarrow R{-}OH_2{}^+ + X^-$$
$$X^- + R{-}OH_2{}^+ \longrightarrow X\ldots R\ldots OH_2 \text{ (transition state)} \longrightarrow X{-}R + OH_2$$

The reaction therefore involves nucleophilic displacement on carbon passing through the transition state indicated: otherwise expressed, the reaction involves nucleophilic displacement in the conjugate acid $R{-}OH_2{}^+$ in which the displaced group is $OH_2{}^+$.

Two alternative mechanisms are possible for esterification, one is dependent upon an acyl-oxy proccss ($R'{-}CO{-}OH + H\ OR$) and the other an alkyl-oxy process ($R'{-}CO{-}O\ H + HO\ R$). The former is by far the more common. The detailed acyl-oxy *mechanism* envisages: (1) a preliminary addition of a proton forming a conjugate acidic ion (or oxonium ion); (2) this then undergoes an exchange reaction with an alcohol molecule which approaches along the line of the $C{-}\overset{+}{O}$ dipole; and (3) loss of a proton to yield the ester.

1.
$$\begin{array}{l} R' \\ | \\ C{-}OH \\ \| \\ O \end{array} + \overset{+}{H} \rightleftharpoons \begin{array}{l} R' \\ | \\ C{-}\overset{+}{O}H_2 \\ \| \\ O \end{array}$$

2. 

3. 

If either R or R′ has a branched chain structure and is therefore bulky, it will exert a hindering influence (steric hindrance) in the formation of the bimolecular complex (in 2) and esterification is accordingly more difficult.

Examples of the preparation of simple aliphatic esters by *Fischer and Speier's method* in which an excess of acid is employed are :—

(i) ***n*-Butyl acetate:** most of the excess of acid is removed by washing the reaction product with water since the ester is sparingly soluble in water.

(ii) **Methyl and ethyl acetates:** these esters are fairly miscible with water. Fractional distillation, however, permits of a good preliminary separation of the esters (methyl, b.p. 57°; ethyl, b.p. 77°) from the excess of acetic acid (b.p. 118°).

***tert.*-Butyl acetate** may be prepared either from the alcohol and acetyl chloride in the presence of sufficient dimethylaniline to remove the hydrogen chloride as formed :

$$(CH_3)_3COH + CH_3COCl + C_6H_5N(CH_3)_2 \longrightarrow CH_3COOC(CH_3)_3 + C_6H_5N(CH_3)_2HCl$$

or from the alcohol and acetic anhydride in the presence of a little anhydrous zinc chloride :

$$(CH_3)_3COH + (CH_3CO)_2O \xrightarrow{ZnCl_2} CH_3COOC(CH_3)_3 + CH_3COOH$$

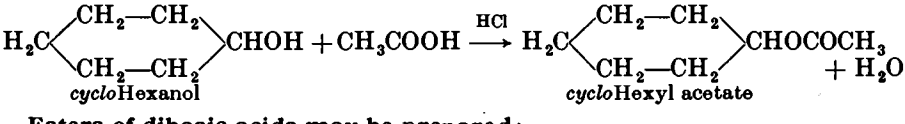
Sometimes a large proportion of sulphuric acid is employed (see below under esters of dibasic acids). The good yields thus obtained are partially due to the removal of water by the acid as well as to the catalytic effect.

In some instances the use of sulphuric acid leads to unsatisfactory results. Thus with formic acid carbon monoxide would be evolved. Esters of formic acid are most simply prepared from the alcohol and excess of formic acid, for example :

$$\underset{\text{Formic acid}}{HCOOH} + \underset{n\text{-Butyl alcohol}}{C_4H_9{}^{\alpha}OH} \longrightarrow \underset{n\text{-Butyl formate}}{HCOOC_4H_9{}^{\alpha}} + H_2O$$

Formic acid is a comparatively strong acid and acts as its own catalyst.

Esterification with *cyclo*aliphatic alcohols is comparatively easy when the alcohol is saturated with hydrogen chloride and treated with excess of the acid, but a very impure ester results from the use of sulphuric acid as a catalyst, for example :



*cyclo*Hexanol — *cyclo*Hexyl acetate

Esters of dibasic acids may be prepared:

(*a*) By distilling a mixture of the acid, excess of alcohol, toluene and a little concentrated sulphuric acid (1 per cent. by weight of the acid). An azeotropic mixture of alcohol, toluene and water passes over first, then alcohol and toluene, and finally the ester, for example :

$$\underset{\text{Adipic acid}}{HOOC(CH_2)_4COOH} + 2C_2H_5OH \xrightarrow[\text{(toluene)}]{H_2SO_4} \underset{\text{Diethyl adipate}}{C_2H_5OOC(CH_2)_4COOC_2H_5} + 2H_2O$$

(*b*) By refluxing a mixture of the acid (1 mol), alcohol (3–4 mols), dry benzene (375 ml.) and concentrated sulphuric acid (58-60 g.). The ester as formed passes into the benzene layer. Upon the addition of water, separating the benzene layer, and distilling the latter (after washing and drying), benzene and alcohol pass over first, followed by the ester, for example:

$$\underset{\text{Oxalic acid}}{HOOCCOOH} + 2C_2H_5OH \xrightarrow[\text{(benzene)}]{H_2SO_4} \underset{\text{Diethyl oxalate}}{C_2H_5OOCCOOC_2H_5} + 2H_2O$$

Both of these methods are more economical in the consumption of alcohol and more convenient than that in which the acid is refluxed with a large excess of alcohol in the presence of concentrated sulphuric acid. An example of the latter procedure is described:

$$\underset{\text{Sebacic acid}}{HOOC(CH_2)_8COOH} + 2C_2H_5OH \xrightarrow{H_2SO_4} \underset{\text{Diethyl sebacate}}{C_2H_5OOC(CH_2)_8COOC_2H_5} + 2H_2O$$

The benzene - alcohol method is useful for the esterification of valuable monobasic acids, but the b.p. of the ester must be at least 50° higher than that of benzene, for example:

$$\underset{n\text{-Valeric acid}}{CH_3(CH_2)_3COOH} + \underset{n\text{-Propyl alcohol}}{C_3H_7{}^{\alpha}OH} \xrightarrow[\text{(benzene)}]{H_2SO_4} \underset{n\text{-Propyl } n\text{-valerate}}{CH_3(CH_2)_3COOC_3H_7{}^{\alpha}} + H_2O$$

When either of the reactants is sensitive to mineral acids, the esterification can often be successfully accomplished with the aid of a **cation exchange resin** (hydrogen form) in the presence of benzene. Zeo-Karb 225/H, a unifunctional sulphonated polystyrene resin in the hydrogen form, may be used. Thus good yields of *iso*propyl lactate may be obtained:

$$\underset{\text{Lactic acid}}{CH_3CH(OH)COOH} + \underset{\textit{iso}\text{-Propyl alcohol}}{(CH_3)_2CH(OH)} \xrightarrow[\text{benzene}]{\text{Zeo-Karb 225/H;}} \underset{\textit{iso}\text{-Propyl lactate}}{CH_3CH(OH)COOCH(CH_3)_2} + H_2O$$

Lactic acid tends to pass into the lactide $\begin{matrix} CH_3CH—O—CO \\ | \qquad\quad | \\ CO—O—CHCH_3 \end{matrix}$ when heated in the presence of sulphuric acid. Likewise *n*-butyl oleate is readily prepared from the alcohol and acid in the presence of Zeo-Karb 225/H. The esterification of acetic acid with the acid-sensitive furfuryl alcohol gives a 25 per cent. yield of ester in the presence of the resin; furfuryl acetate is, however, more easily prepared by boiling furfuryl alcohol with acetic anhydride and sodium acetate in the presence of benzene.

2. **From the silver salt.** By refluxing the dry silver salt with an alkyl halide in anhydrous ether, benzene or absolute alcohol solution, for example:

$$\underset{\text{Silver maleate}}{\begin{matrix} CHCOOAg \\ \| \\ CHCOOAg \end{matrix}} + 2C_2H_5I \xrightarrow{\text{(Ether)}} \underset{\text{Diethyl maleate}}{\begin{matrix} CHCOOC_2H_5 \\ \| \\ CHCOOC_2H_5 \end{matrix}} + 2AgI$$

The method is generally applicable when other modes of esterification are either slow, inefficient, or likely to cause isomerisation; it is, however, time-consuming and expensive. Small quantities of acid impurities are sometimes produced, hence it is advisable to wash the ester with saturated sodium bicarbonate solution. The silver salt can usually be prepared by dissolving the acid in the calculated quantity of standard ammonium hydroxide solution and

adding an excess of silver nitrate solution: the precipitated salt is washed with water and dried at 40-50° or in a vacuum desiccator. It must be prepared in the dark.

3. **From the nitrile.** By refluxing a mixture of the nitrile with alcohol and concentrated sulphuric acid; the intermediate isolation of the acid is unnecessary. The net result may be represented by, for example:

$$\underset{n\text{-Butyl cyanide}}{C_4H_9{}^{\alpha}CN} + H_2O + C_2H_5OH + H_2SO_4 \longrightarrow \underset{\text{Ethyl } n\text{-valerate}}{C_4H_9{}^{\alpha}COOC_2H_5} + NH_4HSO_4$$

Two mechanisms of the transformation have been proposed:

(*a*) The intermediate formation of an amide:

$$RCN + H_2O \longrightarrow RCONH_2$$
$$RCONH_2 + C_2H_5OH \longrightarrow RCOOC_2H_5 + NH_3$$

(*b*) The intermediate formation of an imino-ether:

$$RCN + C_2H_5OH \longrightarrow RC(=NH)OC_2H_5$$
$$RC(=NH)OC_2H_5 + H_2O \longrightarrow RCOOC_2H_5 + NH_3$$

4. **From the acid chloride.** By the interaction of the acid chloride (prepared from the acid and thionyl chloride) and the calculated quantity of the alcohol at 0°, for example:

$$\underset{\text{Vinylacetyl chloride}}{CH_2{=}CHCH_2COCl} + C_2H_5OH \longrightarrow \underset{\text{Ethyl vinylacetate}}{CH_2{=}CHCH_2COOC_2H_5} + HCl$$

This procedure is generally applied to the esterification of highly sensitive acids, which might otherwise undergo isomerisation. Thus in the example given, no ethyl crotonate is formed.

III,95. *n*-BUTYL ACETATE

Mix together 37 g. (46 ml.) of *n*-butyl alcohol and 60 g. (60 ml.) of glacial acetic acid in a 250 or 500 ml. round-bottomed flask, and add cautiously 1 ml. of concentrated sulphuric acid (use a small measuring cylinder or a burette or a calibrated dropper pipette). Attach a reflux condenser and reflux the mixture on a wire gauze for 3–6 hours (1). Pour the mixture into about 250 ml. of water in a separatory funnel, remove the upper layer of crude ester, and wash it again with about 100 ml. of water, followed by about 25 ml. of saturated sodium bicarbonate solution and 50 ml. of water. The ester must, of course, be separated between each washing. Dry the crude ester with 5–6 g. of anhydrous sodium or magnesium sulphate. Filter through a small funnel containing a fluted filter paper (Section **II,29**) or a small plug of cotton or glass wool into a dry 100 ml. distilling flask. Add 2–3 fragments of porous porcelain and distil on a wire gauze or from an air bath (Fig. *II*, *5*, 3). Collect the pure *n*-butyl acetate at 124–125°. The yield is 40 g.

Note.

(1) A slightly better yield of ester can be obtained by increasing the quantity of acetic acid to 90–120 g. and refluxing for 12–18 hours. This modification is not worth while in a student's preparation.

Cognate Preparations

sec.-Butyl acetate. Pass dry hydrogen chloride gas into 37 g. (46 ml.) of *sec.*-butyl alcohol until 1·5 g. is absorbed. Mix the solution with

60 g. of glacial acetic acid, and reflux for 10 hours. Isolate the ester as for *n*-butyl acetate. B.p. 110–112°. Yield : 35 g.

***n*-Propyl acetate.** Use 40 g. (50 ml.) of *n*-propyl alcohol, 160 g. of glacial acetic acid and 2 g. of concentrated sulphuric acid. Reflux for 12 hours. Add an equal volume of water, saturate with salt to isolate the crude ester. Treat the crude ester with saturated sodium bicarbonate solution until effervescence ceases, saturate with salt, remove the ester and dry it with anhydrous sodium or magnesium sulphate. B.p. 101-102°. Yield : 36 g.

***iso*-Propyl acetate.** Use 40 g. (51 ml.) of *iso*-propyl alcohol, 160 g. of glacial acetic acid and 2 g. of concentrated sulphuric acid. Reflux for 18 hours. Proceed as for *n*-propyl acetate. B.p. 87–88°. Yield : 31 g.

***n*-Amyl acetate.** Use 40 g. (49 ml.) of *n*-amyl alcohol, 120 g. of glacial acetic acid and 2·5 g. of concentrated sulphuric acid, and reflux for 20 hours. Isolate the ester as for *n*-butyl acetate. B.p. 146–148°. Yield : 47 g.

Methyl acetate. Use 48 g. (61 ml.) of absolute methyl alcohol, 270 g. of glacial acetic acid and 3 g. of concentrated sulphuric acid. Reflux for 5 hours. Distil the reaction mixture through a simple fractionating column (*e.g.*, a Hempel column filled with $\frac{1}{4}''$ glass or porcelain rings, or an all-glass Dufton column) ; the crude ester passes over at 55–56° (112 g.) and the excess of acid, etc., remaining in the flask weighs 209 g. Wash once with a *little* water, saturate with salt, wash with saturated sodium bicarbonate solution, saturate with salt, remove the ester layer, and dry with anhydrous sodium and magnesium sulphate, and distil. The methyl acetate passes over constantly at 55–56°. The yield is 92 g.

Ethyl acetate. Use 58 g. (73·5 ml.) of absolute ethyl alcohol, 225 g. of glacial acetic acid and 3 g. of concentrated sulphuric acid. Reflux for 6–12 hours. Work up as for *n*-propyl acetate. B.p. 76-77°. Yield : 32 g. Much ethyl acetate is lost in the washing process. A better yield may be obtained, and most of the excess of acetic acid may be recovered, by distilling the reaction mixture through an efficient fractionating column and proceeding as for methyl acetate.

Ethyl *n*-butyrate. Use a mixture of 88 g. (92 ml.) of *n*-butyric acid, 23 g. (29 ml.) of ethanol and 9 g. (5 ml.) of concentrated sulphuric acid. Reflux for 14 hours. Pour into excess of water, wash several times with water, followed by saturated sodium bicarbonate solution until all the acid is removed, and finally with water. Dry with anhydrous magnesium sulphate, and distil. The ethyl *n*-butyrate passes over at 119·5–120·5°. Yield : 40 g. An improved yield can be obtained by distilling the reaction mixture through an efficient fractionating column until the temperature rises to 125°, and purifying the crude ester as detailed above under methyl acetate.

III,96. *tert.*-BUTYL ACETATE

Method A. Fit a 1-litre three-necked flask with a mercury-sealed stirrer, a reflux condenser, and a dropping funnel. Place 57 g. (73·5 ml.) of dry *tert.*-butyl alcohol (1), 101 g. (106 ml.) of A.R. dimethylaniline and 100 ml. of anhydrous ether in the flask, set the stirrer in motion, and

heat the mixture to gentle refluxing on a water bath. Run in 62 g. (56·5 ml.) of redistilled acetyl chloride at such a rate that moderate refluxing continues after the source of heat is removed. When about two-thirds of the acetyl chloride has been introduced, the dimethylaniline hydrochloride commences to crystallise and the mixture refluxes very vigorously. Cool immediately in an ice bath, and, after refluxing ceases, add the remainder of the acetyl chloride; then heat the mixture on a water bath for 1 hour. Cool to room temperature, add about 100 ml. of water, and continue the stirring until all the precipitated solid has dissolved. Separate the ether layer and extract with 25 ml. portions of cold 10 per cent. sulphuric acid until the acid extract does not become cloudy when rendered alkaline with sodium hydroxide solution. Finally, wash with 15 ml. of saturated sodium bicarbonate solution and dry the ethereal solution with 5 g. of anhydrous magnesium sulphate overnight. Remove the ether by distillation through an efficient fractionating column (*e.g.*, of the Widmer type) and distil the residue through the same column. Collect the *tert.*-butyl acetate at 96–98° (mainly 97–98°). The yield is 55 g.

Note.

(1) The *tert.*-butyl alcohol should be dried over quicklime or anhydrous calcium sulphate and distilled.

COGNATE PREPARATION

***tert.*-Butyl propionate.** Use 85·5 g. (110·5 ml.) of *tert.*-butyl alcohol, 151·5 g. (159 ml.) of A.R. dimethylaniline, and 110 g. (103 ml.) of propionyl chloride (compare Section **III,87**) and reflux for 3 hours. B.p. 117·5–118·5°. Yield: 92 g.

Method B. Fit a 500 ml. round-bottomed flask with a reflux condenser carrying a cotton wool or calcium chloride guard tube. Place 100 ml. of redistilled acetic anhydride, 100 ml. of dry *tert.*-butyl alcohol (see *Note* in *Method A*) and 0·3 g. of anhydrous zinc chloride in the flask and shake. Heat the mixture gradually to the reflux temperature, maintain at gentle refluxing for 2 hours, and then cool. Replace the reflux condenser by an efficient fractionating column and distil until the temperature reaches 110°. Wash the crude distillate, weighing 100–125 g., with two 25 ml. portions of water, then with 25 ml. portions of 10 per cent. potassium carbonate solution until the ester layer is neutral to litmus, and finally dry with 10 g. of anhydrous potassium carbonate. Filter off the desiccant, and distil through an efficient fractionating column (*e.g.*, Widmer column, modified Hempel column, etc.; compare Section **II,17**) and collect the pure *tert.*-butyl acetate at 96–98°. The yield is 70 g.

III,97. *n*-BUTYL FORMATE

Into a 250 or 500 ml. round-bottomed flask provided with a reflux condenser place 46 g. (38 ml.) of A.R. formic acid (98/100 per cent.) and 37 g. (46 ml.) of *n*-butyl alcohol. Reflux for 24 hours. Wash the cold mixture with small volumes of saturated sodium chloride solution, then with saturated sodium bicarbonate solution in the presence of a little

solid sodium bicarbonate until effervescence ceases, and finally with saturated sodium chloride solution. Dry with anhydrous sodium or magnesium sulphate, and distil from a Claisen flask with fractionating side arm. Collect the *n*-butyl formate at 106–107°. Yield : 38 g.

COGNATE PREPARATIONS

Ethyl formate. Reflux a mixture of 61 g. (50 ml.) of A.R. formic acid (98/100 per cent.) and 31 g. (39·5 ml.) of absolute ethyl alcohol for 24 hours. Transfer to a Claisen flask with fractionating side arm (or attach a fractionating column to the flask), distil and collect the liquid passing over below 62°. Wash the distillate with saturated sodium bicarbonate solution and saturate with salt before removing the ester layer. Dry with anhydrous sodium or magnesium sulphate, filter, and distil. The ethyl formate passes over at 53–54°. The yield is 36 g.

***n*-Propyl formate.** Use 46 g. (38 ml.) of A.R. formic acid (98/100 per cent.) and 30 g. (37·5 ml.) of *n*-propyl alcohol, and reflux for 24 hours. Proceed as for ethyl formate, but collect the crude *n*-propyl formate up to 86°. B.p. 80·5–82°. Yield : 28 g.

III,98. *cyclo*HEXYL ACETATE

Pass dry hydrogen chloride into 75 g. of pure *cyclo*hexanol until 1·5 g. are absorbed, mix with 135 g. of glacial acetic acid in a 500 ml. round-bottomed flask, attach a reflux condenser, and reflux for 14 hours. Pour into excess of water, wash the upper layer successively with water, saturated sodium bicarbonate solution until effervescence ceases, and water. Dry with anhydrous calcium chloride. Distil through a well-lagged fractionating column (*e.g.*, an all-glass Dufton column). A small fraction of low boiling point (containing *cyclo*hexene) passes over first, followed by *cyclo*hexyl acetate (57 g.) at 168–170°. Upon redistillation from a Claisen flask, the boiling point is 170-172°, mainly 171–172° (1).

Note.

(1) Boiling points over the range 150–200° appear to be about 2° lower when determined by distillation through an efficient, lagged fractionating column.

COGNATE PREPARATION

***cyclo*Hexyl formate.** Use 103 g. (84·5 ml.) of A.R. formic acid (98/100 per cent.) and 75 g. of *cyclo*hexanol in which 1·5 g. of dry hydrogen chloride gas are dissolved. Reflux for 14 hours. Work up as above and distil through a well-lagged column ; 5·5 g. of *cyclo*hexene and 57 g. of *cyclo*hexyl formate, b.p. 156–158·5° (mainly 157-158·5°) are obtained. When distilled from a Claisen flask, the sample boils at 158–160° (mainly 159–160°).

III,99. DIETHYL ADIPATE (*Azeotropic Mixture Method*)

Place 146 g. of adipic acid, 360 ml. (285 g.) of absolute ethyl alcohol 180 ml. of toluene and 1·5 g. of concentrated sulphuric acid in a 1-litre round-bottomed flask, attach a *short* fractionating column connected to a downward condenser, and heat in an oil bath at 115°. When the acid

has dissolved, an azeotropic mixture of alcohol, toluene and water commences to distil at 75°; the temperature of the oil bath may then be lowered to 100–110°. Collect the distillate in a flask containing 150 g. of anhydrous potassium carbonate. Continue the distillation until the temperature at the top of the column rises to 78°. Shake the distillate thoroughly with the potassium carbonate, filter through a Buchner funnel or fluted filter paper, and return the filtrate to the flask. Heat the flask again until the temperature rises to 78–80° (1). Transfer the warm solution to a Claisen flask of suitable size and distil under reduced pressure. Alcohol and toluene pass over first, the temperature rises abruptly and the ethyl adipate distils at 138°/20 mm. (2). The yield is 195 g.

Notes.

(1) The distillate contains alcohol, toluene and water, and may be dried with anhydrous potassium carbonate and used again for esterification after the addition of the necessary quantity of alcohol; alternatively, the toluene may be recovered by washing with water, drying with anhydrous calcium chloride or anhydrous magnesium sulphate, and distilling.

(2) The b.p. may rise several degrees towards the end of the distillation owing to superheating.

III,100. DIETHYL ADIPATE (*Benzene Method*)

Place 100 g. of adipic acid in a 750 ml. round-bottomed flask and add successively 100 g. (127 ml.) of absolute ethyl alcohol, 250 ml. of sodium-dried benzene and 40 g. (22 ml.) of concentrated sulphuric acid (the last-named cautiously and with gentle swirling of the contents of the flask). Attach a reflux condenser and reflux the mixture gently for 5–6 hours. Pour the reaction mixture into excess of water (2–3 volumes), separate the benzene layer (1), wash it with saturated sodium bicarbonate solution until effervescence ceases, then with water, and dry with anhydrous magnesium or calcium sulphate. Remove most of the benzene by distillation under normal pressure until the temperature rises to 100° using the apparatus of Fig. *II*, *13*, 4 but substituting a 250 ml. Claisen flask for the distilling flask; then distil under reduced pressure and collect the ethyl adipate at 134–135°/17 mm. The yield is 130 g.

Note.

(1) One extraction of the aqueous solution with ether is recommended.

Cognate Preparations

Diethyl oxalate. Reflux a mixture of 45 g. of anhydrous oxalic acid (1), 81 g. (102·5 ml.) of absolute ethyl alcohol, 190 ml. of sodium-dried benzene and 30 g. (16·5 ml.) of concentrated sulphuric acid for 24 hours. Work up as for *Diethyl Adipate* and extract the aqueous layer with ether; distil under atmospheric pressure. The yield of ethyl oxalate, b.p. 182–183°, is 57 g.

Note.

(1) Anhydrous oxalic acid may be prepared by heating the finely-powdered A.R. crystallised acid, spread upon large clock glasses, in an electric oven at 105° for 6 hours, allowing to cool in a desiccator and storing in a tightly stoppered bottle.

Diethyl succinate. Reflux a mixture of 58 g. of A.R. succinic acid, 81 g. (102·5 ml.) of absolute ethyl alcohol, 190 ml. of sodium-dried

benzene and 20 g. (11 ml.) of concentrated sulphuric acid for 8 hours. Pour the reaction mixture into excess of water, separate the benzene-ester layer, and extract the aqueous layer with ether. Work up the combined ether and benzene extracts as described for *Diethyl Adipate*. B.p. 81°/3 mm. Yield: 75 g. The boiling point under atmospheric pressure is 217–218°.

Diethyl sebacate. *Method A.* Reflux a mixture of 100 g. of sebacic acid, 81 g. (102·5 ml.) of absolute ethyl alcohol, 190 ml. of sodium-dried benzene and 20 g. (11 ml.) of concentrated sulphuric acid for 36 hours. Work up as for *Diethyl Adipate*. B.p. 155–156°/6 mm. Yield: 114 g.

Method B. Reflux a mixture of 101 g. of sebacic acid, 196 g. (248 ml.) of absolute ethyl alcohol and 20 ml. of concentrated sulphuric acid for 12 hours. Distil off about half of the alcohol on a water bath dilute the residue with 500–750 ml. of water, remove the upper layer of crude ester, and extract the aqueous layer with ether. Wash the combined ethereal extract and crude ester with water, then with saturated sodium bicarbonate solution until effervescence ceases, and finally with water. Dry with anhydrous magnesium or sodium sulphate, remove the ether on a water bath, and distil the residue under reduced pressure. B.p. 155–157°/6 mm. Yield: 110 g.

III,101. *n*-PROPYL *n*-VALERATE

Place a mixture of 25·5 g. of *n*-valeric acid (Sections **III,83** and **III,84**), 30 g. (37·5 ml.) of dry *n*-propyl alcohol, 50 ml. of sodium-dried benzene and 10 g. (5·5 ml.) of concentrated sulphuric acid in a 250 ml. round-bottomed flask equipped with a vertical condenser, and reflux for 36 hours. Pour into 250 ml. of water and separate the upper layer. Extract the aqueous layer with ether, and add the extract to the benzene solution. Wash the combined extracts with saturated sodium bicarbonate solution until effervescence ceases, then with water, and dry with anhydrous magnesium sulphate. Remove the low boiling point solvents by distillation (use the apparatus of Fig. *II, 13*, 4 but with a Claisen flask replacing the distilling flask); the temperature will rise abruptly and the *n*-propyl *n*-valerate will pass over at 163–164°. The yield is 28 g.

III,102. *iso*PROPYL LACTATE (*Ion Exchange Resin Catalyst Method*)

Place a mixture of 53 g. of A.R. lactic acid (85–88 per cent. acid), 75 g. (85·5 ml.) of commercial anhydrous *iso*propyl alcohol, 300 ml. of benzene and 20 g. of Zeo-Karb 225/H (1) in a 700 ml. bolt-head flask, equipped with an automatic water separator (*e.g.*, a large modified Dean and Stark apparatus with a stopcock at the lower end, see Fig. *III, 126*, 1) carrying an efficient reflux condenser at its upper end, and a mercury-sealed stirrer (alternatively, the liquid-sealed stirrer shown in Fig. *II,7,11,c.* may be used). Reflux the mixture, with stirring, on a steam bath for 5 hours or until water no longer collects in appreciable amount in the water separator; run off the water from time to time. Filter off the resin at the pump and wash it with two 25 ml. portions of benzene. Shake the combined filtrate and washings with about 5 g. of precipitated calcium

carbonate, filter, and wash with a little benzene. Distil the benzene solution under reduced pressure (water pump) from a Claisen flask with fractionating side arm; the *iso*propyl alcohol - benzene azeotrope (2) passes over first, followed by benzene. Collect the *iso*propyl lactate at 76°/24 mm.; it is a colourless liquid and weighs 40 g. The ester boils, with slight decomposition, at 157°/771 mm.

Notes.

(1) The cation exchange resin, hydrogen form, Zeo-Karb 225/H is supplied in small particles (30–80 mesh). If the sodium form of the resin Zeo-Karb 225 (or the equivalent Amberlite IR 105) only is available, it may be converted into the hydrogen form by treating it with about twice its volume of 2*N* sulphuric acid and stirring frequently: the resin is thoroughly washed by decantation with distilled water until the washings have a *p*H of 6–7, filtered and dried in the air.

(2) The b.p. of the *iso*propyl - benzene azeotrope at atmospheric pressure is 71–72°.

COGNATE PREPARATIONS

***n*-Butyl oleate.** Proceed as for iso*Propyl Lactate* using 26·5 g. of redistilled oleic acid, 37·0 g. (45·8 ml.) of *n*-butyl alcohol (the excess of the latter acts as the water carrier) and 8·0 g. of Zeo-Karb 225/H in a 250 ml. bolt-head flask. Reflux the mixture with stirring for 4 hours, allow to cool, separate the resin by suction filtration, and wash it with three 5 ml. portions of *n*-butyl alcohol. Remove the *n*-butyl alcohol from the combined filtrate and washings by distillation under reduced pressure (water pump); the residue consists of crude ester. Distil the residue under diminished pressure (oil pump) and collect the *n*-butyl oleate at 232°/9 mm. The yield is 27 g.

Furfuryl acetate. Reflux a mixture of 39·2 g. (34·8 ml.) of redistilled furfuryl alcohol, 48 g. of glacial acetic acid, 150 ml. of benzene and 20 g. of Zeo–Karb 225/H in a 500 ml. bolt-head flask, using the apparatus described under iso*Propyl Lactate*. After 3 hours, when the rate of collection of water in the water separator is extremely slow, allow to cool, separate the resin by suction filtration, and wash it with three 15 ml. portions of benzene. Remove the benzene, etc., from the combined filtrate and washings under reduced pressure (water pump) and then collect the crude ester at 74–90°/10 mm.; a small solid residue remains in the flask. Redistil the crude ester from a Claisen flask with fractionating side arm; pure furfuryl acetate passes over at 79–80°/17 mm. The yield is 14·5 g.

III,103. DIETHYL MALEATE (*Silver Salt Method*)

Preparation of silver maleate. Dissolve 65 g. of pure maleic acid (Section **III,143**) in the calculated quantity of carefully standardised 3·5*N* aqueous ammonia solution in a 1-litre beaker and add, whilst stirring mechanically, a solution of 204 g. of silver nitrate in 200 ml. of water. Filter off the precipitated silver maleate at the pump, wash it with distilled water, and press well with the back of a large flat glass stopper. Dry in an electric oven at 50–60° to constant weight. The yield of the dry silver salt is 150 g. Store in a vacuum desiccator in the dark.

In a 500 ml. round-bottomed flask, provided with a reflux condenser protected by a cotton wool (or calcium chloride) guard tube, place 90 g. of silver maleate, 84 g. (43·5 ml.) of colourless, dry ethyl iodide and 50 ml. of sodium-dried A.R. benzene. Within a short period of mixing a vigorous reaction sets in and it is necessary to cool the flask in running water. When the reaction has subsided, the mixture possesses the yellow colour of silver iodide. Reflux on a water bath for 10 hours. Filter at the pump on a sintered glass funnel and keep the benzene solution of the ester separately. Wash the solid well with rectified spirit and pour the washings into excess of water; separate the benzene layer and add this to the original filtrate. Wash the combined benzene solutions with water, saturated sodium bicarbonate solution, and finally with water; dry with anhydrous magnesium sulphate. Remove the benzene in a 50 ml. Claisen flask (use the apparatus shown in Fig. *II*, *13*, 4) and distil. Diethyl maleate passes over at 219–220°. The yield is 27 g.

Note.

Ethyl maleate of almost equal purity may be obtained by refluxing a mixture of 29 g. of pure maleic acid, 37 g. (47 ml.) of absolute ethyl alcohol, 95 ml. of sodium-dried benzene and 4 ml. of concentrated sulphuric acid for 12 hours. The ester is isolated as described for *Diethyl Adipate* (Section **III,100**). The yield of diethyl maleate, b.p. 219–220°, is 26 g.

III,104. ETHYL *n*-VALERATE (*from* n-*Butyl Cyanide*)

Place 200 g. (250 ml.) of rectified spirit in a 1-litre round-bottomed flask fitted with a reflux condenser. Cool in ice and run in, slowly and with frequent shaking, 200 g. (109 ml.) of concentrated sulphuric acid. Add 83 g. (104 ml.) of *n*-butyl cyanide (Section **III,113**) to the mixture and reflux the whole for 10 hours. Allow to cool, pour the reaction mixture into ice water, separate the upper layer of ester and alcohol, and dry over anhydrous magnesium or calcium sulphate. Distil through a fractionating column and collect the ethyl *n*-valerate at 143–146°. A further amount of the pure ester may be obtained by redrying the fraction of low boiling point and redistilling. The yield is 110 g.

III,105. ETHYL VINYLACETATE (*Acid Chloride Method*)

Fit a reflux condenser and a dropping funnel into the two necks of a 150 ml. Claisen flask and stopper the side arm (compare Fig. *III*, *31*, 1); place 50 g. (31 ml.) of redistilled thionyl chloride in the flask. Drop 30 g. of vinylacetic acid (Section **III,144**) slowly into the thionyl chloride and when the addition is complete reflux gently for 30 minutes. Rearrange the apparatus and distil the mixture slowly from an air bath (1). The excess of thionyl chloride passes over first, followed by vinylacetyl chloride at 98–99° (27 g.). Place 12·6 g. (16·0 ml.) of absolute ethyl alcohol in a 250 ml. bolt-head flask provided with a reflux condenser and dropping funnel. Cool the flask in ice and introduce the vinylacetyl chloride into the dropping funnel; insert a cotton wool (or calcium chloride) guard tube into the mouth of the funnel. Add the acid chloride dropwise (45 minutes) to the alcohol with frequent shaking. Remove the ice and allow to stand for 1 hour. Pour the reaction mixture into water,

wash with a little sodium bicarbonate solution, then with water, and dry with anhydrous magnesium or calcium sulphate. Distil from a 50 ml. Claisen flask with fractionating side arm, and collect the ethyl vinylacetate at 125–127°. The yield is 22 g.

Note.

(1) It is preferable to use an all-glass apparatus for all the operations described in this preparation (see Section **II,60**).

COGNATE PREPARATION

Ethyl *cyclo*propane-carboxylate. Use 22 g. of *cyclo*propane-carboxylic acid (Section **V,33**) and 40 g. (24·5 ml.) of redistilled thionyl chloride to prepare the acid chloride, b.p. 118–119° (22 g.). Treat the latter with 10·1 g. of absolute ethyl alcohol. The yield of ethyl *cyclo*propane-carboxylate, b.p. 132–133°, is 13 g.

III,106. REACTIONS AND CHARACTERISATION OF ALIPHATIC ESTERS

Hydrolysis (or saponification) of *n*-butyl acetate. Boil 4–5 g. of *n*-butyl acetate (Section **III,95**) with 50 ml. of 10 per cent. sodium hydroxide solution under reflux until the odour of the ester can no longer be detected (about 1 hour). Set the condenser for downward distillation and collect the first 10 ml. of distillate. Saturate it with potassium carbonate, allow to stand for 5 minutes, and withdraw all the liquid into a small pipette or dropper pipette. Allow the lower layer of carbonate solution to run slowly into a test-tube, and place the upper layer into a small test-tube or weighing bottle. Dry the alcohol with about one quarter of its bulk of anhydrous potassium carbonate. Remove the alcohol with a dropper pipette and divide it into two parts ; use one portion for the determination of the b.p. by the Siwoloboff method (Section **II,12**) and convert the other portion into the 3 : 5-dinitrobenzoate (Section **III, 27**) and determine the m.p.

Acidify the residue in the flask with dilute sulphuric acid and distil off 10–15 ml. of the solution. Test a small portion of the distillate for acidity, and also observe the odour. Neutralise the main portion with sodium hydroxide solution (add a drop of phenolphthalein to act as indicator), evaporate to small bulk, and convert the sodium salt into the *p*-bromophenacyl ester or into some other suitable derivative (Section **III,85**) ; determine the m.p. of the derivative.

The above example serves to illustrate the basis of the procedure employed for the characterisation of aliphatic esters, *viz.*, hydrolysis to, and identification of, the parent acids and alcohols. Most esters are liquids ; a notable exception is dimethyl oxalate, m.p. 54°. Many have pleasant, often fruit-like, odours. Many dry esters react with sodium, but less readily than do alcohols : hydrogen is evolved particularly on warming, and a solid sodio derivative may separate on cooling (*e.g.*, ethyl acetate yields ethyl sodioacetoacetate ; ethyl adipate gives ethyl sodio *cyclo*pentanone carboxylate).

In the routine examination of esters it is often a good plan to carry out two hydrolyses, one for the isolation and characterisation of the

parent acid, and the other for the isolation and identification of the parent alcohol.

1. Drop 1 g. of sodium into 10 ml. of ethyl alcohol in a small flask provided with a small water condenser; heat the mixture until all the sodium has dissolved. Cool, and add 1 g. of the ester and 0·5 ml. of water. Frequently the sodium salt of the acid will be deposited either at once or after boiling for a few minutes. If this occurs, filter off the solid at once, wash it with a little absolute ethyl alcohol (or absolute methylated spirit), and convert it into the *p*-bromophenacyl ester, *p*-nitrobenzyl ester or S-benzyl-*iso*-thiuronium salt (for experimental details, see Section **III,85**). If no solid separates, continue the boiling for 30–60 minutes, boil off the alcohol, allow to cool, render the product just neutral to phenolphthalein with dilute sulphuric or hydrochloric acid, convert the sodium salt present in solution into a crystalline derivative (Section **III,85**), and determine its melting point.

2. Boil 2 g. of the ester with 30 ml. of 10 per cent. sodium or potassium hydroxide solution under reflux for at least 1 hour. If the alcohol formed is water (or alkali) soluble, the completion of the hydrolysis will be indicated by the disappearance of the ester layer. Distil off the liquid through the same condenser and collect the first 3–5 ml. of distillate. If a distinct layer separates on standing (or upon saturation of half the distillate with potassium carbonate), remove this layer with a capillary dropper, dry it with a little anhydrous potassium carbonate or anhydrous calcium sulphate, and determine the b.p. by the Siwoloboff method (Section **II,12**). Whether an insoluble alcohol separates out or not, prepare a crystalline derivative (*e.g.*, the 3 : 5-dinitrobenzoate, Section **III,27**) and determine its m.p.

The residue in the flask will contain the sodium (or potassium) salt of the acid together with excess of alkali. Just acidify with dilute sulphuric acid and observe whether a crystalline acid separates; if it does, filter, recrystallise and identify (Section **III,85**). If no crystalline solid is obtained, the solution may be just neutralised to phenolphthalein and the solution of the alkali salt used for the preparation of a crystalline derivative. This will confirm, if necessary, the results of hydrolysis by method 1. If the time factor is important, either method 1 or the product of the caustic alkali hydrolysis may be used for the identification of the acid.

The following notes may be useful:

(1) The b.p., density and refractive index are valuable constants for the final characterisation of liquid esters.

(2) Some esters, *e.g.*, methyl formate, methyl oxalate, methyl succinate, methyl and ethyl tartrate, are appreciably soluble in water. These are usually easily hydrolysed by alkali.

(3) Of the common esters, methyl oxalate (solid, m.p. 54°) and ethyl oxalate (liquid) give amides almost immediately upon shaking with concentrated ammonia solution. The resulting oxamide, m.p. 417°, is valueless as a derivative. The esters may, however, be easily hydrolysed and identified as above.

(4) If the original ester is a fat or oil and produces an odour of acrolein when heated, it may be a glyceride. Esters of ethylene glycol and of glycol with simple fatty acids are viscous and of high b.p. They are hydrolysed (method 1) and the ethyl alcohol distilled off. The residue is diluted (a soap may be formed) and acidified with hydrochloric acid (Congo red paper). The acid is filtered or

extracted with ether. If no acid can be isolated by these methods, it must be simple and volatile, and should be separated by distillation. The residual aqueous solution of glycol or glycerol is neutralised, evaporated to a syrup on a water bath, and extracted with ethyl alcohol or with ethyl acetate; the alcohol is evaporated and the glycol or glycerol in the residue is identified as usual.

(5) **β-Keto esters** (*e.g.*, ethyl acetoacetate) are soluble in solutions of caustic alkalis but not in sodium carbonate solution. They give colours with freshly prepared ferric chloride solution; a little alcohol should be added to bring the ester into solution. Sodium ethoxide solution reacts to yield sodio compounds, which usually crystallise out in the cold. Phenylhydrazine yields pyrazolones. They are hydrolysed by boiling sulphuric acid to the corresponding ketones, which can be identified as usual (Section III,74).

(6) **Unsaturated esters** decolourise a solution of bromine in carbon tetrachloride and also neutral potassium permanganate solution.

It is frequently advisable in the routine examination of an ester, and before any derivatives are considered, to determine the **saponification equivalent** of the ester. In order to ensure that complete hydrolysis takes place in a comparatively short time, the quantitative saponification is conducted with a standardised alcoholic solution of caustic alkali—preferably potassium hydroxide since the potassium salts of organic acids are usually more soluble than the sodium salts. A knowledge of the b.p. and the saponification equivalent of the unknown ester would provide the basis for a fairly accurate approximation of the size of the ester molecule. It must, however, be borne in mind that certain structures may effect the values of the equivalent: thus aliphatic halogenated esters may consume alkali because of hydrolysis of part of the halogen during the determination, nitro esters may be reduced by the alkaline hydrolysis medium, etc.

Determination of the Saponification Equivalent of an Ester

The **saponification equivalent** or the **equivalent weight of an ester** is that weight in grams of the ester from which one equivalent weight of acid is obtainable by hydrolysis, *or* that quantity which reacts with one equivalent of alkali. The saponification equivalent is determined in practice by treating a known weight of the ester with a known quantity of caustic alkali used in excess. The residual alkali is then readily determined by titration of the reaction mixture with a standard acid. The amount of alkali that has reacted with the ester is thus obtained: the equivalent can then be readily calculated.

Obtain a 250 ml. round-bottomed flask and attach an efficient reflux condenser to it by means of a clean rubber stopper. (The rubber stopper is cleaned by warming with dilute alkali, and then thoroughly washing with distilled water.) Place the sample of ester in a weighing bottle fitted with a cork carrying a small dropper pipette (compare Fig. *II*, *27*, 1) transfer about 1 g. of the ester, accurately weighed, to the flask. Then introduce 50 ml. of standard 0·5*N* alcoholic potassium hydroxide solution by means of a pipette into the flask, add a few chips of broken glass, attach the reflux condenser, and heat the flask gently on a water bath until hydrolysis is complete (1·5–2 hours). When cold, pour about 50 ml. of distilled water through the condenser, add 2–3 drops of phenolphthalein indicator, and titrate the excess of alkali with standard 0·5*N* or 0·25*N* hydrochloric or sulphuric acid. The end point should be a faint pink. If too much acid is accidentally added, back titrate the excess of

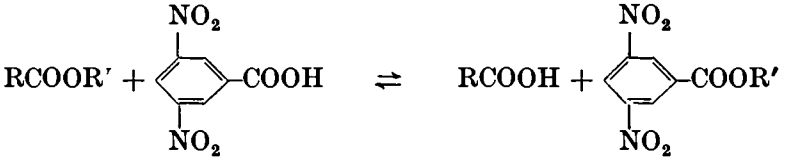
acid with the original alkali. Calculate the saponification equivalent from the expression :

$$\text{Saponification Equivalent} = \frac{\text{Weight of ester} \times 1000}{\text{Ml. of } N \text{ KOH used}}$$

The 0·5N alcoholic potassium hydroxide solution is prepared by dissolving 8 g. of potassium hydroxide pellets in 250 ml. of rectified spirit contained in a bottle closed by a cork ; shaking is necessary. After standing for 24 hours, the clear solution is decanted or filtered from the residue of potassium carbonate.

It is essential to standardise the alcoholic potassium hydroxide solution immediately before use by titration with standard 0·5*N* or 0·25*N* hydrochloric or sulphuric acid using phenolphthalein as indicator.

Identification of the alcohol components of simple esters. The alcohol components of many simple esters may be identified as the crystalline 3 : 5-dinitrobenzoates (compare Section **III,27**) by heating them with 3 : 5-dinitrobenzoic acid in the presence of a little concentrated sulphuric acid :



The reaction does not appear to be applicable to esters that react readily with concentrated sulphuric acid nor to those with a molecular weight in excess of about 250.

Dissolve 2 drops of concentrated sulphuric acid in 2 ml. of the ester and add 1·5 g. of 3 : 5-dinitrobenzoic acid. If the b.p. of the ester is below 150°, reflux the mixture gently ; if the b.p. is above 150° heat the mixture, with frequent shaking at first, in an oil bath at about 150°. If the 3 : 5-dinitrobenzoic acid dissolves within 15 minutes, heat the mixture for 30 minutes, otherwise 60 minutes heating is required. Allow the reaction mixture to cool, dissolve it in 25 ml. of ether, and extract thoroughly with 5 per cent. sodium carbonate solution (*ca.* 25 ml.). Wash the ethereal solution with water, and remove the ether. Dissolve the residue (which is usually an oil) in 5 ml. of hot alcohol, add hot water cautiously until the 3 : 5-dinitrobenzoate commences to separate, cool and stir. Recrystallise the derivative from dilute alcohol : the yield is 0·1–0·2 g.

Successful results have been obtained (Renfrow and Chaney, 1946) with ethyl formate ; methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec.*-butyl and *iso*-amyl acetates ; ethyleneglycol diacetate ; ethyl monochloro- and trichloroacetates ; methyl, *n*-propyl, *n*-octyl and *n*-dodecyl propionates ; ethyl butyrate ; *n*-butyl and *n*-amyl valerates ; ethyl laurate ; ethyl lactate ; ethyl acetoacetate ; diethyl carbonate ; dimethyl and diethyl oxalates ; diethyl malonate ; diethyl adipate ; di-*n*-butyl tartrate ; ethyl phenylacetate ; methyl and ethyl benzoates ; methyl and ethyl salicylates ; diethyl and di-*n*-butyl phthalates. The method fails for vinyl acetate, *tert.*-butyl acetate, *n*-octadecyl propionate, ethyl and *n*-butyl stearate, phenyl, benzyl- and guaicol-acetate, methyl and ethyl cinnamate, diethyl sulphate and ethyl *p*-aminobenzoate.

Identification of the acidic components of simple esters. The following procedures may be regarded as alternative to that described above involving hydrolysis of the ester.

Anilides or p-toluidides of acids from esters. Esters are converted into the corresponding anilides or *p*-toluidides by treatment with anilino- or with *p*-toluidino-magnesium bromide, which are readily obtained from any simple Grignard reagent and aniline or *p*-toluidine:

$$ArNH_2 + RMgX \longrightarrow ArNHMgX + RH$$

$$2ArNHMgX + R'COOR'' \longrightarrow R'C(OMgX)(NHAr)_2 + Mg(OR'')X$$

$$\xrightarrow{H_2O} R'CONHAr + ArNH_2 + Mg(OH)X$$

This procedure is speedy, economical, and employs materials which are readily available. It is not satisfactory for esters of dibasic acids.

Add 4·0 g. (4·0 ml.) of pure aniline dropwise to a cold solution of ethyl magnesium bromide (or iodide) prepared from 1·0 g. of magnesium, 5·0 g. (3·5 ml.) of ethyl bromide (or the equivalent quantity of ethyl iodide), and 30 ml. of pure, sodium-dried ether. When the vigorous evolution of ethane has ceased, introduce 0·02 mol of the ester in 10 ml. of anhydrous ether, and warm the mixture on a water bath for 10 minutes; cool. Add dilute hydrochloric acid to dissolve the magnesium compounds and excess of aniline. Separate the ethereal layer, dry it with anhydrous magnesium sulphate and evaporate the ether. Recrystallise the residual anilide, which is obtained in almost quantitative yield, from dilute alcohol or other suitable solvent.

Alternatively, add a solution of 4·5 g. of *p*-toluidine in dry ether to the Grignard reagent prepared from 1·0 g. of magnesium as detailed above. Then introduce 1·0 g. (or 0·02 mol) of the ester and proceed as described for anilides.

N-*Benzylamides of acids from esters.* Esters are converted into the *N*-benzylamides of the corresponding acids by heating with benzylamine in the presence of a little ammonium chloride as catalyst:

$$RCOOR' + C_6H_5CH_2NH_2 \longrightarrow RCONHCH_2C_6H_5 + R'OH$$

The reaction (which is essentially the direct aminolysis of esters with benzylamine) proceeds readily when R' is methyl or ethyl. Esters of higher alcohols should preferably be subjected to a preliminary methanolysis by treatment with sodium methoxide in methanol:

$$RCOOR' + CH_3OH \xrightarrow{CH_3ONa} RCOOCH_3 + R'OH$$

N-Benzylamides are recommended when the corresponding acid is liquid and/or water-soluble so that it cannot itself serve as a derivative. The benzylamides derived from the simple fatty acids or their esters are not altogether satisfactory (see Table below); those derived from most hydroxy-acids and from polybasic acids or their esters are formed in good yield and are easily purified. The esters of aromatic acids yield satisfactory derivatives but the method must compete with the equally simple process of hydrolysis and precipitation of the free acid, an obvious derivative when the acid is a solid. The procedure fails with esters of keto, sulphonic, inorganic and some halogenated aliphatic esters.

Reflux a mixture of 1 g. of the ester, 3 ml. of benzylamine and 0·1 g. of powdered ammonium chloride for 1 hour in a Pyrex test-tube fitted with a short condenser. Wash the cold reaction mixture with water to remove the excess of benzylamine. If the product does not crystallise, stir it with a little water containing a drop or two of dilute hydrochloric acid. If crystallisation does not result, some unchanged ester may be present:

boil with water for a few minutes in an evaporating dish to volatilise the ester. Collect the solid *N*-benzylamide on a filter, wash it with a little light petroleum, b.p. 100–120°, and recrystallise it from dilute alcohol, ethyl acetate or acetone.

If the ester does not yield a benzylamide by this procedure, convert it into the methyl ester by refluxing 1 g. for 30 minutes with 5 ml. of absolute methanol in which about 0·1 g. of sodium has been dissolved. Remove the methanol by distillation and treat the residual ester as above.

The melting points of the *N*-benzylamides are collected in the following Table :

N-BENZYLAMIDES OF SOME CARBOXYLIC ACIDS

Formic	60°	Oxalic	223°	Benzoic	106°
Acetic	61	Malonic	142	*p*-Aminobenzoic	90
Propionic	44	Succinic	206	*m*-Hydroxybenzoic	142
n-Butyric	38	Glutaric	170	*m*-Nitrobenzoic	101
iso-Butyric	87	Adipic	189	*p*-Nitrobenzoic	142
n-Valeric	42	Pimelic	154	*o*-Iodobenzoic	110
iso-Valeric	54	Sebacic	167	Phenylacetic	122
n-Caproic	53	Carbonic	169	*m*-Toluic	75
Lauric	83	Ethylmalonic	138	*p*-Toluic	133
Palmitic	95	*n*-Butylmalonic	149	Anisic	132
Myristic	90	*d*-Tartaric	199	Salicylic	136
Stearic	97	*dl*-Tartaric	210	Anthranilic	125
Glycollic	104	*meso*-Tartaric	205	Cinnamic	225
Cyanoacetic	124	*d*-Malic	157	Hydrocinnamic	85
Crotonic	114	Maleic	150	Phthalic	179
2-Furoic	111	Fumaric	205	Terephthalic	266
Acrylic	237	Citric	170		
		Saccharic	201		

Acid hydrazides from esters. Methyl and ethyl esters react with hydrazine to give acid hydrazides :

$$RCOOCH_3 + H_2NNH_2 \longrightarrow RCONHNH_2 + CH_3OH$$

The hydrazides are often crystalline and then serve as useful derivatives. Esters of higher alcohols should be converted first to the methyl esters by boiling with sodium methoxide in methanol (see under *N*-benzylamides).

Place 1·0 ml. of hydrazine hydrate (*CAUTION :* corrosive chemical) in a test-tube fitted with a short reflux condenser. Add 1·0 g. of the methyl or ethyl ester dropwise (or portionwise) and heat the mixture gently under reflux for 15 minutes. Then add just enough absolute ethanol through the condenser to produce a clear solution, reflux for a further 2–3 hours, distil off the ethyl alcohol, and cool. Filter off the crystals of the acid hydrazide, and recrystallise from ethanol, dilute ethanol or from water.

The melting points of the hydrazides of some acids are collected in Table **III,85**.

In Table **III,106** the boiling points, densities and refractive indices of a number of selected esters are collected.

TABLE III,106. ALIPHATIC ESTERS

Ester	B.P.	$d_{4^\circ}^{20^\circ}$	$n_D^{20^\circ}$
Methyl formate	32°	0·974	1·344
Ethyl formate	53	0·923	1·360
n-Propyl formate	81	0·904	1·377
iso-Propyl formate	71	0·873	1·368
n-Butyl formate	106	0·892	1·389
iso-Butyl formate	98	0·876	1·386
sec.-Butyl formate	97	0·884	1·384
tert.-Butyl formate	83	—	—
n-Amyl-formate	131	0·885	1·400
iso-Amyl formate	124	0·882	1·398
n-Hexyl formate	154	0·879	1·407
*cyclo*Pentyl formate	138	1·000	1·432
*cyclo*Hexyl formate	161	0·994	1·443
Allyl formate	84	0·946	—
Methyl acetate	56	0·939	1·362
Ethyl acetate	77	0·901	1·372
n-Propyl acetate	101	0·887	1·384
iso-Propyl acetate	88	0·872	1·377
n-Butyl acetate	124	0·881	1·394
iso-Butyl acetate	116	0·871	1·390
sec.-Butyl acetate	112	0·872	1·389
tert.-Butyl acetate	97	0·867	1·386
n-Amyl acetate	148	0·875	1·402
iso-Amyl acetate	141	0·872	1·400
n-Hexyl acetate	169	0·872	1·409
*cyclo*Pentyl acetate	153	0·975	1·432
*cyclo*Hexyl acetate	172	0·970	1·442
Allyl acetate	104	0·928	1·404
Tetrahydrofurfuryl acetate	195	1·061	1·438
Furfuryl acetate	176	1·118	—
Methyl propionate	79	0·915	1·377
Ethyl propionate	98	0·892	1·384
n-Propyl propionate	122	0·882	1·393
iso-Propyl propionate	111	—	—
n-Butyl propionate	145	0·875	1·401
n-Amyl propionate	169	0·881	—
iso-Amyl propionate	160	0·859	1·412
n-Hexyl propionate	190	0·870	1·419
Allyl propionate	123	0·914	1·410
Methyl *n*-butyrate	102	0·898	1·387
Ethyl *n*-butyrate	120	0·879	1·392
n-Propyl *n*-butyrate	142	0·872	1·400
iso-Propyl *n*-butyrate	128	—	—
n-Butyl *n*-butyrate	165	0·869	1·406
n-Amyl *n*-butyrate	185	0·866	1·412
iso-Amyl *n*-butyrate	179	0·864	1·411
n-Hexyl *n*-butyrate	208	0·866	1·420
Allyl *n*-butyrate	142	0·902	1·416
Methyl *iso*-butyrate	91	0·888	1·383
Ethyl *iso*-butyrate	110	0·869	1·387

TABLE III,106. ALIPHATIC ESTERS (*continued*)

Ester	B.P.	$d_{4°}^{20°}$	$n_D^{20°}$
n-Propyl *iso*-butyrate	134°	0·864	1·396
iso-Propyl- *iso*-butyrate	121	—	—
n-Butyl *iso*-butyrate	156	0·862	1·402
Methyl *n*-valerate	127	0·890	1·397
Ethyl *n*-valerate	144	0·874	1·400
n-Propyl *n*-valerate	164	0·870	1·407
iso-Propyl *n*-valerate	154	0·858	1·401
n-Butyl *n*-valerate	184	0·868	1·412
Methyl *iso*-valerate	116	0·881	1·393
Ethyl *iso*-valerate	133	0·865	1·396
n-Propyl *iso*-valerate	156	0·862	1·403
n-Butyl *iso*-valerate	176	0·861	1·409
iso-Butyl *iso*-valerate	171	0·853	1·406
Methyl *n*-caproate (*n*-hexoate)	149	0·885	1·405
Ethyl *n*-caproate	168	0·871	1·407
n-Propyl *n*-caproate	187	0·867	1·417
n-Butyl *n*-caproate	208	0·865	1·421
n-Amyl *n*-caproate	226	0·863	1·426
Methyl *n*-heptoate (oenanthiate)	171	0·882	1·412
Ethyl *n*-heptoate	186	0·870	1·413
n-Propyl *n*-heptoate	208	0·866	1·421
n-Butyl *n*-heptoate	226	0·864	1·426
Methyl *n*-octoate (*n*-caprylate)	192	0·878	1·417
Ethyl *n*-octoate	206	0·869	1·418
Methyl pelargonate (*n*-nonoate)	214	—	—
Ethyl pelargonate	227	0·866	1·422
Methyl *n*-decoate (caprate)	228	0·873	1·426
Ethyl *n*-decoate	242	0·865	1·426
n-Propyl *n*-decoate	115°/5 mm.	0·862	1·428
n-Butyl *n*-decoate	123°/4	0·861	1·430
Methyl *n*-dodecanoate (laurate)	262	0·870	1·432
Ethyl *n*-dodecanoate	273	0·862	1·431
n-Propyl *n*-dodecanoate	140°/4	0·862	1·434
n-Butyl *n*-dodecanoate	154°/5	0·860	1·436
Methyl stearate	M.p. 39	—	—
Ethyl stearate	M.p. 33	—	—
Methyl chloroacetate	129	1·234	1·422
Ethyl chloroacetate	142	1·150	1·422
Methyl dichloroacetate	143	1·377	1·443
Ethyl dichloroacetate	156	1·283	1·438
Methyl trichloroacetate	152	1·488	1·457
Ethyl trichloroacetate	164	1·380	1·450
Methyl bromoacetate	144 (d)	—	—
Ethyl bromoacetate	169	1·506	1·451

TABLE III,106. ALIPHATIC ESTERS (*continued*)

Ester	B.P.	$d_{4°}^{20°}$	$n_D^{20°}$
Methyl iodoacetate	170°	—	—
Ethyl iodoacetate	180	1·818*	1·508*
Methyl chlorocarbonate (chloroformate)	73	1·223	1·387
Ethyl chlorocarbonate	94	1·136	1·397
n-Propyl chlorocarbonate	115	1·090	1·404
n-Butyl chlorocarbonate	138	1·079	1·412
Methyl carbonate	90	1·071	1·369
Ethyl carbonate	126	0·976	1·384
n-Propyl carbonate	165	0·943	1·400
n-Butyl carbonate	205	0·925	1·412
iso-Butyl carbonate	188	0·914	1·407
Methyl crotonate	119	0·946	1·425
Ethyl crotonate	137	0·918	1·425
n-Propyl crotonate	157	0·908	1·428
n-Butyl crotonate	55°/4 mm.	0·899	1·432
n-Amyl crotonate	72°/5	0·894	1·436
iso-Amyl crotonate	60°/4	0·891	1·434
Methyl lactate	145	1·089	1·414
Ethyl lactate	154	1·030	1·415
Methyl glycollate	151	1·166	—
Ethyl glycollate	160	1·082	—
Methyl furoate	181	1·180	1·486
Ethyl furoate	197 (M.p. 34)	1·117†	1·480
Methyl orthoformate	105	0·968	1·379
Ethyl orthoformate	143	0·893	1·390
n-Propyl orthoformate	91°/17	0·879	1·407
n-Butyl orthoformate	127°/16	0·871	1·416
Ethyleneglycol diformate	177	1·229	—
Ethyleneglycol diacetate	190	1·104	1·415
Methyl "cellosolve" acetate	144	1·088	—
"Cellosolve" acetate	156	0·976	—
"Carbitol" acetate	217	1·013	—
n-Butyl "carbitol" acetate	246	0·983	—
Trimethyleneglycol diacetate	210	1·069	—
Propyleneglycol diacetate	191	1·059	1·417
α-Monoacetin (glycerol 1-acetate)	158°/15	1·206	1·416
Diacetin (mixture of αα and αβ)	143°/12	1·180	—
Triacetin (glycerol triacetate)	153°/22	1·161	—
Methyl oxalate	M.p. 54	—	—
Ethyl oxalate	183	1·079	1·410
n-Propyl oxalate	212	1·019	1·416
iso-Propyl oxalate	191	0·995	1·413
n-Butyl oxalate	241	0·987	1·423
n-Amyl oxalate	139°/9	0·966	1·429
iso-Amyl oxalate	127°/7	0·961	1·427

* (13°) † Values at 21° with supercooled liquid.

TABLE III,106. ALIPHATIC ESTERS (*continued*)

Ester	B.P.	$d_{4^\circ}^{20^\circ}$	$n_D^{20^\circ}$
Methyl malonate	179°	1·119	1·420
Ethyl malonate	197	1·055	1·414
Methyl succinate	195	1·120	1·420
Ethyl succinate	218	1·042	1·420
n-Propyl succinate	102°/3 mm.	1·006	1·425
iso-Propyl succinate	82°/3	0·985	1·418
n-Butyl succinate	120°/3	0·977	1·430
iso-Butyl succinate	116°/4	0·968	1·427
n-Amyl succinate	129°/2	0·960	1·434
iso-Amyl succinate	130°/4	0·958	1·434
Allyl succinate	104	1·051	1·452
Methyl glutarate	109°/21	1·087	1·424
Ethyl glutarate	118°/15	1·023	1·424
Methyl adipate	121°/17	1·063	1·428
Ethyl adipate	134°/17	1·009	1·428
n-Propyl adipate	146°/9	0·981	1·431
iso-Propyl adipate	120°/6	0·966	1·425
n-Butyl adipate	159°/17	0·945	1·435
n-Amyl adipate	186°/10	0·948	1·439
iso-Amyl adipate	184°/13	0·945	1·437
Methyl pimelate	128°/16	1·038	1·431
Ethyl pimelate	149°/18	0·993	1·430
Methyl suberate	120°/6	1·024	1·434
Ethyl suberate	131°/5	0·981	1·432
n-Propyl suberate	165°/8	0·962	1·435
n-Butyl suberate	176°/4	0·948	1·439
Methyl azelate	156°/20	1·007	1·436
Ethyl azelate	291	0·973	1·435

TABLE III,106. ALIPHATIC ESTERS (*continued*)

Ester	B.P.	M.P.	$d_{4^\circ}^{20^\circ}$	$n_D^{20^\circ}$
Methyl sebacate	293°	27°	—	—
Ethyl sebacate	307	—	0·964	1·437
n-Propyl sebacate	179°/5 mm.	—	0·950	1·439
Methyl maleate	201	—	1·150	1·442
Ethyl maleate	220	—	1·066	1·440
n-Propyl maleate	126°/12	—	1·025	1·443
n-Butyl maleate	147°/12	—	0·994	1·445
Methyl fumarate	193	102	—	—
Ethyl fumarate	214	—	1·052	1·441
n-Propyl fumarate	110°/5	—	1·013	1·444
n-Butyl fumarate	139°/5	—	0·987	1·447
Methyl mesaconate	205	—	1·120	1·454
Ethyl mesaconate	225	—	1·043	1·448
Methyl citraconate	210	—	1·112	1·448
Ethyl citraconate	228	—	1·041	1·444
Methyl *d*-tartrate	280	61	—	—
Ethyl *d*-tartrate	280	18	1·203	1·447
n-Propyl *d*-tartrate	297	—	1·139	—
n-Butyl *d*-tartrate	200°/18	22	—	—
Methyl *dl*-tartrate	282	90	—	—
Ethyl *dl*-Tartrate	280	18	1·203	1·447
n-Propyl *dl*-tartrate	286	25	—	—
n-Butyl *dl*-tartrate	320	—	1·086	—
Methyl malate	242	—	1·233	1·442
Ethyl malate	253	—	1·129	1·436
Methyl mucate	—	167	—	—
Ethyl mucate	—	164	—	—
Methyl citrate	—	76	—	—
Ethyl citrate	294	—	1·137	1·466

ALIPHATIC AMIDES

Amides of aliphatic acids may be prepared:—

1. By the dehydration of the ammonium salt of the corresponding acid by heat or by distillation, for example:

$$\underset{\text{Ammonium acetate}}{CH_3COONH_4} \longrightarrow \underset{\text{Acetamide}}{CH_3CONH_2} + H_2O$$

An excess of acetic acid is usually added before heating in order to repress the hydrolysis (and also the thermal dissociation) of the ammonium acetate, thus preventing the escape of ammonia. The excess of acetic acid, together with the water, is removed by slow fractional distillation. The method is rarely used except for the preparation of acetamide.

2. By heating the acid or its ammonium salt with urea:

$$\underset{\text{Acetic acid}}{CH_3COOH} + \underset{\text{Urea}}{NH_2CONH_2} \longrightarrow \underset{\text{Acetamide}}{CH_3CONH_2} + \underset{\text{Carbamic Acid}}{NH_2COOH} \ (\longrightarrow CO_2 + NH_3)$$

The reaction commences at about 120°: the carbamic acid formed decomposes immediately into carbon dioxide and ammonia. The latter may form the ammonium salt with unreacted acid; the ammonium salt also reacts with urea at temperatures above 120° to yield the amide:

$$CH_3COONH_4 + NH_2CONH_2 \longrightarrow CH_3CONH_2 + CO_2 + 2NH_3$$

This reaction is applicable to many aliphatic acids and their ammonium salts.

3. By the action of concentrated aqueous ammonia solution upon esters. This process is spoken of as **ammonolysis** of the ester, by analogy with hydrolysis applied to a similar reaction with water. If the amide is soluble in water, *e.g.*, acetamide, it may be isolated by distillation, for example:

$$\underset{\text{Ethyl acetate}}{CH_3COOC_2H_5} + NH_3 \longrightarrow \underset{\text{Acetamide}}{CH_3CONH_2} + C_2H_5OH$$

Sparingly soluble amides crystallise out from the reaction mixture upon standing, for example:

$$\underset{\text{Dimethyl succinate}}{\begin{matrix}CH_2COOCH_3\\|\\CH_2COOCH_3\end{matrix}} + 2NH_3 \longrightarrow \underset{\text{Succinamide}}{\begin{matrix}CH_2CONH_2\\|\\CH_2CONH_2\end{matrix}} + 2CH_3OH$$

4. By the action of ammonia upon the acid chloride. The acid chloride need not be isolated, and can be obtained either by warming the acid with phosphorus trichloride until action ceases and then pouring off the crude acid chloride from the phosphorous acid, or by refluxing the acid with excess of thionyl chloride, removing the excess of the reagent by fractional distillation or by heating on a water bath. The acid chloride is then added dropwise to a well-stirred concentrated ammonia solution cooled in a freezing mixture of ice and salt. The mixture is allowed to stand overnight and the amide crystallises out. The amides of acetic, propionic and butyric acids are soluble in water and must be isolated by evaporating to dryness and extracting the residue with absolute ethyl alcohol. The following example is given:

$$\underset{n\text{-Caproic acid}}{CH_3(CH_2)_4COOH} \xrightarrow{SOCl_2} CH_3(CH_2)_4COCl \xrightarrow{NH_3} \underset{n\text{-Caproamide}}{CH_3(CH_2)_4CONH_2}$$

III,107. ACETAMIDE (*from Ammonium Acetate or from Acetic Acid*)

1. *Ammonium acetate method.* Place 77 g. of ammonium acetate and 84 g. (80 ml.) of glacial acetic acid in a 250 ml. round-bottomed flask (1)

and add a few chips of porous porcelain. Equip the flask with a fractionating column (2) carrying a thermometer and leading to a condenser set for downward distillation (Fig. *II*, *16*, 1). Heat the flask, preferably in an air bath (Fig. *II*, *5*, 3), so that the mixture boils very gently and the vapours do not rise appreciably in the fractionating column. After one hour increase the heat slightly so that the water formed in the reaction and a part of the acetic acid distils off very slowly at a uniform rate : collect the distillate in a 100 ml. measuring cylinder. The temperature rises to about 110° and remains at 110–112° during 2·5 hours ; 85 ml. (90 g.) of liquid are collected. The temperature may rise to 115° towards the end of the distillation, but soon drops below 100°, indicating that all the acetic acid has been removed. The residue in the flask crystallises completely upon cooling ; it consists of almost pure acetamide and melts at 78° after drying upon a porous tile. The yield of crude acetamide is 68 g. Redistil the crude amide from a 100 ml. distilling (or Claisen) flask equipped with an air condenser. There is a small low boiling point fraction (b.p. up to 195°) consisting of the " hold-up " of the fractionating column, and the acetamide passes over at 195–230°, largely at 215°. The yield of pure colourless acetamide, m.p. 81°, is 57 g.

The acetamide often contains a minute amount of impurity having an odour resembling mice excrement ; this can be removed by washing with a small volume of a 10 per cent. solution of ethyl alcohol in ether or by recrystallisation. Dissolve 5 g. of impure acetamide in a mixture of 5 ml. of benzene and 1·5 ml. of dry ethyl acetate ; warm on a water bath until all is dissolved and cool rapidly in ice or cold water. Filter off the crystals, press between filter paper and dry in a desiccator. The unpleasant odour is absent and the pure acetamide melts at 81°. Beautiful large crystals may be obtained by dissolving the acetamide (5 g.) in warm methyl alcohol (4 ml.), adding ether (40 ml.) and allowing to stand.

Notes.

(1) If desired, the ammonium acetate may be prepared by adding to 60 g. (57 ml.) of glacial acetic acid, contained in a large dish and gently warmed upon a water bath, solid ammonium carbonate (about 66 g. are required) with stirring until all the acid is neutralised ; this may be detected by diluting a sample with a little water and testing with litmus. Add a further 84 g. (80 ml.) of glacial acetic acid to produce a mixture equivalent to that employed in the experiment.

(2) The fractionating column employed by the author was of the Hempel type (Fig. *II*, *15*, 3). The dimensions were : total length, 46 cm. ; diameter of column, 20 mm. ; diameter of lower end, 10 mm. ; effective length of column, *i.e.*, below the side arm, 31 cm. ; length filled with hollow glass rings, $\frac{1}{4} \times \frac{1}{4}''$, 26 cm. Alternatively, an all-glass Dufton column (Fig. *II*, *15*, 2) may be employed.

2. *Urea method.* Place 25 g. of glacial acetic acid and 25 g. of urea in a 100 ml. Claisen flask. Fit an air condenser into the short neck and a 360° thermometer (with bulb in the mixture and 1 cm. from the bottom of the flask) into the long neck ; close the side arm with a small cork. Tilt the flask at an angle of about 30° from the vertical so that liquid does not collect in the side arm (compare Fig. *III*, *31*, 1). Heat the mixture gently either on a wire gauze or in an air bath (Fig. *II*, *5*, 3). When the urea melts, shake the flask gently in order to mix the acid and urea layers. Gradually raise the temperature so that the liquid *just* refluxes in the condenser. The temperature is about 150° after 30 minutes and a white

solid (probably ammonium carbamate) commences to form in the condenser: push the solid back into the flask by means of a stout glass rod when complete blocking of the condenser appears likely. Continue the heating until the temperature of the liquid is 195–200°; this temperature is attained after a heating period of 3–3·5 hours. Both carbon dioxide and ammonia are evolved. Allow the apparatus to cool and rearrange it for distillation. Heat the flask slowly at first; some ammonium carbamate first sublimes into the air condenser. When the acetamide just reaches the condenser, stop the distillation momentarily, replace the condenser by another of similar size and continue the distillation. Collect the acetamide at 200–216° (most of it passes over at 214–216°); if it crystallises in the condenser, it may be melted by the cautious application of a flame. The yield of almost pure, colourless acetamide, m.p. 80·5°, is 22 g. It may be recrystallised, if desired, as detailed under 1.

III,108. ACETAMIDE (*from Ethyl Acetate*)

Mix 44 g. (49 ml.) of pure ethyl acetate and 90 ml. of concentrated ammonia solution (sp. gr. 0·88) in a 250 ml. distilling flask. Place a cork in the neck of the flask and close the side arm (use a small cork or insert into a hole bored part of the way through a larger cork or a short length of rubber tubing closed with a screw clip). Allow the mixture to stand with occasional shaking until it becomes homogeneous (1–2 days: a longer period of standing is not harmful). Arrange the flask for distillation in the fume cupboard using the assembly of Fig. *II*, *13*, 1, but attach the side arm of the filter flask to a device (Fig. *II*, *8*, 1, *a*, *b* or preferably *c*) for the absorption of the ammonia evolved in the first part of the distillation. Distil (best with the aid of an air bath, Fig. *II*, *5*, 3) somewhat rapidly (in order to reduce the losses due to the hydrolysis of the acetamide) until the temperature rises to 170–180°; empty the water in the jacket of the Liebig condenser when the temperature reaches about 135°. Allow the liquid remaining in the flask to cool somewhat and pour it while still fluid into a dry 100 ml. distilling flask attached to an air condenser; use a beaker as a receiver. The liquid solidifies completely on cooling and melts at 79–80° after spreading on a porous tile; it is almost pure acetamide and weighs 25 g. Upon distillation with a naked flame, it passes over almost completely at 216° (1) and solidifies upon cooling to a colourless crystalline solid, m.p. 81°. The yield of pure acetamide is 24 g.

Note.

(1) If the acetamide crystallises in the condenser, it may be melted by the cautious application of a flame.

Cognate Preparation

Succinamide. Add 5 g. (4·8 ml.) of dimethyl succinate to 25 ml. of concentrated ammonia solution (sp. gr. 0·88) in a 100 ml. conical flask. Cork the flask and shake the contents for a few minutes: allow to stand for 24 hours with occasional shaking. Filter off the crystals of succinamide, and wash with a little cold water. Recrystallise from a little hot water. Dry in the steam oven and determine the m.p. The yield is 3·5 g. Pure succinamide melts at 254° with decomposition.

III,109. *n*-CAPROAMIDE

Fit a reflux condenser into the short neck of a 125 ml. Claisen flask, a separatory funnel into the long neck, and plug the side arm with a small cork (compare Fig. *III, 31,* 1). Place 58 g. (62 ml.) of commercial *n*-caproic acid (1) in the flask and heat on a water bath. Add 75 g. (46 ml.) of redistilled thionyl chloride through the separatory funnel during 45 minutes; shake the flask from time to time to ensure thorough mixing. Reflux the mixture for 30 minutes. Arrange the apparatus for distillation from an air bath (Fig. *II, 5,* 3); the excess of thionyl chloride passes over first, followed by *n*-caproyl chloride at 145–155° (mainly at 150–155°). The yield of acid chloride is 56 g.

Place 125 ml. of concentrated ammonia solution (sp. gr. 0·88) in a 600 ml. beaker and surround the latter with crushed ice. Stir the ammonia solution mechanically, and introduce the *n*-caproyl chloride slowly by means of a suitably supported separatory funnel with bent stem. The rate of addition must be adjusted so that no white fumes are lost. The amide separates immediately. Allow to stand in the ice water for 15 minutes after all the acid chloride has been introduced. Filter off the amide at the pump; use the filtrate to assist the transfer of any amide remaining in the beaker to the filter (2). Spread the amide on sheets of filter or drying paper to dry in the air. The crude *n*-caproamide (30 g.) has m.p. 98–99° and is sufficiently pure for conversion into the nitrile (Section **III,112**) (3). Recrystallise a small quantity of the amide by dissolving it in the minimum volume of hot water and allowing the solution to cool; dry on filter paper in the air. Pure *n*-caproamide has m.p. 100°.

Notes.

(1) Improved yields may be obtained by first drying the acid either by adding a little anhydrous magnesium or calcium sulphate or by adding about 45 per cent. of its weight of benzene and distilling through a short column until the temperature of the vapour reaches 100° (compare n-*Valeric Acid*, Section III, 84, *Note* (3)).

(2) The filtrate will deposit small amounts of *n*-caproamide upon concentration to half its original volume.

(3) The process is of general application for higher (*i.e.*, $> C_8$) fatty acids.

III,110. REACTIONS AND CHARACTERISATION OF ALIPHATIC AMIDES

The student should carry out the following simple experiments with acetamide or with any other aliphatic amide, *e.g.*, *n*-caproamide; they illustrate some of the general reactions of primary aliphatic amides.

(i) Boil 0·5 g. of acetamide with 3 ml. of 10 per cent. sodium hydroxide solution. Note that ammonia is evolved. Acidify and test for acetic acid in the solution.

$$CH_3CONH_2 + NaOH \longrightarrow CH_3COONa + NH_3$$

(ii) Boil 0·5 g. of acetamide with 3 ml. of dilute hydrochloric acid (1 : 1) or, better, with 10 per cent. sulphuric acid. Observe that acetic acid is evolved.

$$CH_3CONH_2 + HCl + H_2O \longrightarrow CH_3COOH + NH_4Cl$$

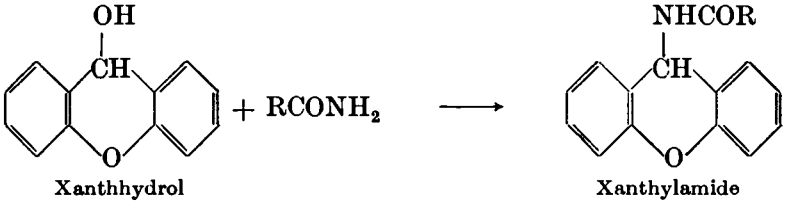
(iii) Dissolve 1 g. of acetamide in 2 ml. of water, add about 0·1 g. of yellow mercuric oxide, and warm gently. The mercuric oxide passes into solution, and a water-soluble, non-ionic mercury derivative is produced (compare Section **IV,189**) :

$$2CH_3CONH_2 + HgO \longrightarrow (CH_3CONH)_2Hg + H_2O$$

Characterisation

Aliphatic amides may be hydrolysed by boiling with 10 per cent. sodium hydroxide solution to the corresponding acid (as the sodium salt) : the alkaline solution should be acidified with dilute sulphuric acid; any water-soluble acid may then be distilled from the solution. Alternatively, hydrolysis may be effected with 10–20 per cent. sulphuric acid. The resulting aliphatic acid (usually a liquid) may be characterised as detailed in Section **III,85.**

Crystalline derivatives may be prepared with xanthhydrol (9-hydroxyxanthen), but the reagent is comparatively expensive. Xanthhydrol reacts with primary amides with the formation of crystalline **xanthylamides** or **9-acylamidoxanthens :**



Xanthhydrol Xanthylamide

Commercial xanthhydrol may be used, but the pure white product, m.p. 120–121°, obtained by the reduction of xanthone with sodium amalgam (Section **VII,16**) gives better results.

1. **Xanthylamides.** Dissolve 0·25 g. of xanthhydrol in 3·5 ml. of glacial acetic acid ; if an oil separates (as is sometimes the case with commercial material), allow to settle for a short time and decant the supernatant solution. Add 0·25 g. of the amide, shake and allow to stand. If a crystalline derivative does not separate in about 10 minutes, warm on a water bath for a period not exceeding 30 minutes, and allow to cool. Filter off the solid xanthylamide (9-acylamidoxanthen) and recrystallise it from dioxan-water or from acetic acid-water, dry at 80° for 15 minutes and determine the m.p.

Some amides do not dissolve in glacial acetic acid ; in such cases a mixture of 2 ml. of glacial acetic acid and 3 ml. of water may be used as a solvent for the reaction.

Di- and tri-chloroacetamide, oxamide, guanidine, and cyanoguanidine (dicyanodiamide) do not give satisfactory results.

The melting points of the xanthylamides of a number of aliphatic primary amides are collected in Table **III,110.**

TABLE III,110. PRIMARY ALIPHATIC AMIDES

Amide	M.P.	Xanthylamide
Formamide	2°(b.p.193°d.)	184°
Acetamide	82°	245°
Propionamide	79°	214°
n-Butyramide	115°	187°
iso-Butyramide	129°	211°
n-Valeramide	106°	167°
iso-Valeramide	136°	183°
n-Caproamide	101°	160°
n-Heptamide	96°	154°
n-Octamide	107°	148°
Palmitamide	106°	142°
Stearamide	109°	141°
Furoamide	142°	210°
Methyl carbamate	54°	193°
Ethyl carbamate	49°	169°
Urea	132°	274°
Methyl urea	102°	230°
Succinamide	260°d.	275°
Succinimide	126°	246°
Chloroacetamide	120°	209°
Cyanoacetamide	120°	223°

ALIPHATIC CYANIDES (NITRILES)

Aliphatic nitriles (cyanides) may be prepared:—

1. By the dehydration of primary amides with phosphorus pentoxide or with thionyl chloride, for example:

$$\underset{\text{Acetamide}}{CH_3CONH_2} \xrightarrow{P_2O_5} \underset{\text{Acetonitrile (methyl cyanide)}}{CH_3CN} + H_2O$$

$$\underset{n\text{-Caproamide}}{2CH_3(CH_2)_4CONH_2} \xrightarrow{SOCl_2} \underset{n\text{-Capronitrile } (n\text{-amyl cyanide})}{2CH_3(CH_2)_4CN} + H_2SO_3 + 2HCl$$

2. By refluxing an alkyl halide with sodium or potassium cyanide in aqueous - alcoholic solution, for example:

$$\underset{n\text{-Butyl bromide}}{CH_3(CH_2)_2CH_2Br} + NaCN \longrightarrow \underset{n\text{-Butyl cyanide}}{CH_3(CH_2)_2CH_2CN} + NaBr$$

$$\underset{\text{Trimethylene dibromide}}{Br(CH_2)_3Br} + 2NaCN \longrightarrow \underset{\text{Trimethylene dicyanide}}{CN(CH_2)_3CN} + 2NaBr$$

The resulting nitrile contains a little (< 1 per cent.) of *iso*nitrile (*iso*cyanide); this may be removed by washing with concentrated hydrochloric acid.

III,111. ACETONITRILE

Attach a short Liebig condenser to a dry 250 ml. distilling flask; use a small conical flask as a receiver. Owing to the extremely hygroscopic character of phosphoric oxide (1), the latter must be weighed out and transferred to the flask as rapidly as possible. Wrap some glazed paper around a glass tube and insert it into the flask until the lower end enters the bulb; upon removing the glass tube, the paper roll expands and thus lines the neck of the distilling flask. Weigh out on pieces of glazed paper (using a rough balance) first 20 g. of acetamide, and then, *as rapidly as possible*, 30 g. of phosphorus pentoxide. Immediately transfer, with the aid of a spatula, the phosphoric oxide down the glazed paper cylinder into the distilling flask, then introduce the acetamide similarly, remove the paper, and at once cork the flask and mix the contents well by gentle shaking (2). Heat the flask cautiously with a small luminous flame kept in constant motion and applied uniformly over the bottom of the flask. A reaction, accompanied by much frothing, takes place. After the mixture has been heated for 4–5 minutes, distil the acetonitrile into the receiver using a somewhat larger luminous flame kept in constant motion around the flask. Add half the volume of water to the distillate, and then anhydrous potassium carbonate until the aqueous layer is saturated (about 9 g. of potassium carbonate are required for every 10 ml. of water); cool the flask in cold or ice water during the addition of the solid to prevent the loss of methyl cyanide by evaporation (3). Allow the excess of solid potassium carbonate to settle and decant the liquid to a small separatory funnel. Run off the lower carbonate layer, and transfer the upper layer through the mouth of the funnel to a small (25 ml.) distilling flask into which 2–3 g. of phosphorus pentoxide have been placed.

Fit a thermometer and small condenser to the flask, add 2–3 fragments of porous porcelain and distil slowly. Collect the fraction boiling at 79–82° as acetonitrile. The yield is 10 g.

Notes.

(1) Phosphorus pentoxide must be handled with great care since it produces painful burns if allowed to come in contact with the skin.

(2) Wet the papers thoroughly with water before throwing them away, as the residual phosphoric oxide may cause them to smoulder.

(3) The functions of the potassium carbonate are (*a*) to neutralise the acetic acid arising from the action of the phosphoric acid upon the acetamide, and (*b*) to "salt out" the otherwise soluble methyl cyanide as an upper layer.

III,112. *n*-AMYL CYANIDE (*n*-CAPRONITRILE) *

Place 29 g. of *n*-caproamide (Section **III,109**) into a 200 ml. distilling flask, and assemble the apparatus shown in Fig. *III*, *28*, 1. Remove the trap momentarily and introduce 45 g. (27·5 ml.) of redistilled thionyl chloride: no apparent reaction takes place in the cold. Warm the mixture on a water bath or by means of a small flame for 1 hour. Arrange the apparatus for distillation and distil off the excess of thionyl chloride (*i.e.*, until the temperature reaches about 90°) and allow to cool. When cold, transfer the residue to a 100 ml. distilling flask (1). Distil from an air bath (Fig. *II*, *5*, 3); the *n*-capronitrile passes over at 161–163° (2). The yield is 21 g.

Notes.

(1) If the residue is dark and contains some solid matter, it is advisable to add a little anhydrous ether, and to filter the ethereal extract into the 100 ml. distilling flask; the ether is removed first by distillation from a water bath using the apparatus of Fig. *II*, *13*, 1 or Fig. *II*, *13*, 4.

(2) The *n*-capronitrile is sometimes slightly turbid; the turbidity is readily removed by shaking with a little anhydrous calcium sulphate.

Cognate Preparation

***n*-Octonitrile.** Use *n*-octamide (*n*-caprylamide) and redistilled thionyl chloride in the proportion of 1 mol to 1·5 mols. Warm the mixture on a water bath for 1 hour, distil off the excess of thionyl chloride at atmospheric pressure, and distil the residual *n*-octonitrile under diminished pressure. B.p. 87°/10 mm. The yield is almost quantitative.

III,113. *n*-BUTYL CYANIDE (*n*-VALERONITRILE) †

Into a 1500 ml. round-bottomed flask place 97·5 g. of finely-powdered sodium cyanide (1), 125 ml. of water, and a few chips of porous porcelain. Attach a reflux condenser and warm on a water bath until all the sodium cyanide dissolves. Introduce a solution of 250 g. (196 ml.) of *n*-butyl bromide (Sections **III,35** and **III,37**) in 290 ml. of pure methyl alcohol, and reflux gently on a water bath for 28–30 hours. Cool to room temperature and remove the sodium bromide which has separated by filtration through a sintered glass funnel at the pump; wash the crystals with about 100 ml. of methyl alcohol. Transfer the filtrate and washings to

* From *n*-caproamide by $SOCl_2$ method.

† From *n*-butyl bromide and aqueous-alcoholic sodium cyanide.

a 1-litre round-bottomed flask, and distil off the methyl alcohol slowly from a water bath through an efficient fractionating column (*e.g.*, a Hempel or a modified Hempel column, a Widmer column, etc. ; see Section **II,17**). The temperature should not rise above 68–69°. Remove the fractionating column, add 500 ml. of water, connect the flask by means of a wide, bent delivery tube to a condenser set for downward distillation (Fig. *II*, *13*, 3, but without the thermometer), and distil the mixture from a wire gauze until no more oily drops pass over. The residue in the flask contains sodium bromide, some unreacted sodium cyanide, and high boiling by-products ; allow it to cool, pour it down the main drain of the laboratory (whilst a liberal stream of water is simultaneously run from the tap), wash the flask well with water and finally with a little methylated spirit.

Separate the upper layer of crude *n*-butyl cyanide (100 g.) from the distillate. Upon drying over anhydrous calcium chloride or magnesium sulphate and then distilling from a 200 ml. flask using an air bath or a wire gauze, it boils, for the most part, at 139–141°. A small fraction of low boiling point may be obtained ; this should be dried over anhydrous calcium chloride and redistilled, thus giving a little more *n*-butyl cyanide. The resulting nitrile contains a small quantity (< 1 per cent.) of *n*-butyl *iso*-cyanide, to which the unpleasant odour is due ; it is, however, quite satisfactory for most purposes, *e.g.*, for conversion into *n*-valeric acid (Section **III,83**).

The *iso*-nitrile may be removed by the following procedure. Shake the crude (undistilled) *n*-butyl cyanide twice with about half its volume of concentrated hydrochloric acid and separate carefully after each washing ; then wash successively with water, saturated sodium bicarbonate solution and water. Dry with anhydrous calcium chloride or anhydrous calcium sulphate, and distil. Collect the pure *n*-butyl cyanide at 139–141°. If a fraction of low boiling point is obtained (because of incomplete drying), dry it again with anhydrous calcium sulphate and redistil. The yield is 95 g.

Note.

(1) *Sodium cyanide is very poisonous and must be handled with great care.* The hands should be washed immediately after using it. All the residual solutions containing alkali cyanides must be emptied into the main drain of the laboratory and washed down with a liberal supply of water ; they should never be treated with acid.

COGNATE PREPARATION

***n*-Hexyl cyanide.** Use 30 g. of sodium cyanide dissolved in 40 ml. of water ; 82 g. (70 ml.) of *n*-hexyl bromide (Section **III,37**) in 150 ml. of methyl alcohol. Remove the methyl alcohol through an efficient fractionating column, add 500 ml. of water, and separate the upper layer of crude nitrile. Purify the crude *n*-hexyl cyanide by the hydrochloric acid method. B.p. 182–184°. Yield : 40 g.

III,114. TRIMETHYLENE DICYANIDE (GLUTARONITRILE)

Fit a 2-litre round-bottomed flask with a two-holed stopper carrying a separatory funnel and a reflux condenser (Fig. *III*, *71*, 1). Place 147 g. of finely-powdered sodium cyanide and 150 ml. of water in the flask and

heat on a water bath until most of the solid passes into solution. Add a solution of 250 g. (126 ml.) of trimethylene dibromide (Section **III,35**) in 500 ml. of rectified spirit through the separatory funnel over a period of 30 minutes. Reflux the mixture on a water bath for 35 hours ; then remove the solvent (compare Fig. *III, 35,* 1), using a boiling water bath. The residue in the flask consists of sodium bromide, unreacted sodium cyanide and trimethylene cyanide ; the last-named alone is soluble in ethyl acetate. Extract the residue with 200 ml. of ethyl acetate. Filter the solution through a sintered glass funnel and wash the solid with about 50 ml. of ethyl acetate. Dry the filtrate, after removing the aqueous layer, with anhydrous magnesium or calcium sulphate, distil off the ethyl acetate at atmospheric pressure (about 245 ml. are recovered), allow to cool somewhat, and distil the liquid under reduced pressure. Collect the trimethylene dicyanide at 139–140°/8 mm. The yield is 95 g.

III,115. REACTIONS AND CHARACTERISATION OF ALIPHATIC NITRILES (CYANIDES)

Aliphatic nitriles are usually liquids or low melting point solids. The most important reaction of a nitrile is its hydrolysis either by an alkali or by an acid to the corresponding aliphatic acid : characterisation of the acid enables the identity of the original nitrile to be established.

(i) **Hydrolysis with alkali.** When nitriles are treated with 20–40 per cent. sodium or potassium hydroxide solution, there is no reaction in the cold ; upon prolonged boiling hydrolysis proceeds comparatively slowly (compare primary amides which are rapidly hydrolysed) to the sodium salt of the acid and ammonia. The reaction is complete when ammonia is no longer evolved :

$$RCN + H_2O + NaOH \longrightarrow RCOONa + NH_3$$

The excess of alkali is then neutralised with dilute hydrochloric acid (phenolphthalein) and the solution is evaporated to dryness on the water bath. The acid may then be characterised as the S-benzyl-*iso*-thiuronium salt or as the *p*-bromophenacyl ester (Section **III,85**). In many instances the derivative may be prepared directly from the neutralised solution.

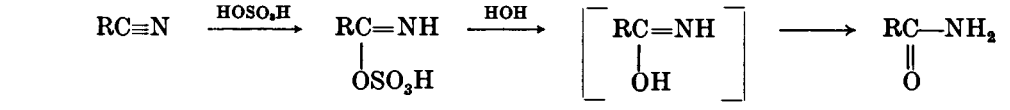
(ii) **Hydrolysis with acid.** Most nitriles are hydrolysed by boiling with 5–8 times the weight of 50–75 per cent. sulphuric acid under reflux for 2–3 hours :

$$2RCN + H_2SO_4 + 4H_2O \longrightarrow 2RCOOH + (NH_4)_2SO_4$$

The acid, if monobasic, can usually be distilled directly from the reaction mixture. If this procedure is not possible, the reaction mixture is poured into excess of crushed ice, and the acid is isolated by ether extraction or by other suitable means. The acid is then characterised (Section **III,85**). The addition of hydrochloric acid (as sodium chloride ; say 5 per cent. of the weight of sulphuric acid) increases the rate of the reaction.

For those nitriles which yield water-insoluble amides (*e.g.*, the higher alkyl cyanides), *hydrolysis to the amide* often leads to a satisfactory derivative. The hydration is effected by warming a solution of the nitrile in concentrated sulphuric acid for a few minutes, cooling and pouring

into water; an imino-sulphate is probably formed intermediately and this is hydrolysed:



Warm a solution of 0·5 g. of the nitrile in 2 ml. of concentrated sulphuric acid to 80–90° and allow the solution to stand for 5 minutes. Cool under the tap and pour the sulphuric acid solution into 20 ml. of cold water. Filter off the precipitated solid and stir it with 5 ml. of cold 5 per cent. sodium hydroxide solution. Collect the insoluble crude amide and recrystallise it from dilute alcohol.

For practice, the student should carry out both alkaline (compare Section **III,83**) and acid hydrolysis of acetonitrile, *n*-valeronitrile (*n*-butyl cyanide) and *n*-capronitrile (*n*-amyl cyanide).

(iii) Nitriles may also be identified by **reduction to primary amines** and conversion into substituted phenylthioureas. Reduction of a nitrile with sodium and alcohol yields the primary amine, which may be identified by direct conversion into a substituted phenylthiourea.

$$RCN + 2H_2 \xrightarrow[ROH]{Na+} RCH_2NH_2$$

Dissolve 1·0 g. of the nitrile in 20 ml. of absolute ethanol in a dry 200 ml. round-bottomed flask fitted with a reflux condenser. Add through the top of the condenser 1·5 g. of clean sodium (previously cut into small pieces) at such a rate that the reaction, although vigorous, remains under control. When all the sodium has reacted (10–15 minutes), cool the reaction mixture to about 20°, and add 10 ml. of concentrated hydrochloric acid dropwise through the condenser whilst swirling the contents of the flask vigorously: the final solution should be acid to litmus. Transfer to a 100 ml. distilling flask connected to a condenser, and distil off about 20 ml. of liquid (dilute ethanol). Cool the flask and fit a small dropping funnel into the neck of the distilling flask. Place 15 ml. of 40 per cent. sodium hydroxide solution in the dropping funnel, attach an adapter to the end of the condenser and so arrange it that the end dips into about 3 ml. of water contained in a 50 ml. conical flask. Add the sodium hydroxide solution dropwise and with shaking: a vigorous reaction ensues. When all the alkali has been added, separate the amine by distillation until the contents of the flask are nearly dry.

Add 0·5 ml. of phenyl *iso*thiocyanate to the distillate and shake the mixture vigorously for 3–4 minutes. If no derivative separates, crystallisation may be induced by cooling the flask in ice and "scratching" the walls with a glass rod. Filter off the crude product, wash it with a little 50 per cent. ethanol, and recrystallise from hot dilute alcohol. (See Table **III,123** for melting points of phenylthiourea derivatives of amines.)

The physical properties of a number of aliphatic nitriles (cyanides) are given in Table **III,115.**

TABLE III,115. ALIPHATIC NITRILES (CYANIDES)

Cyanide	Nitrile	B.P.	M.P.	$d_{4°}^{20°}$	$n_D^{20°}$
Methyl	Aceto-	81°	—	0·784	1·344
Ethyl	Propio-	97	—	0·783	1·366
n-Propyl	*n*-Butyro-	118	—	0·791	1·384
iso-Propyl	*iso*-Butyro-	108	—	—	—
n-Butyl	*n*-Valero-	141	—	0·799	1·397
iso-Butyl	*iso*-Valero-	131	—	0·788	—
n-Amyl	*n*-Capro-	162	—	0·805	1·407
iso-Amyl	*iso*-Capro-	154	—	0·803	1·406
n-Hexyl	*n*-Hepto (oenantho-)	183	—	0·810	1·414
n-Heptyl	*n*-Octo (caprylo-)	199	—	0·817*	1·422*
n-Octyl	*n*-Nono- (pelargono-)	224	—	0·822*	—
n-Nonyl	*n*-Decano- (caprino-)	244	—	0·829*	1·432*
n-Decyl	*n*-Undecano-	254	—	—	—
n-Undecyl	*n*-Dodecano- (lauro-)	275	—	0·827*	—
Vinyl	Acrylo-	78	—	0·806	1·391
Allyl	Vinylaceto-	118	—	0·838	1·406
Chloromethyl	Chloroaceto-	127	—	1·193	—
Methylene	Malono-	220	31°	—	—
Ethylene	Succino-	267d	54	—	—
Trimethylene	Glutaro-	286	9	0·988	1·429
Tetramethylene	Adipo-	295	—	0·962	1·439
Pentamethylene	Pimelo-	169°/15	—	0·945	1·441
Hexamethylene	Subero-	185°/15	—	0·933	1·445
Phenyl	Benzo-	189	—	1·006	1·528
Benzyl	Phenylaceto-	109°/15	—	1·016	1·523
Acetaldehyde cyanohydrin	α-Hydroxypropio-	183	—	0·988	—
Ethylene cyanohydrin	β-Hydroxypropio-	221	—	—	—
Trimethylene cyanohydrin	γ-Hydroxybutyro-	240	—	—	—
Trimethylene chlorocyanide	γ-Chlorobutyro-	197	1·079	—	—
Methyl cyanoacetate		200	—	1·101	—
Ethyl cyanoacetate		207	—	1·063	1·418
Furan-α-	Furo-	147	—	1·082	1·480

* 15°.

ALIPHATIC AMINES

Aliphatic amines may be prepared:—

1. By treatment of an amide with sodium hypobromite or sodium hypochlorite solution (or with the halogen and alkali), the amine of one less carbon atom is produced, the net result being the elimination of the carbonyl group. An example is:

$$\underset{\text{Acetamide}}{CH_3CONH_2} + Br_2 + 2NaOH \longrightarrow \underset{\text{Methylamine}}{CH_3NH_2} + 2NaBr + CO_2 + H_2O$$

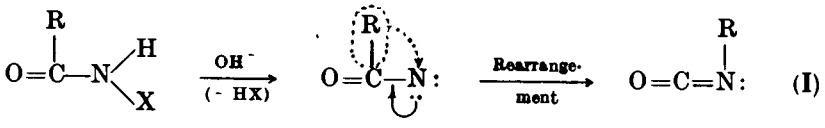
The conversion of an amide into an amine in this way is termed the **Hofmann reaction** or the **Hofmann rearrangement.**

The *mechanism* of the reaction probably involves the following stages:

(*a*) The formation of a *N*-haloamide:

$$RCONH_2 \longrightarrow RCONHX$$

(*b*) In the presence of alkali, hydrogen halide is eliminated producing presumably an electronically-deficient nitrogen fragment, which rearranges to the isocyanate (I):



(*c*) Hydrolysis of the isocyanate to the primary amine:

$$R—N=C=O + H_2O \longrightarrow RNH_2 + CO_2$$

The reaction is applicable to the preparation of amines from amides of aliphatic aromatic, aryl-aliphatic and heterocyclic acids. A further example is given in Section **IV,170** in connexion with the preparation of anthranilic acid from phthalimide. It may be mentioned that for aliphatic monoamides containing more than eight carbon atoms aqueous alkaline hypohalite gives poor yields of the amines. Good results are obtained by treatment of the amide (C > 8) in methanol with sodium methoxide and bromine, followed by hydrolysis of the resulting *N*-alkyl methyl carbamate:

$$RCONH_2 \xrightarrow[\text{in MeOH}]{Br_2,\ NaOMe} RNHCOOCH_3 \xrightarrow{OH^-} RNH_2$$

2. By the reduction of nitriles with sodium and absolute alcohol, for example:

$$\underset{n\text{-Butyl cyanide}}{CH_3(CH_2)_3CN} \xrightarrow{4H} \underset{n\text{-Amylamine}}{CH_3(CH_2)_3CH_2NH_2}$$

3. By the reduction of oximes with sodium and absolute ethyl alcohol, for example:

$$\underset{n\text{-Heptaldoxime}}{CH_3(CH_2)_5CH=NOH} \xrightarrow{4H} \underset{n\text{-Heptylamine}}{CH_3(CH_2)_5CH_2NH_2} + H_2O$$

$$\underset{\text{Methyl } n\text{-hexyl ketoxime}}{CH_3(CH_2)_5C(=NOH)CH_3} \xrightarrow{4H} \underset{\text{2-Amino-}n\text{-octane}}{CH_3(CH_2)_5CH(NH_2)CH_3} + H_2O$$

4. By the hydrolysis of dialkyl cyanamides with dilute sulphuric acid; this method gives pure **secondary amines.** The appropriate dialkyl cyanamide is prepared by treating sodium cyanamide (itself obtained in solution from

calcium cyanamide and aqueous sodium hydroxide solution) with an alkyl halide, for example :

$$CaNCN + 2NaOH \longrightarrow Na_2NCN + Ca(OH)_2$$

$$Na_2NCN + 2C_4H_9{}^{\alpha}Br \longrightarrow (C_4H_9{}^{\alpha})_2NCN + 2NaBr$$

$$\underset{\text{Di-}n\text{-butyl cyanamide}}{(C_4H_9{}^{\alpha})_2NCN} + 2H_2O \longrightarrow \underset{\text{Di-}n\text{-butylamine}}{(C_4H_9{}^{\alpha})_2NH} + CO_2 + NH_3$$

The above methods are of general application, but special procedures are available for individual amines depending upon the unique reactivity of formaldehyde. Thus when 2 parts by weight of formalin (*ca.* 35 per cent. formaldehyde) is heated with 1 part by weight of ammonium chloride at 104°, the main product is **methylamine hydrochloride** (methylammonium chloride). Allowing for the ammonium chloride recovered (about 35 per cent.), this corresponds roughly to the molecular ratios $2CH_2O : NH_4Cl$ and suggests the following mechanism of the reaction :

$$HCHO + NH_3,HCl \longrightarrow HCH(OH)NH_2(HCl) \longrightarrow CH_2{=}NH(HCl) + H_2O$$

$$CH_2{=}NH(HCl) + HCHO + H_2O \longrightarrow \underset{\text{Methylamine hydrochloride}}{CH_3NH_2,HCl} + HCOOH$$

If the methylamine hydrochloride in solution from the previous reaction be heated with a further quantity of formalin at 115°, **dimethylamine hydrochloride** (dimethylammonium chloride) may be isolated :

$$HCHO + NH_2CH_3,HCl \longrightarrow CH_2{=}N(CH_3),HCl + H_2O$$

$$CH_2{=}N(CH_3),HCl + HCHO + H_2O \longrightarrow \underset{\text{Dimethylamine hydrochloride}}{(CH_3)_2NH,HCl} + HCOOH$$

When ammonium chloride is heated to a higher temperature (160°) with a large excess of anhydrous formaldehyde (as paraformaldehyde), **trimethylamine hydrochloride** (trimethylammonium chloride) may be obtained :

$$3(HCHO)_3 + 2NH_4Cl \longrightarrow \underset{\text{Trimethylamine hydrochloride}}{2(CH_3)_3N,HCl} + 3CO_2 + 3H_2O$$

III,116. METHYLAMINE HYDROCHLORIDE (*from Acetamide*)

Place 25 g. of dry acetamide in a 350 ml. conical or flat-bottomed flask, and add 69 g. (23 ml.) of bromine (*CAUTION !*) : a deep red liquid is produced. Cool the flask in ice water and add 10 per cent. sodium hydroxide solution (about 210 ml.) in small portions and with vigorous shaking until the solution acquires a pale yellow colour. At this stage the bromoacetamide is present in the alkaline solution. If any solid should crystallise out, add a little water.

Assemble the apparatus shown in Fig. *III*, *56*, 1, using a 1-litre distilling flask ; replace the filter flask receiver by a small funnel attached to the end of the condenser by a short length of rubber tubing and dipping about 0·5 cm. below 100 ml. of dilute hydrochloric acid (1 : 1) contained in a beaker. Place a solution of 60 g. of sodium hydroxide in 150 ml. of water, together with a few fragments of porous porcelain, in the flask and the bromoacetamide solution in the separatory funnel. Warm the solution in the flask until the thermometer in the liquid reads 60-70°. Allow the bromoacetamide solution to run slowly into the flask at such a rate that the temperature does not rise above about 70° ; heat is evolved

in the reaction and if the temperature rises above 75° the flask should be surrounded momentarily by a bath of cold water. When all the solution has been added, maintain the temperature of the mixture in the flask for about 15 minutes at 65–70°; by this time the solution should be clear and colourless. Gently boil the solution and thus drive off the methylamine vapour into the dilute hydrochloric acid. As soon as the distillate is no longer alkaline (40–60 minutes), concentrate the hydrochloric acid solution by placing it in a 250 ml. distilling flask connected with a water condenser and distilling carefully from an air bath until about 25 ml. remains; then transfer the solution to an evaporating dish, evaporate to dryness on a water bath, and finally for a short time in an air oven at 100–105°. The yield of crude dry product (which is contaminated with some ammonium chloride) is about 24 g. Transfer the finely-powdered, dry solid to a 250 ml. round-bottomed flask fitted with a reflux condenser and cotton wool (or calcium chloride) guard tube. Add about 120 ml. of *absolute* ethyl alcohol (which dissolves only the methylamine hydrochloride) and boil the mixture for 10 minutes. Filter through a hot water funnel. Extract the residue with a further 50 ml. of boiling absolute alcohol and filter again. Cool the combined alcoholic extracts when colourless crystals of methylamine hydrochloride will separate out. Filter rapidly at the pump, and transfer the crystals (which are deliquescent) to a stoppered bottle. Evaporate the filtrate to about one third of the original volume, when a further crop of crystals will be obtained. Dry all the crystals in a desiccator. The yield is about 18 g.

III,117. METHYLAMINE HYDROCHLORIDE (*from Formalin*)

Place 250 g. of ammonium chloride and 500 g. of technical formaldehyde solution (formalin, 35–40 per cent. formaldehyde) in a 1-litre distilling flask: insert a thermometer dipping well into the liquid and attach a condenser for downward distillation. Heat the flask on a wire gauze or in an air bath *slowly* until the temperature reaches 104° and maintain the temperature at this point until no more distillate is collected (4–5 hours) (1). Cool the contents of the flask rapidly to room temperature and filter off the ammonium chloride (*ca.* 62 g.) which separates rapidly at the pump. Concentrate the filtrate to one half of the original volume on a water bath, when more ammonium chloride (*ca.* 19 g.) will crystallise out on cooling to room temperature. After filtration at the pump, evaporate on a water bath until a crystalline scum forms on the surface of the hot solution. Allow to cool and filter off the methylamine hydrochloride (about 96 g.) (2). Concentrate again on a water bath and thus obtain a second crop (about 18 g.) of methylamine hydrochloride. Evaporate the mother liquor as far as possible on a water bath and leave it in a vacuum desiccator over sodium hydroxide pellets for 24 hours; digest the semi-solid residue with chloroform (to remove the dimethylamine hydrochloride), filter off (2) the methylamine hydrochloride (about 20 g.) at the pump and wash it with a little chloroform. [Upon concentrating the chloroform solution to about half the original bulk, about 27 g. of dimethylamine hydrochloride may be obtained: the mother

liquor should be discarded.] Purify the crude methylamine hydrochloride by placing it together with 250 ml. of *absolute* alcohol in a 500 ml. round-bottomed flask fitted with a reflux condenser carrying a cotton wool (or calcium chloride) guard tube. Heat the mixture to boiling for about half an hour, allow the undissolved material to settle and decant the clear solution. Cool the solution when pure methylamine hydrochloride will separate : filter (2) and use the filtrate for another extraction. Four or five extractions are required to extract all the methylamine hydrochloride. The yield of recrystallised material is about 100 g.

Notes.

(1) The distillate weighs about 110 g. and contains methyl formate and methylal. If it is placed in a flask provided with a reflux condenser and a solution of 25 g. of sodium hydroxide in 40 ml. of water is added, the methyl formate is hydrolysed to sodium formate and the methylal separates on the surface. The latter may be removed, dried with anhydrous calcium chloride and distilled : about 30 g. of methylal, b.p. 37–42°, are obtained. If the aqueous layer is evaporated to dryness, about 25 g. of sodium formate are isolated.

(2) The best method of drying the precipitate of methylamine hydrochloride is by centrifuging ; the compound is hygroscopic.

III,118. DIMETHYLAMINE HYDROCHLORIDE

Proceed as in the preparation of methylamine hydrochloride (previous Section) using 200 g. of ammonium chloride and 400 g. of formalin, and heat the mixture at 104° until no more liquid distils. Cool to room temperature and filter off the ammonium chloride (*ca.* 50 g.) : add 300 g. of formalin to the filtrate, return the solution to the distilling flask, heat until the temperature reaches 115° and maintain it as nearly as possible at this temperature until no more liquid passes over (about 3–4 hours). Concentrate the residue in the distilling flask on a water bath until a scum appears on the surface of the hot liquid. Cool to room temperature and filter off the solid (*ca.* 32 g. ; impure methylamine hydrochloride containing about 25 per cent. of ammonium chloride). Pour back the filtrate into the distilling flask and heat to 120° until a sample of the liquid, on cooling, becomes semi-solid. Transfer it to a vacuum desiccator charged with sodium hydroxide pellets and leave it there for 2 days. Extract the residue with hot chloroform and filter ; on cooling, crystals of dimethylamine hydrochloride separate. A further crop can be obtained by evaporating the filtrate to about half its original volume. The yield is 120 g.

III,119. TRIMETHYLAMINE HYDROCHLORIDE

Mix 100 g. of ammonium chloride and 266 g. of paraformaldehyde in a 1-litre round-bottomed flask fitted with a long reflux condenser containing a wide inner tube (*ca.* 2 cm. diameter) ; the last-named is to avoid clogging the condenser by paraformaldehyde which may sublime. Immerse the flask in an oil bath and gradually raise the temperature. The mixture at the bottom of the flask liquefies between 85° and 105° and a vigorous evolution of carbon dioxide commences ; at once remove the burner beneath the oil bath and if the reaction becomes too violent remove

the oil bath also. Permit the reaction to proceed without further heating until the evolution of gas subsides (60–90 minutes); then raise the temperature of the bath to about 160° and maintain it at this temperature until the evolution of gas almost ceases (2·5–3·5 hours). The reaction is then complete.

When the reaction mixture has cooled somewhat, insert a separatory funnel into the neck of the flask and arrange the reflux condenser for downward distillation (as in Fig. *III*, *35*, 1); fit the lower end of the condenser into the neck of a distilling flask or a filter flask (1) and attach the side arm by means of rubber tubing to an inverted funnel immersed to a depth of 1 cm. in 190 ml. of concentrated hydrochloric acid in a beaker. All joints must fit well as trimethylamine is very volatile and can easily be lost. Place a solution of 220 g. of sodium hydroxide in 400 ml. of water in the separatory funnel and allow it to run slowly into the warm reaction mixture. The amine distils and collects largely in the hydrochloric acid. Finally, heat the mixture for about 15 minutes to ensure that all the trimethylamine has been expelled from the reaction flask. Evaporate the hydrochloric acid solution on a water bath; the trimethylamine hydrochloride gradually crystallises out and is filtered off from time to time (2); it is dried for a few minutes at 100-105° and preserved in a tightly stoppered bottle. The solid (*ca.* 14 g.) obtained by evaporation to dryness may be tinged slightly yellow. The yield is about 150 g. (3).

Notes.

(1) The object of the intermediate flask is to trap any water which may distil with the amine; this water is generally coloured yellow and if allowed to pass into the hydrochloric acid in the receiver will contaminate the product.

(2) The most satisfactory method of drying is by centrifuging: the salt is hygroscopic.

(3) The absence of ammonium chloride and methylamine hydrochloride may be shown by the complete solubility of the product in chloroform.

III,120. *n*-AMYLAMINE

Equip a three-necked 1-litre flask with a dropping funnel, an efficient mechanical stirrer and a reflux condenser (Fig. *II*, *7*, 11). Place 55 g. of clean sodium and 200 ml. of sodium-dried toluene in the flask, heat the mixture until the toluene commences to boil, and then stir the molten sodium vigorously thus producing an emulsion. Run in through the dropping funnel a mixture of 33 g. (41·5 ml.) of *n*-butyl cyanide (Section **III,113**) and 60 g. (76 ml.) of absolute ethyl alcohol during 1 hour. During the addition and the subsequent introduction of alcohol and of water, the stirring should be vigorous and the temperature adjusted so that the refluxing is continuous; the heat of reaction will, in general, be sufficient to maintain the refluxing. After the *n*-butyl cyanide solution has been added, introduce gradually a further 60 g. (76 ml.) of absolute alcohol. In order to destroy any residual sodium, treat the reaction mixture slowly with 40 g. (50 ml.) of rectified spirit and then with 20 g. of water. Steam distil the contents of the flask (compare Fig. *II*, *41*, 1) (about 2 hours) and add 40 ml. of concentrated hydrochloric acid to the distillate. Separate the toluene layer; distil the aqueous layer, which

contains alcohol and *n*-amylamine hydrochloride, until most of the alcohol is removed. Pour the contents of the flask into a large porcelain basin and evaporate to dryness on a water bath. Treat the resulting *n*-amylamine hydrochloride with a solution of 40 g. of sodium hydroxide in 200 ml. of water. Separate the *n*-amylamine layer, dry it by shaking with sodium hydroxide pellets (prolonged contact is required for complete drying), and distil. Collect the fraction boiling at 102–105° as pure *n*-amylamine. Dry the fraction of low boiling point again over sodium hydroxide and redistil; this gives an additional quantity of amine. The total yield is 30 g.

III,121. *n*-HEPTYLAMINE

In a 3-litre round-bottomed flask, equipped with a long (*ca.* 150 cm.) reflux condenser with wide (*ca.* 2·5 cm.) inner tube, place a solution of 64·5 g. of *n*-heptaldoxime (Section **III,76**) in 1 litre of "super-dry" ethyl alcohol (Section **II,47,5**) and heat on a water bath. Immediately the alcohol boils, remove the flask from the water bath and introduce 125 g. of sodium, cut in small pieces, as rapidly as possible through the condenser consistent with keeping the vigorous reaction under control. The last 30 g. of sodium melts in the hot mixture and may be added very rapidly without appreciable loss of alcohol or of amine. As soon as the sodium has completely dissolved (some warming may be necessary), cool the contents of the flask and dilute with 1250 ml. of water. At once equip the flask with a condenser set for downward distillation and arrange for the distillate to be collected in a solution of 75 ml. of concentrated hydrochloric acid in 75 ml. of water contained in a 3-litre flask. Continue the distillation as long as amine passes over. Towards the end of the reaction considerable frothing sets in; then add a further 750 ml. of water to the distillation flask. The total distillate is 2–2·2 litres and contains alcohol, water, and some unreacted oxime as well as the amine hydrochloride. Evaporate the solution under reduced pressure (20–30 mm.) on a water bath (compare Fig. *II*, *37*, 1); the amine hydrochloride will crystallise out in the flask. Cool the flask, attach a reflux condenser, and introduce 250 ml. of 40 per cent. potassium hydroxide solution. Rotate the flask to wash down the hydrochloride from the sides of the flask, cool the mixture to room temperature and transfer it to a separatory funnel. Run off the lower alkaline layer and add solid potassium hydroxide to the amine in the funnel. Again remove the lower aqueous layer, add more solid potassium hydroxide and repeat the process until no further separation of an aqueous layer occurs. Finally, transfer the amine to a small flask and leave it in contact with potassium hydroxide pellets for 24 hours. Decant the amine into a Claisen flask with fractionating side arm (the latter should be well-lagged) and distil. Collect the *n*-heptylamine at 153–157°. The yield is 40 g.

Cognate Preparation

2-Amino-*n*-octane. Convert methyl *n*-hexyl ketone (Section **III,71**) into the ketoxime, b.p. 106–108°/12 mm., as detailed for n-*Heptaldoxime* (Section **III,76**). Reflux a solution of 50 g. of the oxime in 200 ml. of

" super-dry " ethyl alcohol on a water bath whilst adding 75 g. of sodium ; introduce more alcohol (about 300 ml.) to maintain a vigorous reaction. When all the sodium has passed into solution, cool, dilute with 250 ml. of water and distil gently until the b.p. reaches 96° ; add a further 200 ml. of water and repeat the distillation to ensure the complete removal of the alcohol. The amine remains as a layer on the strongly alkaline solution : extract it with ether, dry the ethereal solution with sodium hydroxide or anhydrous calcium sulphate, remove the ether on a water bath, and distil the residue under diminished pressure. Collect the 2-amino-*n*-octane at 58–59°/13 mm. ; the b.p. under atmospheric pressure is 163–164°. The yield is 31 g.

III,122. DI-*n*-BUTYLAMINE

Equip a 1500 ml. three-necked flask with a reflux condenser and a mercury-sealed stirrer. Place 222 ml. of water and 44 g. of finely crushed ice in the flask and add slowly, with vigorous stirring, 67 g. of commercial calcium cyanamide (1). As soon as the solid is thoroughly suspended, fit a separatory funnel into the third neck of the flask and introduce through it a cold solution of 34 g. of sodium hydroxide in 67 ml. of water ; replace the funnel by a cork carrying a thermometer. Continue the vigorous stirring for 1 hour to complete the decomposition of the calcium cyanamide ; if the temperature rises above 25°, add a little more ice. Add to the resulting solution of sodium cyanamide a solution of 134 g. (105 ml.) of *n*-butyl bromide (Sections **III,35** and **III,37**) in 222 ml. of rectified spirit. Heat the mixture, with stirring on a water bath until it refluxes gently ; continue the refluxing and stirring for 2·5 hours. Replace the reflux condenser by one set for downward distillation and distil the mixture until 165–170 ml. of liquid are collected : stir during distillation. Cool the residue in the flask and filter it, with suction, through a Buchner or sintered glass funnel, and wash the residue with alcohol. Extract the filtrate, which separates into two layers, first with 90 ml. and then with 45 ml. of benzene. Dry the combined benzene extracts with anhydrous magnesium or calcium sulphate, and remove the benzene in a Claisen flask (compare Fig. *II*, *13*, 4). Finally distil under reduced pressure and collect the **di-*n*-butyl cyanamide**, $(C_4H_9^{\alpha})_2NCN$, at 147–151°/35 mm. The yield is 33 g.

Into a 750 ml. round-bottomed flask furnished with a reflux condenser place a solution of 34 g. (18·5 ml.) of concentrated sulphuric acid in 100 ml. of water : add 33 g. of di-*n*-butyl cyanamide and a few fragments of porous porcelain. Reflux gently for 6 hours. Cool the resulting homogeneous solution and pour in a cold solution of 52 g. of sodium hydroxide in 95 ml. of water down the side of the flask so that most of it settles at the bottom without mixing with the solution in the flask. Connect the flask with a condenser for downward distillation and shake it to mix the two layers ; the free amine separates. Heat the flask when the amine with some water distils : continue the distillation until no amine separates from a test portion of the distillate. Estimate the weight of water in the distillate anp add about half this amount of potassium hydroxide in the form of sticks, so that it dissolves slowly.

Cool the solution in ice while the alkali hydroxide is dissolving; some ammonia gas is evolved. When the potassium hydroxide has dissolved, separate the amine, and dry it for 24 hours over sodium hydroxide pellets. Filter into a Claisen flask and distil. Collect the di-*n*-butylamine at 157-160°. The yield is 31 g.

Note.

(1) Also known as "nitrolim" and "lime nitrogen." The fresh product contains approximately 55 per cent. of calcium cyanamide, 20 per cent. of lime, 12 per cent. of graphite and small amounts of other impurities. It should be protected from moisture when stored in order to prevent slow polymerisation to dicyanodiamide.

III,123. REACTIONS AND CHARACTERISATION OF ALIPHATIC AMINES

The more important reactions of aliphatic amines, which will assist in their detection, are given below.

Salts of amines are generally soluble in water. Upon treatment with 10 per cent. sodium hydroxide solution, the amine will separate if it is insoluble or sparingly soluble in water; if the amine is water-soluble, it can be partially volatilised by gentle warming and its presence will be suggested by a characteristic odour.

PRIMARY AMINES

(i) **Reaction with nitrous acid.** Dissolve 0·2 g. of the substance in 5 ml. of 2*N* hydrochloric acid; cool in ice and add 2 ml. of ice-cold 10 per cent. aqueous sodium nitrite solution. Warm gently upon a water bath, when nitrogen will be freely evolved:

$$RNH_2 + HNO_2 \longrightarrow ROH + N_2 + H_2O$$

If desired, the alcohol may be identified as the 3 : 5-dinitrobenzoate (Section **III,27**); it is then best to repeat the experiment on a larger scale and to replace the dilute hydrochloric acid by dilute sulphuric acid. It must, however, be pointed out that the reaction is not always so simple as indicated in the above equation. Olefine formation and rearrangement of the alcohol sometimes occur: thus *n*-propylamine yields *n*-propyl alcohol, *iso*propyl alcohol and propylene.

(ii) **Rimini's test.** To a suspension or solution of 1 drop of the compound or to an equivalent quantity of the solution, add 1 ml. of pure acetone and 1 drop of freshly prepared 1 per cent. aqueous solution of sodium nitroprusside. A violet-red colour will develop within 1 minute.

(iii) **Carbylamine test.** To 1 ml. of 0·5*N* alcoholic potassium hydroxide solution (or to a solution prepared by dissolving a fragment of potassium hydroxide half the size of a pea in 1 ml. of alcohol) add 0·05–0·1 g. of the amine and 3 drops of chloroform, and heat to boiling. A carbylamine (*iso*cyanide) is formed and will be readily identified by its extremely nauseating odour:

$$RNH_2 + CHCl_3 + 3KOH \longrightarrow RNC + 3KCl + 3H_2O$$

When the reaction is over, add concentrated hydrochloric acid to decompose the *iso*cyanide and pour it away after the odour is no longer discernible. The test is extremely delicate and will often detect traces of primary amines in secondary and tertiary amines; it must therefore be used with due regard to this and other factors.

(iv) **5-Nitrosalicylaldehyde reagent test.** This test is based upon the fact that 5-nitrosalicylaldehyde and nickel ions when added to a primary amine produce an immediate precipitate of the nickel derivative of the "imine" or Schiff's base.

To 5 ml. of water add 1–2 drops of the amine; if the amine does not dissolve, add a drop or two of concentrated hydrochloric acid. Add 0·5–1 ml. of this amine solution to 2–3 ml. of the reagent; an almost immediate precipitate indicates the presence of a primary amine. A slight turbidity indicates the presence of a primary amine as an impurity. (Primary aromatic amines generally require 2–3 minutes for the test. Urea and other amides, as well as amino acids, do not react.)

The **5-nitrosalicylaldehyde reagent is prepared** as follows. Add 0·5 g. of 5-nitrosalicylaldehyde (m.p. 124–125°) to 15 ml. of pure triethanolamine and 25 ml. of water; shake until dissolved. Then introduce 0·5 g. of crystallised nickel chloride dissolved in a few ml. of water, and dilute to 100 ml. with water. If the triethanolamine contains some ethanolamine (thus causing a precipitate), it may be necessary to add a further 0·5 g. of the aldehyde and to filter off the resulting precipitate. The reagent is stable for long periods.

SECONDARY AMINES

(v) **Reaction with nitrous acid.** Oily nitrosoamines (compare Sections **III,124** and **IV,100**) are generally formed: no nitrogen is evolved (see (i)).

(vi) **Simon's test.** To a solution or suspension of 1 drop of the compound (or an equivalent quantity of solution) in 3 ml. of water, add 1 ml. of freshly prepared acetaldehyde solution,* followed by 1 drop of a 1 per cent. aqueous solution of sodium nitroprusside. A blue colouration is produced within 5 minutes, after which the colour gradually changes through greenish-blue to pale yellow.

(vii) **Carbon disulphide reagent test.** This test is based upon the formation from a secondary amine and carbon disulphide of a dialkyldithiocarbamate; the latter readily forms a nickel derivative with a solution of a nickel salt:

$$R_2NH + CS_2 \xrightarrow[aq.]{NH_3} R_2N{-}C(=S){-}SNH_4 \xrightarrow{NiII_2} (R_2N{-}C(=S){-}S{-})_2Ni$$

To 5 ml. of water add 1–2 drops of the secondary amine; if it does not dissolve, add a drop or two of concentrated hydrochloric acid. Place 1 ml. of the reagent in a test-tube, add 0·5–1 ml. of concentrated ammonia solution, followed by 0·5–1 ml. of the above amine solution. A precipitate indicates a secondary amine. A slight turbidity points to the presence of a secondary amine as an impurity.

* Prepare the acetaldehyde solution by plunging a red hot oxidised copper coil (made by winding a copper wire round a glass tube and heating the resulting coil in a Bunsen flame) into 5 ml. of 50 per cent. alcohol in a Pyrex test-tube. Withdraw the coil, cool the test-tube under the tap, repeat the oxidation several times, and use the cooled solution for the test.

The **carbon disulphide reagent is prepared** by adding to a solution of 0·5 g. of crystallised nickel chloride in 100 ml. of water enough carbon disulphide so that after shaking a globule of carbon disulphide is left at the bottom of the bottle. The reagent is stable for long periods in a well-stoppered bottle. If all the carbon disulphide evaporates, more must be added.

CRYSTALLINE DERIVATIVES OF PRIMARY AND SECONDARY ALIPHATIC AMINES

1. **Benzenesulphonyl or *p*-toluenesulphonyl derivatives.** These are generally very satisfactory. For experimental details, see under *Aromatic Amines*, Section **IV,100,***3.*

2. **Phenylthioureas.** Primary and secondary amines react with phenyl *iso*thiocyanate to yield phenylthioureas :

$$C_6H_5N{=}C{=}S + RNH_2 \longrightarrow C_6H_5NHCSNHR$$
$$C_6H_5N{=}C{=}S + R_2NH \longrightarrow C_6H_5NHCSNR_2$$

Phenyl *iso*thiocyanate is not sensitive to water ; the reaction may be carried out with an aqueous solution of an amine.

Dissolve equivalent quantities of the reagent and of the amine in a small amount of rectified spirit. If no reaction appears to take place in the cold, reflux the mixture for 5–15 minutes. Upon cooling (and " scratching " with a glass rod, if necessary) the crystalline thiourea separates. Recrystallise it from rectified spirit or from 60–80 per cent. alcohol.

Alternatively, mix equal amounts (say, 0·2 g. of each) of the amine and phenyl *iso*thiocyanate in a test-tube and shake for 2 minutes. If no reaction occurs, heat the mixture gently for 2 minutes and then cool in ice until the mass solidifies. Powder the solid, wash it with a little light petroleum (b.p. 100–120°), and recrystallise from rectified spirit.

α-Naphthyl *iso*thiocyanate yields crystalline α-naphthylthioureas and is similarly applied.

3. **Picrates.** Picric acid combines with amines to yield molecular compounds (picrates), which usually possess characteristic melting points. Most picrates have the composition 1 mol amine : 1 mol picric acid. The picrates of the amines, particularly of the more basic ones, are generally more stable than the molecular complexes formed between picric acid and the hydrocarbons (compare Section **IV,9,***1*).

If the amine is soluble in water, mix it with a slight excess (about 25 per cent.) of a saturated solution of picric acid in water (the solubility in cold water is about 1 per cent.). If the amine is insoluble in water, dissolve it by the addition of 2–3 drops of dilute hydrochloric acid (1 : 1) for each 2–3 ml. of water, then add a slight excess of the reagent. If a heavy precipitate does not form immediately after the addition of the picric acid solution, allow the mixture to stand for some time and then shake vigorously. Filter off the precipitated picrate and recrystallise it from boiling water, alcohol or dilute alcohol, boiling 10 per cent. acetic acid, chloroform or, best, benzene.

The following alternative procedure may sometimes be employed. Dissolve 0·5 g. of the amine in 5 ml. of rectified spirit and add 5 ml. of a cold saturated solution of picric acid in alcohol. Warm on a *water bath*

for 5 minutes and allow to cool. Collect the precipitated picrate and recrystallise it as above.

4. **N-Substituted phthalimides.** Phthalic anhydride reacts with primary amines only to yield N-substituted phthalimides :

Dissolve 0·5 g. of the primary amine and 0·5 g. of pure phthalic anhydride in 5 ml. of glacial acetic acid and reflux for 20–30 minutes. (If the amine salt is used, add 1 g. of sodium acetate.) The N-substituted phthalimide separates out on cooling. Recrystallise it from alcohol or from glacial acetic acid.

Experimental details for the preparation of derivatives with **benzoyl chloride** and with **3-nitrophthalic anhydride** are given in Section **IV,100,***2* and *7*.

The melting points of the derivatives of some primary and secondary aliphatic amines are collected in Table **III,123.**

Tertiary aliphatic amines are discussed under *Aromatic Tertiary Amines* in Section **IV,100.**

TABLE III,123. **PRIMARY AND SECONDARY ALIPHATIC AMINES**

Amine	B.P.	M.P.	$d_{4^\circ}^{20^\circ}$	$n_D^{20^\circ}$	Benzene-sulphonamide	*p*-Toluene-sulphonamide	Phenyl-thiourea	α-Naphthyl-thiourea	Picrate	*N*-Substituted Phthalimide	Benzamide
Methylamine	−7°	—	—	—	30°	75°	113°	192°	215°	134°	80°
Ethylamine	17	—	—	—	58	63	106	121	165	78	71
n-Propylamine	49	—	0·717	1·388	36	52	63	103	135	66	84
iso-Propylamine	35	—	0·689	1·374	26	51	101	143	150	86	100
n-Butylamine	77	—	0·741	1·401	—	—	65	109	151	34	42
iso-Butylamine	68	—	0·735	1·397	53	78	82	137	151	93	57
sec.-Butylamine	63	—	0·725	1·393	70	55	101	—	140	—	76
n-Amylamine	105	—	0·754	1·411	—	—	69	103	139	—	—
iso-Amylamine	97	—	0·749	1·408	—	65	102	97	138	—	—
n-Hexylamine	129	—	0·768	—	96	—	77	79	127	—	40
n-Heptylamine	155	—	0·777	—	—	—	75	—	121	—	—
Allylamine	55	—	0·762	1·420	39	64	98	—	140	70	—
*cyclo*Hexylamine	134	—	0·819	1·437	—	—	—	142	—	158	149
Ethylenediamine	117	—	0·898	1·457	168	160	102	—	233	—	244
Propylenediamine	120	—	0·874	—	—	—	—	—	137	—	193
Ethanolamine	171	—	1·022	1·454	—	—	—	—	160	127	—
l-Menthylamine	212	—	0·854	—	—	—	135	—	—	—	157
Benzylamine	185	—	0·982	1·544	88	116	147	172	196	115	105
α-Phenylethylamine	187	—	—	—	—	—	—	—	189	—	120
β-Phenylethylamine	198	—	0·854	—	69	—	135	—	174	130	116
Dimethylamine	7	—	—	—	47	79	135	168	158	—	41
Diethylamine	56	—	0·707	1·386	42	60	34	108	155	—	42
Di-*n*-propylamine	110	—	0·738	1·405	51	—	—	161	75	—	—
Di-*iso*-propylamine	84	—	0·717	1·392	94	—	—	—	140	—	—
Di-*n*-butylamine	159	—	0·760	1·418	—	—	86	123	59	—	—
Di-*iso*-butylamine	137	—	0·746	1·409	—	—	—	—	—	—	—
Di-*sec.*-butylamine	135	—	0·753	1·411	—	—	—	—	—	—	—
Di-*n*-amylamine	67°/4	—	0·777	1·427	—	—	—	—	—	—	—
Di-*iso*-amylamine	186	—	0·771	1·423	—	—	—	118	—	—	—
Diallylamine	111	—	—	—	—	—	—	—	—	—	—

TABLE III,123. PRIMARY AND SECONDARY ALIPHATIC AMINES—*continued*

Amine	B.P.	M.P.	$d_{4°}^{20°}$	$n_D^{20°}$	Benzene-sulphonamide	*p*-Toluene-sulphonamide	Phenyl-thiourea	α-Naphthyl-thiourea	Picrate	*N*-Substituted Phthalimide	Benzamide
Piperidine	106°	—	0·861	1·453	94°	96°	—	—	152°	—	48
Pyrrolidine	89	—	0·854	1·424	—	123	—	—	112	—	—
Morpholine	130	—	1·000	1·455	119	147	—	136	148	—	75
Diethanolamine	270d	28°	1·097	1·478	130	99	—	—	110	—	—
Piperazine	140	104	—	—	292 (di)	173 (mono)	—	—	280	—	196 (di)

ESTER-AMIDES (DERIVATIVES OF AMINOFORMIC ACID, NH_2COOH)

	B.P.	M.P.	$d_{4°}^{20°}$	$n_D^{20°}$	Derivatives
Methyl carbamate (NH_2COOCH_3)	177°	54°			
Ethyl carbamate (urethane)	184	50			*N*-*p*-Nitrobenzoyl, 152°; Benzal, 179°
n-Propyl carbamate	195	61			
n-Butyl carbamate	204d	54			
n-Amyl carbamate	—	57			
iso-Amyl carbamate	—	67			
N-Methylurethane (Ethyl *N*-methyl carbamate)	170	—			
N-Ethylurethane (Ethyl *N*-ethyl carbamate)	170	—	0·981	1·422	
N-*n*-Propylurethane	192				
N-*n*-Butylurethane	202				
N-*sec*.-Butylurethane	194				
N-Phenylurethane (Ethyl *N*-phenyl carbamate)	237	53			*N*-Acetyl, 59°; *N*-Benzoyl, 161°; *N*-Nitroso, 62°
Ethyl oxanilate ($C_6H_5NHCOCOOC_2H_5$)	—	67			*N*-Acetyl, 65°

Note.—Esters of carbamic acid upon boiling with aniline yield carbanilide (m.p. 238°), ammonia and the corresponding alcohol.

III,124. N-NITROSODIMETHYLAMINE (DIMETHYL-NITROSAMINE)

Secondary amines upon treatment with nitrous acid yield nitrosamines, which are stable, neutral yellow liquids (or low melting point solids), for example :

$$\underset{\text{Dimethylamine}}{(CH_3)_2NH} + HNO_2 \longrightarrow \underset{\text{N-Nitrosodimethylamine}}{(CH_3)_2N.NO} + H_2O$$

They are readily hydrolysed by boiling dilute hydrochloric acid and the original amine can be recovered by neutralisation with alkali and steam distillation. Primary aliphatic amines liberate nitrogen with nitrous acid whilst tertiary amines are unaffected.

Fit a 100 ml. distilling flask with a condenser for downward distillation. Dissolve 50 g. of dimethylamine hydrochloride (Section **III,118**) in 25 ml. of water and add dilute sulphuric acid until acid to Congo red paper. Place the resulting solution in the distilling flask and add gradually a solution of 45 g. of pure sodium nitrite in 50 ml. of hot water. Distil the mixture rapidly to dryness, when the nitrosamine passes over (although it is not visible as a separate layer) together with a little of the base as dimethylamine nitrite. To remove the latter, redistil the distillate with a little more dilute sulphuric acid. Add excess of solid potassium carbonate to the distillate ; the nitrosamine will appear as a yellow oil. Separate the yellow oil and treat it with more solid potassium carbonate, removing the water layer as it appears, until no further action occurs. Finally transfer to a small flask and dry the liquid over fresh anhydrous potassium carbonate. Distil from a 100 ml. flask and collect the dimethylnitrosamine at 150–151°. The yield is 35 g.

Cognate Preparation

N-Nitrosodiethylamine. Add 36·5 g. (51·5 ml.) of diethylamine slowly to the calculated quantity of carefully standardised 5*N*-hydrochloric acid cooled in ice (1). Introduce the solution of the hydrochloride into a solution of 39 g. of sodium nitrite (assumed to be of 90 per cent. purity) in 45 ml. of water contained in a 250 ml. distilling flask. Distil the mixture rapidly to dryness. Separate the yellow upper layer of the nitrosamine from the distillate ; saturate the aqueous layer with solid potassium carbonate and remove the nitroso compound which separates and add it to the main product. Dry over anhydrous potassium carbonate and distil. Collect the diethylnitrosamine at 172-173·5°. The yield is 41 g.

Note.

(1) The experimental details describe the use of a free secondary amine for the preparation of a nitrosamine. Identical results are, of course, obtained by employing solid diethylamine hydrochloride.

SUBSTITUTED ALIPHATIC MONOBASIC ACIDS

Acetic acid can be chlorinated by gaseous chlorine in the presence of red phosphorus as catalyst to yield successively mono-, di-, and tri-chloroacetic acid; the reaction proceeds better in bright sunlight. If the chlorination is stopped when approximately one molecule of chlorine per molecule of acetic acid is absorbed the main product is **monochloroacetic acid**:

$$CH_3COOH + Cl_2 \longrightarrow CH_2ClCOOH + HCl$$

Bromination of fatty acids in the α-position can be effected quite readily in the presence of phosphorus trichloride, red phosphorus or pyridine as catalysts or halogen carriers: with acetic acid, the addition of acetic anhydride (to ensure the absence of water) improves the yield and facilitates the bromination. Examples are:—

$$CH_3COOH + Br_2 \xrightarrow[\text{and } C_5H_5N]{(CH_3CO)_2O} CH_2BrCOOH + HBr$$

$$\underset{n\text{-Caproic acid}}{CH_3(CH_2)_4COOH} + Br_2 \xrightarrow{PCl_5} \underset{\alpha\text{-Bromo-}n\text{-caproic acid}}{CH_3(CH_2)_3CHBrCOOH} + HBr$$

$$\underset{\text{Propionic acid}}{CH_3CH_2COOH} + Br_2 \xrightarrow[\text{or } PCl_5]{\text{Red P}} \underset{\alpha\text{-Bromopropionic acid}}{CH_3CHBrCOOH} + HBr$$

The conversion of an aliphatic carboxylic acid into the α-bromo- (or α-chloro-) acid by treatment with bromine (or chlorine) in the presence of a catalytic amount of phosphorus tribromide (or trichloride) or of red phosphorus is known as the **Hell-Volhard-Zelinsky reaction.** The procedure probably involves the intermediate formation of the acyl halide, since it is known that halogens react more rapidly with acyl halides than with the acids themselves:

$$3RCH_2COOH + PX_3 \longrightarrow 3RCH_2COX + H_3PO_3$$
$$RCH_2COX + X_2 \longrightarrow RCHXCOX + HX$$
$$RCHXCOX + RCH_2COOH \longrightarrow RCHXCOOH + RCH_2COX$$

Dichloroacetic acid is conveniently prepared by the action of calcium carbonate in the presence of a little sodium cyanide upon chloral hydrate, followed by acidification with concentrated hydrochloric acid:

$$2CCl_3CH(OH)_2 + 2CaCO_3 \xrightarrow{NaCN} (CHCl_2COO)_2Ca + CaCl_2 + 2CO_2 + 2H_2O$$
$$(CHCl_2COO)_2Ca + 2HCl \longrightarrow 2CHCl_2COOH + CaCl_2$$

Trichloroacetic acid is best prepared by the oxidation of chloral hydrate with fuming nitric acid:

$$CCl_3CH(OH)_2 + O \xrightarrow{HNO_3} CCl_3COOH + H_2O$$

Amino acids may be prepared by the action of a large excess of concentrated ammonia solution upon α-chloro- or α-bromo-acids; the presence of a considerable amount of ammonium carbonate often increases the yield of monoamino acid, for example:

$$\underset{\text{Monochloroacetic acid}}{CH_2ClCOOH} + 2NH_3 \longrightarrow \underset{\text{Glycine}}{NH_2CH_2COOH} + NH_4Cl$$

$$\underset{\alpha\text{-Bromopropionic acid}}{CH_3CHBrCOOH} + 2NH_3 \longrightarrow \underset{dl\text{-Alanine}}{CH_3CH(NH_2)COOH} + NH_4Br$$

$$\underset{\alpha\text{-Bromo-}n\text{-caproic acid}}{CH_3(CH_2)_3CHBrCOOH} + 2NH_3 \longrightarrow \underset{\text{Norleucine}}{CH_3(CH_2)_3CH(NH_2)COOH} + NH_4Br$$

Ethyl cyanoacetate, a substance of importance in synthetical work, is prepared from chloroacetic acid by the following series of reactions :

$$CH_2ClCOONa + NaCN \longrightarrow NaCl + CH_2(CN)COONa \xrightarrow{HCl} CH_2(CN)COOH$$

$$\underset{\text{Cyanoacetic acid}}{CH_2(CN)COOH} + C_2H_5OH \xrightarrow{H_2SO_4} \underset{\text{Ethyl cyanoacetate}}{CH_2(CN)COOC_2H_5} + H_2O$$

Two compounds, which may be prepared from ethyl cyanoacetate and also find application in synthetical work, may be included here. **Cyanoacetamide**, prepared from ethyl cyanoacetate and concentrated ammonia solution :

$$CH_2(CN)COOC_2H_5 + NH_3 \longrightarrow CH_2(CN)CONH_2 + C_2H_5OH$$

Malononitrile, obtained by the dehydration of cyanoacetamide with phosphorus pentachloride :

$$CH_2(CN)CONH_2 + PCl_5 \longrightarrow CH_2(CN)_2 + POCl_3 + 2HCl$$

$$2CH_2(CN)CONH_2 + POCl_3 \longrightarrow 2CH_2(CN)_2 + HPO_3 + 3HCl$$

The phosphorus oxychloride formed in the reaction is a dehydrating agent also.

III,125. MONOCHLOROACETIC ACID

Assemble an apparatus consisting of a 1-litre three-necked flask carrying a thermometer, a gas distribution tube (a glass tube with a wide fritted disc sealed on at the bottom) and a reflux condenser. Connect the top of the reflux condenser to two wash bottles containing water and to a third containing sodium hydroxide ; the long tubes in the wash bottles should be just above the surface of the liquid. Place 6 g. of purified red phosphorus (Section **II,50,5**) and 150 g. of glacial acetic acid in the flask and weigh the apparatus on a rough balance ; heat the mixture to 100°. Pass chlorine from a cylinder, through two empty wash bottles, into the mixture and adjust the stream of chlorine so that a stream of fine bubbles issues through the gas distributor. Gradually increase the flow of chlorine and maintain the temperature inside the flask at 105–110°. Continue the passage of chlorine until the flask increases in weight by about 85 g. ; this roughly corresponds to the formation of monochloroacetic acid. The time required is 4–6 hours. The action of the chlorine is greatly facilitated by exposure of the apparatus to sunlight.

Transfer the reaction product to a 500 ml. Claisen flask and distil over a wire gauze or from an air bath. Some acetyl chloride and acetic acid passes over first, the temperature then rises, and the fraction, b.p. 150–200°, is collected separately ; run out the water from the condenser when the temperature reaches 150°. The fraction, b.p. 150–200°, solidifies on cooling. Drain off any liquid from the crystals as rapidly as possible, and redistil the solid using an air condenser. Collect the fraction b.p. 182–192° : this sets to a solid mass on cooling and melts at 63°. The yield of monochloroacetic acid is 150–175 g.

Note.

Chloroacetic acid must be handled with great care as it causes blisters on the skin.

III,126. MONOBROMOACETIC ACID AND ETHYL BROMOACETATE

Monobromoacetic acid. Place a mixture of 262 g. (250 ml.) of glacial acetic acid, 54 g. (50 ml.) of acetic anhydride and 0·5 ml. of pyridine in a 1-litre round-bottomed flask equipped with a reflux condenser (carrying a cotton wool or calcium chloride tube) and a dropping funnel, the stem of which reaches below the level of the liquid (1). Introduce a few glass beads into the flask and heat the mixture to boiling. Remove the flame, add about 1 ml. of bromine and allow the reaction to proceed until the liquid becomes colourless; this takes about 10 minutes as there appears to be a time lag in the reaction. Add the remainder of the 281g. (90 ml.) of dry bromine (Section **II,49,8**) as rapidly as it will react and avoiding loss through the condenser; during this period (about 2 hours) keep the acid gently boiling by means of a small flame beneath the flask. When about half of the bromine has been added, the liquid acquires a cherry red colour which it retains throughout the remainder of the bromination. Finally, heat the mixture until it becomes colourless.

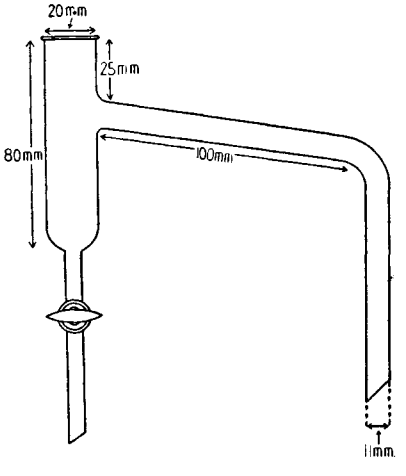


Fig. *III, 126,* 1.

Allow to cool and run in 20 ml. of water slowly to destroy the acetic anhydride. Remove the excess of acetic acid and water by heating on a water bath under reduced pressure (*ca.* 35mm.). The residue (220 g.) crystallises on cooling and consists of almost pure monobromoacetic acid (2). If it is required perfectly pure, distil the crude acid from a Claisen flask and collect the fraction of b.p. 202–204°. When distilled under diminished pressure, the acid boils at 117–118°/15 mm. Pure monobromoacetic acid has m.p. 50°.

Notes.

(1) An all-glass apparatus is recommended. Alternatively, a rubber stopper which has been used previously on several occasions (and therefore hardened somewhat) will be satisfactory.

(2) Bromoacetic acid must not be allowed to come into contact with the hands as it causes serious burns.

Ethyl bromoacetate (1). Fit a large modified Dean and Stark apparatus provided with a stopcock at the lower end (a convenient size is shown in Fig. *III, 126,* 1) to the 1-litre flask containing the crude bromoacetic acid of the previous preparation and attach a double surface condenser to the upper end. Mix the acid with 155 ml. of absolute ethyl alcohol, 240 ml. of sodium-dried benzene and 1 ml. of concentrated sulphuric acid. Heat the flask on a water bath: water, benzene and alcohol will collect in the special apparatus and separate into two layers, the lower layer consisting of approximately 50 per cent. alcohol. Run off the lower layer (*ca.* 75 ml.), which includes all the water formed in the

reaction together with excess of alcohol. When no more water separates, the reaction may be regarded as complete ; add 20 ml. of absolute alcohol to the reaction mixture and continue refluxing for a further 30 minutes. Run off the benzene which has collected in the trap. Transfer the reaction mixture to a separatory funnel, and wash it successively with 400 ml. of water, 400 ml. of 1 per cent. sodium bicarbonate solution and 400 ml. of water. Dry over anhydrous sodium or magnesium sulphate and distil through a short, well-lagged fractionating column (*e.g.*, an all-glass Dufton column). Collect the ethyl bromoacetate at 154–155°. The yield is 205 g.

$$BrCH_2COOH + C_2H_5OH \xrightarrow[(C_6H_6)]{H_2SO_4} BrCH_2COOC_2H_5 + H_2O$$

Note.

(1) Ethyl bromoacetate vapour is extremely irritating to the eyes. The preparation must therefore be conducted in a fume cupboard provided with a good draught : the material should be kept in closed vessels as far as possible.

Cognate Preparations

α-Bromo-*n*-caproic acid. Place 100 g. (107 ml.) of freshly-distilled, dry *n*-caproic acid (b.p. 202–205°) and 150 g. (48 ml.) of dry bromine (Section **II,49,*8***) in a 500 ml. flask equipped with a reflux condenser, the top of which is connected with a trap and absorption vessel containing water (compare Fig. *III, 28*, 1) (1). Momentarily remove the condenser and add cautiously 1·5 ml. of phosphorus trichloride. Heat the mixture on a water bath to 65–70°, when reaction will commence and hydrogen bromide is smoothly evolved. Towards the end of the reaction allow the temperature of the bath to rise to 100°. The reaction is complete when all the bromine has reacted (about 4 hours). Transfer the reaction mixture to a Claisen flask and distil first with a water pump : much hydrogen bromide is evolved and a fraction of low boiling point passes over. When all the low boiling point fraction has distilled, connect the flask to an oil pump or to the laboratory vacuum installation and collect the α-bromo-*n*-caproic acid at 116–125°/8 mm. (or at 132–140°/15 mm.). The yield is 145 g. Upon redistillation the α-bromocaproic acid passes over almost entirely at 128–131°/10 mm.

Note.

(1) The flask should preferably be connected to the condenser by means of a ground glass joint ; if not available, an old rubber stopper may be used.

α-Bromopropionic acid. Proceed as detailed for α-bromo-*n*-caproic acid using 64 g. (64·5 ml.) of freshly-distilled, dry propionic acid (b.p. 139–142°), 150 g. (48 ml.) of dry bromine and 1·5 ml. of phosphorus trichloride. The reaction commences on warming to about 50°. Collect the α-bromopropionic acid at 95–97°/10 mm. or at 100–102°/15 mm. The yield is 110 g.

Ethyl α-bromopropionate. This preparation illustrates the facile bromination of an acid chloride (propionyl chloride) in the presence of red phosphorus, and the subsequent conversion of the bromoacid chloride into the ethyl ester by direct interaction with ethanol.

In a 750 ml. three-necked flask, equipped with a dropping funnel, double-surface condenser and a device for absorbing the sulphur dioxide evolved (see Figs. *II*, *8*, 1-2), place 220 g. (135 ml.) of redistilled thionyl chloride, and heat to boiling. Add 125 g. (126 ml.) of pure propionic acid at such a rate that the mixture refluxes gently (*ca.* 1 hour). Reflux the mixture for 30 minutes to expel dissolved sulphur dioxide, allow to cool, and add 0·5 g. of purified red phosphorus. Introduce 310 g. (100 ml.) of dry bromide during 5-7 hours to the gently boiling propionyl chloride, and then reflux the mixture for 7 hours, by which time the evolution of hydrogen bromide almost ceases. Add the crude α-bromopropionyl chloride during 2 hours to 250 ml. of absolute ethanol contained in a three-necked flask, equipped with a mechanical stirrer and reflux condenser; complete the reaction by heating on a water bath for 4 hours, when hydrogen chloride is slowly evolved. Filter the crude ester into 500 ml. of distilled water, separate the oil and wash it successively with water, sodium bicarbonate solution and water; dry. Distil at normal pressure to remove the low b.p. fraction (largely ethyl bromide: 75 g.) and then under diminished pressure. Collect the ethyl α-bromopropionate as a colourless liquid at 69–70°/25 mm.; the yield is 221 g.

III,127. DICHLOROACETIC ACID

Fit a 1500 ml. bolt-head flask with a reflux condenser and a thermometer. Place a solution of 125 g. of chloral hydrate in 225 ml. of warm water (50-60°) in the flask, add successively 77 g. of precipitated calcium carbonate, 1 ml. of amyl alcohol (to decrease the amount of frothing), and a solution of 5 g. of commercial sodium cyanide in 12 ml. of water. An exothermic reaction occurs. Heat the warm reaction mixture with a small flame so that it reaches 75° in about 10 minutes and then remove the flame. The temperature will continue to rise to 80–85° during 5–10 minutes and then falls; at this point heat the mixture to boiling and reflux for 20 minutes. Cool the mixture in ice to 0–5°, acidify with 107·5 ml. of concentrated hydrochloric acid. Extract the acid with five 50 ml. portions of ether. Dry the combined ethereal extracts with 10 g. of anhydrous sodium or magnesium sulphate, remove the ether on a water bath, and distil the residue under reduced pressure using a Claisen flask with fractionating side arm. Collect the dichloroacetic acid at 105–107°/26 mm. The yield is 85 g.

III,128. TRICHLOROACETIC ACID

Place 40 g. of chloral hydrate in a 250 ml. Claisen flask and heat it so that the solid just melts. Add cautiously through a dropping funnel supported over the long neck of the flask 25 g. (17 ml.) of fuming nitric acid. When the evolution of gases ceases, warm the flask gently until the evolution of brown fumes is complete. Arrange the flask for distillation and collect the liquid boiling at 194–196° (air condenser) as trichloroacetic acid; this solidifies on cooling and melts at 57°. The yield is 25 g.

III,129. GLYCINE (AMINOACETIC ACID)

Dissolve 180 g. of commercial ammonium carbonate in 150 ml. of warm water (40–50°) in a 700 ml. flask. Cool to room temperature and add 200 ml. of concentrated ammonia solution (sp. gr. 0·88). Introduce slowly, with swirling of the contents of the flask, a solution of 50 g. of chloroacetic acid (Section **III,125**) in 50 ml. of water [*CAUTION :* do not allow chloroacetic acid to come into contact with the skin as unpleasant burns will result]. Close the flask with a solid rubber stopper and fix a thin copper wire to hold the stopper in place : do not moisten the portion of the stopper in contact with the glass as this lubrication will cause the stopper to slide out of the flask. Allow the flask to stand for 24–48 hours at room temperature. Transfer the mixture to a distilling flask and distil in a " closed " apparatus until the volume is reduced to 100–110 ml. A convenient arrangement is to insert a drawn-out capillary tube into the flask, attach a Liebig's condenser, the lower end of which fits into a filter flask (compare Fig. *II*, *37*, 1) and connect the latter to a water filter pump. If the solution is not colourless, warm it with about 1 g. of decolourising carbon and filter. Treat the cold filtrate with 400 ml. of methyl alcohol : stir the solution during the addition of the methyl alcohol and cool it in an ice chest (or in a refrigerator) for 4–6 hours to permit of complete crystallisation. Filter off the crude glycine, which contains ammonium chloride as the chief impurity. Most of the latter may be removed by suspending the crystals in 150 ml. of methyl alcohol, stirring well, filtering, and washing with a little methyl alcohol and finally with ether. The yield is 25 g. Further purification may be carried out as follows. Dissolve the glycine (25 g.) in 50 ml. of warm water, shake the solution with 2 g. of decolourising carbon, and filter. Precipitate the glycine by the addition of 200 ml. of methyl alcohol; collect the glycine on a Buchner funnel, wash it with methyl alcohol and ether, and dry it in the air. The resulting glycine darkens at 237° and melts at 240° with decomposition.

Cognate Preparation

***dl*-Alanine.** Use 225 g. of ammonium carbonate, 175 ml. of water, 250 ml. of concentrated ammonia solution and 77 g. of α-bromopropionic acid (Section **III,126**). Proceed exactly as for glycine. The yield of α-aminopropionic acid is 30 g. The m.p., after recrystallisation from water, is 197–198° (decomp.).

III,130. α-AMINO-*n*-CAPROIC ACID (NORLEUCINE)

Place 425 ml. of concentrated ammonia solution (sp. gr. 0·88) in a 500 ml. round-bottomed flask and add slowly 75 g. of α-bromocaproic acid (Section **III,126**). Stopper the flask tightly and allow it to stand in a warm place (50–55°) for 30 hours. Filter the amino acid at the pump and keep the filtrate (*A*) separately. Wash the amino acid (*ca.* 26 g.) well with methyl alcohol to remove the ammonium bromide present. Evaporate the aqueous filtrate (*A*) almost to dryness on a steam bath,

and add 150 ml. of methyl alcohol. A second crop of amino acid, contaminated with ammonium bromide, is thus obtained; wash it with methyl alcohol and recrystallise from hot water, thus affording a further 7 g. of pure norleucine. The total yield is 32 g. The decomposition point is about 327°.

III,131. ETHYL CYANOACETATE

Place 208 g. of chloroacetic acid [*CAUTION:* do not allow the acid to come into contact with the hands] and 315 g. of crushed ice in a battery jar or in a large beaker and neutralise it accurately to litmus with a cold solution of sodium hydroxide (100 g. in 300 ml. of water; about 275 ml. are required): do not allow the temperature to rise above 30° during the neutralisation. Prepare, in the fume cupboard, a solution of 125 g. of sodium cyanide (97–98 per cent. powder) in 250 ml. of water in a 3-litre flask: heat to about 55° for rapid solution and finally to boiling. Add to the resulting hot solution 100 ml. of the solution of sodium chloroacetate and remove the flame immediately the reaction commences. When the vigorous reaction has subsided somewhat, add another 100 ml. portion, followed by the remainder when the temperature commences to fall again. Boil the mixture for 5 minutes but no longer (otherwise some hydrogen cyanide may be lost and some sodium glycollate may form) and then cool with running water for 30 minutes. Filter the solution if it is not clear.

Liberate the cyanoacetic acid by adding with vigorous stirring 250 ml. (290 g.; a slight excess) of hydrochloric acid, sp. gr. 1·156. Evaporate the solution on a water bath at 60–70° under a pressure of 20–30 mm. (Fig. *II*, *37*, 1) until practically no more distillate passes over; do not heat above 75° as considerable loss may result owing to the decomposition of the cyanoacetic acid. Add 250 ml. of rectified spirit to the residue, filter at the pump (1) from the sodium chloride, and wash the residue with another 200 ml. of rectified spirit. Evaporate the alcoholic solution under reduced pressure from a water bath (Fig. *II*, *37*, 1) maintained at 50–60° (2) until no more liquid distils over: the residue weighs about 225 g. Add a mixture of 250 ml. of absolute ethyl alcohol and 4·5 ml. of concentrated sulphuric acid, and reflux on a water bath for 3 hours. Remove the excess of alcohol and some of the water formed by distillation under reduced pressure from a water bath. Heat the residue again with 125 ml. of absolute ethyl alcohol and 2 ml. of concentrated sulphuric acid for 2 hours, and remove the excess of alcohol under diminished pressure as before. Allow the ester to cool to room temperature and neutralise the sulphuric acid with a concentrated solution of sodium carbonate. Separate the upper layer of ester, and extract the aqueous solution with ether or benzene (about 10 per cent. of the yield is in the extract). Dry the combined products with anhydrous magnesium sulphate and transfer to a Claisen flask. Remove the solvent under normal pressure and then distil the ester under reduced pressure. Collect the ethyl cyanoacetate at 97–98°/16 mm. (or at 101–102°/19 mm. or 107–108°/27 mm.). The yield is 180 g.

Notes.

(1) It is easier to remove the sodium chloride by centrifugation. If this method is adopted, wash the salt first with 200 ml. and then with 100 ml. of ethanol.

(2) The solution containing mineral acid should not be heated above 50–60° or diethyl malonate will be formed.

Cognate Preparations

Cyanoacetamide. Place 150 ml. of concentrated aqueous ammonia solution (sp. gr. 0·88) in a 500 ml. wide-mouthed conical flask and add 200 g. (188 ml.) of ethyl cyanoacetate. Shake the cloudy mixture: some heat is evolved and it becomes clear in about 3 minutes. Stand the loosely stoppered flask in an ice-salt mixture for 1 hour, filter rapidly with suction, and wash the solid with two 25 ml. portions of ice-cold ethanol. Dry in the air: the yield of pale yellow cyanoacetamide is 110 g. (1). Recrystallise from 190 ml. of 95 per cent. ethanol; a colourless product, m.p. 119–120°, is deposited with practically no loss.

Note.

(1) A further 25 g. of cyanoacetamide may be obtained by evaporating the original mother liquor to dryness under reduced pressure (water pump) whilst heating the flask on a steam bath. The residue is dissolved in 50 ml. of hot ethanol, the solution shaken for a few minutes with decolourising carbon, filtered with suction whilst hot, and then cooled in ice. The resulting yellowish amide is recrystallised with the addition of decolourising carbon, if necessary.

Malononitrile. Mix 75 g. of cyanoacetamide intimately with 75 g. of dry phosphorus pentachloride in a glass mortar (*FUME CUPBOARD!*). Transfer the mixture as rapidly as possible (with the aid of a large glass funnel with cut-off stem) to a 500 ml. Claisen flask fitted with a wide-bore capillary or (drawn-out) glass tube (to reduce the danger of "blocking") and a thermometer. Attach the Claisen flask by means of a long air condenser to a 200 ml. filter flask, which in turn is connected to a powerful water pump (or two glass water pumps in parallel) and a manometer. Evacuate the system to about 30 mm. of mercury and immerse the Claisen flask in a boiling water bath. The mixture gradually melts, boiling commences about 15 minutes before the solid has melted completely and the pressure rises to about 150 mm. owing to the liberation of hydrogen chloride and phosphorus oxychloride. The evolution of gas slackens in about 30–35 minutes, the boiling is then less vigorous and the pressure falls. At this point, change the receiver and immerse it in ice water. Remove the Claisen flask immediately from the water bath, wipe it dry and immerse it in an oil bath at 140° to within 10 cm. of the top of the flask. The malononitrile commences to pass over at 113°/30 mm. (or 125°/50 mm.): raise the temperature of the oil bath over a period of 25 minutes to 180°. Collect the dinitrile at 113–125°/30 mm.; if it solidifies in the air condenser melt it by the application of a small flame. Remove the oil bath when distillation has almost ceased; discolouration of the product is thus prevented. The yield of crude dinitrile is 45 g. Redistil and collect the pure malononitrile at 113–120°/30 mm. as a colourless liquid (40 g.); this quickly solidifies on cooling, m.p. 29–30°. Store in a brown bottle and protect it from the light.

III,132. REACTIONS AND CHARACTERISATION OF AMINO ACIDS

The aliphatic compounds which contain both an amino and a carboxyl group (amino acids) are generally insoluble (or very sparingly soluble) in organic solvents such as ether or benzene, sparingly soluble in alcohol, very soluble in water and are neutral in reaction. They have no true melting points, but decompose on heating at temperatures between 120° and 300°; the apparent melting points vary considerably according to the conditions of heating and are therefore of no great value for precise identification. These properties resemble those of inorganic salts. In an amino acid $H_2N—A—COOH$, which contains both a basic and an acidic group, salt formation can take place between the two groups. Measurements of the crystal structure of amino acids show that in the solid state they exist as internal salts or zwitterions, $H_3\overset{+}{N}—A—CO_2^-$. Even in aqueous solution an amino acid exists predominantly as the zwitterion, but there is also a minute (almost negligible) quantity of the uncharged molecule present:

$$H_3\overset{+}{N}—A—CO_2^- \rightleftharpoons H_2N—A—CO_2H$$

Amino acids give the following reactions:—

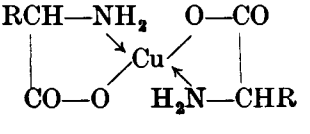
(i) They dissolve slowly in 5 per cent. sodium bicarbonate solution; the evolution of carbon dioxide may not be apparent until after 2–3 minutes (compare the corresponding test for *Acids*, Section **III,85,** (i)).

(ii) They give the " carbylamine " (or *iso*cyanide) reaction (see under *Amines*, Section **III,123,**(iii)).

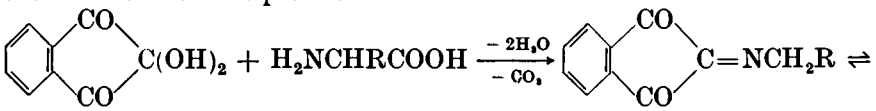
(iii) They yield nitrogen and a hydroxy acid when treated with nitrous acid (from sodium nitrite and dilute acetic acid), for example:

$$H_3\overset{+}{N}—CH_2—CO_2^- \rightleftharpoons H_2N—CH_2—CO_2H + HNO_2 \longrightarrow HO—CH_2—CO_2H + N_2 + H_2O$$

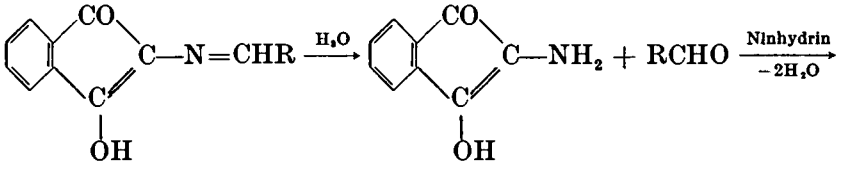
(iv) Upon adding an aqueous solution of an amino acid to copper sulphate solution, a deep blue colouration is obtained. The deep blue copper derivative may be isolated by boiling a solution of the amino acid with precipitated copper hydroxide or with copper carbonate, filtering and concentrating the solution. These blue complexes are co-ordination compounds of the structure:

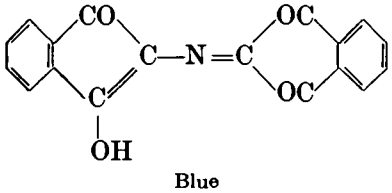


(v) Upon treating a solution of an α-amino acid with a few drops of a 0·25 per cent. aqueous solution of **ninhydrin** (triketohydrindene hydrate), a blue colouration is produced.



Ninhydrin





Blue

The colour test is not specific for α-amino acids: other primary amino compounds and also ammonia give a blue colouration with ninhydrin.

Crystalline derivatives of amino acids are usually produced by reaction at the amino group by treatment with appropriate reagents in alkaline solution:

$$H_3\overset{+}{N}—CHR—CO_2^- + Na^+OH^- \longrightarrow (H_2N—CHR—CO_2)^-Na^+ + H_2O;$$

the derivative is finally precipitated by acidification of the alkaline mixture.

Crystalline Derivatives of Amino Acids

1. **Benzoates.** Dissolve 0·5 g. of the amino acid in 10 ml. of 10 per cent. sodium bicarbonate solution and add 1 g. of benzoyl chloride. Shake the mixture vigorously in a stoppered test-tube; remove the stopper from time to time since carbon dioxide is evolved. When the odour of benzoyl chloride has disappeared, acidify with dilute hydrochloric acid to Congo red and filter. Extract the solid with a little cold ether to remove any benzoic acid which may be present. Recrystallise the benzoyl derivative which remains from hot water or from dilute alcohol.

2. **3 : 5-Dinitrobenzoates.** The following experimental details are for glycine (aminoacetic acid) and may be easily adapted for any other amino acid. Dissolve 0·75 g. of glycine in 20 ml. of *N* sodium hydroxide solution and add 2·32 g. of finely powdered 3 : 5-dinitrobenzoyl chloride. Shake the mixture vigorously in a stoppered test-tube; the acid chloride soon dissolves. Continue the shaking for 2 minutes, filter (if necessary) and acidify with dilute hydrochloric acid to Congo red. Recrystallise the derivative immediately from water or 50 per cent. alcohol.

Excess of the reagent should be avoided, if possible. If excess of dinitrobenzoyl chloride is used, this appears as the acid in the precipitate obtained upon acidifi-

cation : the acid can be removed by shaking in the cold with a mixture of 5 volumes of light petroleum (b.p. 40-60°) and 2 volumes of alcohol. The glycine derivative is insoluble in this medium. For some amino acids (leucine, valine and phenylalanine) acetic acid should be used for acidification.

3. **α-Naphthylureido acids (or α-naphthylhydantoic acids).** Amino acids react in alkaline solution with α-naphthyl *iso*cyanate to yield the sodium salts of the corresponding α-naphthylureido acids, which remain in solution : upon addition of a mineral acid, the ureido acid is precipitated.

$$\begin{array}{l} RCH(CH_2)_nNH_2 \\ \quad | \\ \quad COONa \end{array} + C_{10}H_7{}^{\alpha}N{=}C{=}O \longrightarrow \begin{array}{l} RCH(CH_2)_nNHCONHC_{10}H_7{}^{\alpha} \\ \quad | \\ \quad COONa \end{array} \xrightarrow[HCl]{Dilute}$$

$$\begin{array}{l} RCH(CH_2)_nNHCONHC_{10}H_7{}^{\alpha} \\ \quad | \\ \quad COOH \end{array}$$

Dissolve 0·5 g. of the amino acid in slightly more than the equivalent quantity of *N* sodium hydroxide solution in a small glass bottle or flask. Add a quantity of α-naphthyl *iso*cyanate just equivalent to the alkali (if the molecular weight of the compound is not known, use 1 g. of the reagent and the corresponding quantity of alkali), stopper the bottle or flask and shake vigorously until the odour of the reagent has disappeared. Filter off any insoluble di-α-naphthylurea (resulting from the action of water upon the excess of the reagent), and acidify the filtrate to Congo red with dilute hydrochloric acid. Filter the α-naphthylhydantoic acid at the pump, wash it with a little cold water, and recrystallise from hot water or dilute alcohol.

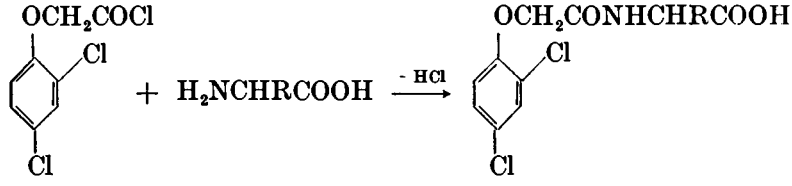
The phenylhydantoic acid is prepared similarly, using phenyl *iso*cyanate. The latter is more sensitive to water than α-naphthyl *iso*cyanate and therefore does not keep so well.

4. ***p*-Toluenesulphonates.** Amino acids react with *p*-toluenesulphonyl chloride (compare Section **IV,100,***3*) under the following experimental conditions to yield, in many cases, crystalline *p*-toluenesulphonates.

Dissolve 0·01 g. equivalent of the amino acid in 20 ml. of *N* sodium hydroxide solution and add a solution of 2 g. of *p*-toluenesulphonyl chloride in 25 ml. of ether ; shake the mixture mechanically or stir vigorously for 3–4 hours. Separate the ether layer : acidify the aqueous layer to Congo red with dilute hydrochloric acid. The derivative usually crystallises out rapidly or will do so on standing in ice. Filter off the crystals and recrystallise from 4–5 ml. of 60 per cent. alcohol.

With phenylalanine and tyrosine, the sodium salt of the derivative is sparingly soluble in water and separates during the initial reaction. Acidify the suspension to Congo red : the salts pass into solution and the mixture separates into two layers. The derivative is in the ethereal layer and crystallises from it within a few minutes. It is filtered off and recrystallised.

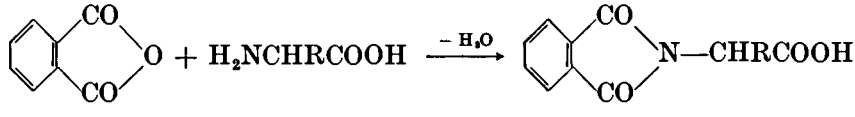
5. **2 : 4-Dichlorophenoxyacetates.** Amino acids react with 2 : 4-dichlorophenoxyacetyl chloride to give crystalline derivatives :



Dissolve 0·01 g. equivalent of the amino acid in 0·03 g. equivalent of *N* sodium hydroxide solution and cool to 5° in a bath of ice. Add, with rapid stirring, 0·01 g. equivalent of 2 : 4-dichlorophenoxyacetyl chloride dissolved in 5 ml. of dry benzene at such a rate (5–10 minutes) that the temperature of the mixture does not rise above 15° ; if the reaction mixture gels after the addition of the acid chloride, add water to thin it. Remove the ice bath and stir for 2–3 hours. Extract the resulting mixture with ether, and acidify the aqueous solution to Congo red with dilute hydrochloric acid. Collect the precipitate by filtration and recrystallise it from dilute alcohol.

Commercial 2 : 4-dichlorophenoxyacetic acid may be recrystallised from benzene ; m.p. 139–140°. Reflux 10 g. of the acid with 15 ml. of thionyl chloride on a steam bath for 1 hour, distil off the excess of thionyl chloride at atmospheric pressure and the residue under reduced pressure : 2 : 4-dichlorophenoxyacetyl chloride (8 g.) passes over at 155–157°/22–23 mm. It occasionally crystallises (m.p. 44·5–45·5°), but usually tends to remain as a supercooled liquid.

6. **Phthalyl derivatives.** Many amino acids condense with phthalic anhydride at 180–185° to yield crystalline phthalyl derivatives :



Place 0·5 g. of the amino acid and 1·0 g. of phthalic anhdride in a Pyrex test-tube and immerse the lower part of the tube in an oil bath, which has previously been heated to 180–185°. Stir the mixture occasionally during the first 10 minutes and push down the phthalic anhydride which sublimes on the walls into the reaction mixture with a glass rod. Leave the mixture undisturbed for 5 minutes. After 15 minutes, remove the test-tube from the bath : when the liquid mass solidifies, invert the test-tube and scrape out the excess of phthalic anhydride on the walls. Recrystallise the residue from 10 per cent ethanol or from water.

The melting points of the derivatives of a number of amino acids are collected in Table **III,132.** Most α-amino acids decompose on heating so that the melting points would be more accurately described as decomposition points : the latter vary somewhat with the rate of heating and the figures given are those obtained upon rapid heating.

Amino Acid	M.P.*	Benzoate	3 : 5-Dinitro-benzoate	Phenyl-ureido Acid	*p*-Toluene-sulphonate	2 : 4-Dichloro-phenoxy-acetate	α-Naphthyl-ureido Acid	Phthalyl Derivative
Glycine	232°	187°	179°	163°	150°	235°	191°	192°
dl-α-Alanine	295	166	177	174	139	213	198	161
d- or *l*-α-Alanine	297	151	—	190	139	199	202	—
β-Alanine	196	165	202	174	—	—	236	—
dl-Valine	298	132	—	164	110	159	204	102
d- or *l*-Valine	315	127	181	147	149	—	—	—
dl-Leucine	332	141	—	165	—	138	—	141
d- or *l*-Leucine	337	107	187	115	124	150	163	116
dl-iso-Leucine	292	118	—	—	141	143	—	—
d- or *l-iso*-Leucine	284	117	—	120	132	—	178	121
dl-nor-Leucine	327	—	—	—	124	—	—	112
dl-Serine	246	171	183	169	213	195	191	—
dl-Threonine	235	148	—	—	—	139	—	103
d- or *l*-Threonine	253	148	—	—	—	—	—	—
dl-Aspartic Acid	280	165	—	—	—	217	—	—
d- or *l*-Aspartic Acid	272	185	—	162	140	202	115	—
dl-Asparagine	—	—	—	—	—	—	—	—
d- or *l*-Asparagine	227	189	196	164	175	—	119	—
dl-Glutamic acid	227	156	—	—	213	192	—	—
d- or *l*-Glutamic acid	198	138	217	—	117	—	236	189
dl-Histidine	—	—	—	—	—	129	—	—
d- or *l*-Histidine	277	249	189	—	204	—	—	296
dl-Arginine	238	230	—	—	—	—	—	—
dl-Lysine	—	249	—	196	—	176	—	171
d- or *l*-Lysine	224	150	169	184	—	87	199	—
N-Phenylglycine	126	63	—	195	—	—	—	—
dl-Phenylalanine	274	188	93	182	135	180	—	175
d- or *l*-Phenylalanine	320	146	93	181	165	155	—	—
dl-Tyrosine	318	197	254	—	—	—	—	268

* For footnote, see p. 440.

TABLE III,132. **AMINO ACIDS—*Continued***

Amino Acid	M.P.*	Benzoate	3 : 5-Dinitro-benzoate	Phenyl-ureido Acid	*p*-Toluene-sulphonate	2 : 4-Dichloro-phenoxy-acetate	α-Naphthyl-ureido Acid	Phthalyl Derivative
d- or *l*-Tyrosine	344°	166°	—	104°	119°	—	205°	—
dl-Tryptophane	275	188	240°	—	176	148°	—	—
d- or *l*-Tryptophane	289	104	233	166	176	—	158	—
d- or *l*-Cystine	260	181	180	160	205	216	—	—
dl-Methionine	272	151	—	—	105	145	—	—
d- or *l*-Methionine	283	150	95	—	—	134	186	—
dl-Proline	203	—	217	170	—	145	—	—
d- or *l*-Proline	222	—	—	170	133	106	—	—
Sarcosine	210	103	153	—	102	—	—	—
Anthranilic acid	145	182	278	181	217	—	—	—
m-Aminobenzoic acid	174	248	270	270	—	—	—	—
p-Aminobenzoic acid	186	278	290	300	223	—	—	—
p-Aminophenylacetic acid	200	206	—	—	—	—	—	—
dl-α-Amino-*n*-butyric acid	307	147	—	170	—	—	194	—
α-Amino-*iso*-butyric acid	280 Sub.	202d	—	—	—	—	198	—

* These melting points are probably better described as decomposition points; their values will depend somewhat upon the rate of heating.

III,133. UREA

Wohler's classical synthesis of urea from ammonium cyanate may be carried out by evaporating solutions of sodium cyanate and ammonium sulphate :

$$2NaCNO + (NH_4)_2SO_4 \longrightarrow 2NH_4CNO + Na_2SO_4$$
$$NH_4CNO \longrightarrow CO(NH_2)_2$$

In aqueous solution at 100° the change is reversible and equilibrium is reached when 95 per cent. of the ammonium cyanate has changed into urea. Urea is less soluble in water than is ammonium sulphate, hence if the solution is evaporated, urea commences to separate, the equilibrium is disturbed, more ammonium cyanate is converted into urea to maintain the equilibrium and eventually the change into urea becomes almost complete. The urea is isolated from the residue by extraction with boiling methyl or ethyl alcohol. The mechanism of the reaction which is generally accepted involves the dissociation of the ammonium cyanate into ammonia and cyanic acid, and the addition of ammonia to the latter :

$$NH_4CNO \longrightarrow NH_3 + HNC{=}O \longrightarrow HN{=}C(OH)NH_2 \longrightarrow CO(NH_2)_2$$

The industrial methods of preparation are :—

(i) by partial hydrolysis of cyanamide, itself derived from calcium cyanamide :

$$CaCN_2 \longrightarrow H_2NC{\equiv}N + H_2O \longrightarrow CO(NH_2)_2$$

(ii) by heating ammonium carbamate (from carbon dioxide and ammonia) under pressure :

$$NH_2COONH_4 \longrightarrow H_2O + CO(NH_2)_2$$

Dissolve 20 g. of sodium cyanate in 75 ml. of distilled water in an evaporating dish and mix this with a solution of 25 g. of ammonium sulphate in 75 ml. of water. Evaporate to *complete* dryness on a water bath ; break the crystalline crust from time to time by stirring with a glass rod. Transfer the residue to a 250 ml. flask fitted with a reflux condenser, add 30 ml. of absolute ethyl or methyl alcohol, and boil gently for 5–10 minutes in order to extract the urea. Filter the boiling solution through a fluted filter paper (preferably contained in a hot water funnel). Return the residue to the flask and extract again with 30 ml. of methyl or ethyl alcohol ; filter as before and wash the residue on the filter with 10 ml. of boiling alcohol. Combine the filtrates and cool in crushed ice. Filter the crystals of urea at the pump and allow to dry in the air. The yield is 8 g., m.p. 132°. A further small quantity of urea may be obtained by evaporating the alcoholic filtrate to about 10 ml. and cooling in ice.

Reactions of Urea

The student should carry out the following reactions of urea :

(i) **Solubility.** Confirm that urea is very soluble in water and dissolves in hot methyl, ethyl and amyl alcohol, but is almost insoluble in ether.

(ii) **Sodium hydroxide solution.** Dissolve 0·2 g. of urea in 5 ml. of dilute sodium hydroxide solution and warm. Observe that ammonia is evolved.

$$CO(NH_2)_2 + 2NaOH \longrightarrow Na_2CO_3 + 2NH_3$$

(iii) **Nitrous acid.** Dissolve 0·2 g. of urea in 2–3 ml. of dilute hydrochloric acid and add 3 ml. of dilute (about 5 per cent.) sodium nitrite solution. Effervescence occurs, and nitrogen and carbon dioxide are evolved :

$$CO(NH_2)_2 + 2HNO_2 \longrightarrow CO_2 + 2N_2 + 3H_2O$$

(iv) **Sodium hypobromite (or hypochlorite) solution.** Dissolve 0·5 g. of urea in 3 ml. of water and add 5–10 ml. of dilute sodium hypochlorite or hypobromite solution.* Nitrogen is evolved.

$$CO(NH_2)_2 + 3NaOBr + 2NaOH \longrightarrow N_2 + 3H_2O + Na_2CO_3 + 3NaBr$$

(v) **Urea nitrate.** Dissolve 0·5 g. of urea in 3 ml. of water and add 1 ml. of concentrated nitric acid. White crystals of urea nitrate ($CO(NH_2)_2,HNO_3$) separate immediately.

(vi) **Urea oxalate.** Dissolve 0·5 g. of urea in 3 ml. of water and add a solution of 0·6 g. of oxalic acid in 7 ml. of water. Upon stirring urea oxalate ($2CO(NH_2)_2,H_2C_2O_4$) crystallises out.

Urea oxalate is also sparingly soluble in amyl alcohol and since urea is soluble in this alcohol, the property may be utilised in separating urea from mixtures. An aqueous extract of the mixture is rendered slightly alkaline with sodium hydroxide solution and extracted with ether ; this removes all the basic components, but not urea. The residual aqueous solution is extracted with amyl alcohol (to remove the urea) : upon adding this extract to a solution of oxalic acid in amyl alcohol crystalline urea oxalate is precipitated.

(vii) **Biuret reaction.** Place 0·5 g. of urea in a dry test-tube and heat gently just above the m.p. for 1–2 minutes. Ammonia is first evolved and the residue solidifies with the formation of biuret :

$$CO(NH_2)_2 \longrightarrow NH_3 + HCNO$$

$$HCNO + H_2NCONH_2 \longrightarrow H_2NCONHCONH_2 \text{ (biuret)}$$

The latter may be identified by dissolving the residue in 5 ml. of water and adding 1 drop of very dilute copper sulphate solution and 2 drops of 10 per cent. sodium hydroxide solution : a violet colour is produced.

(viii) **Xanthhydrol reaction.** Add a solution of 0·1 g. of urea in 2 ml. of acetic acid to 1–2 ml. of a 5 per cent. solution of xanthhydrol in acetic acid or in methyl alcohol (see Section **III,110**) and warm. Filter off the dixanthhydryl urea and recrystallise it from aqueous dioxan ; wash with a little alcohol and ether, and dry at 80°. Determine the m.p. (274°).

III,134. THIOUREA (THIOCARBAMIDE)

Thiourea (II) may be obtained from ammonium thiocyanate (I) by an isomeric change analogous to ammonium cyanate, but the equilibrium relationship is very different (compare Section **III,133**) :

$$NH_4CNS \text{ (I)} \rightleftharpoons NH_3 + HCNS \rightleftharpoons HN{=}C(SH)NH_2 \rightleftharpoons CS(NH_2)_2 \text{ (II)}$$

* The hypobromite solution may be prepared by treating 5 ml. of bromine water with dilute sodium hydroxide solution, dropwise, until the bromine colour is just discharged.

Between 140° and 180° equilibrium is set up at a fairly rapid rate, but only 25 per cent. of thiourea is present in the equilibrium mixture. The yield is therefore far from satisfactory.

It is prepared commercially by treating cyanamide (from calcium cyanamide) with ammonium sulphide :

$$NH_2C{\equiv}N + H_2S \longrightarrow NH_2C(SH){=}NH \longrightarrow CS(NH_2)_2$$

Place 50 g. of ammonium thiocyanate in a small round-bottomed flask and immerse a thermometer in the substance. Heat in an oil bath until the temperature rises to 170° and maintain it at this temperature for 1 hour. Allow the melt to cool and extract it with 60–70 ml. of hot water. Filter the solution and allow to cool when crude thiourea separates; the unchanged ammonium thiocyanate remains in the solution. Filter off the crude product and recrystallise it from a little hot water. The yield of thiourea, m.p. 172°, is 8 g.

POLYHYDRIC ALCOHOLS, FATS AND SOAPS

Polyhydric alcohols are compounds containing two or more hydroxyl groups in the molecule. The two most important are *ethylene glycol* $HOCH_2CH_2OH$ (a dihydric alcohol) and *glycerol* $HOCH_2CH(OH)CH_2OH$ (a trihydric alcohol). Ethylene glycol may be obtained by the hydrolysis of ethylene dibromide or ethylene dichloride with dilute aqueous sodium hydroxide or sodium carbonate solution :

$$BrCH_2CH_2Br + 2NaOH \longrightarrow HOCH_2CH_2OH + 2NaBr$$

Industrially, it is produced directly from ethylene by the addition of hypochlorous acid, followed by treatment of the resulting ethylene chlorohydrin with sodium bicarbonate solution :

$$CH_2{=}CH_2 + HOCl \longrightarrow ClCH_2CH_2OH$$
$$ClCH_2CH_2OH + NaHCO_3 \longrightarrow HOCH_2CH_2OH + CO_2 + NaCl$$

When ethylene chlorohydrin is heated with sodium hydroxide solution, the highly reactive cyclic ether, *ethylene oxide*, is formed :

$$ClCH_2CH_2OH + NaOH \longrightarrow \begin{matrix} CH_2 \\ | \\ CH_2 \end{matrix}\!\!>O + NaCl + H_2O$$

Upon reaction with an alcohol in the presence of a catalyst, the monoalkyl ether of ethylene glycol is obtained :

$$\begin{matrix} CH_2 \\ | \\ CH_2 \end{matrix}\!\!>O + ROH \longrightarrow HOCH_2CH_2OR$$

The monoalkyl ethers with R = CH_3, C_2H_5 and $C_4H_9{}^{\alpha}$, known respectively as *methyl cellosolve*, *cellosolve* and *butyl cellosolve*, are of great commercial value, particularly as solvents, since they combine the properties of alcohols and ethers and are miscible with water. Equally important compounds are the *carbitols* (monoalkyl ethers of diethyleneglycol) prepared by the action of ethylene oxide upon the monoethers of ethylene glycol :

$$\begin{matrix} CH_2 \\ | \\ CH_2 \end{matrix}\!\!>O + HOCH_2CH_2OR \longrightarrow HOCH_2CH_2OCH_2CH_2OR$$

Thus with R = CH_3, C_2H_5 and $C_4H_9{}^{\alpha}$, the compounds are called *methyl carbitol*, *carbitol* and *butyl carbitol* respectively. None of these compounds can be conveniently prepared in the laboratory by elementary students : they are, however, readily available commercially. The preparation of one glycol, pinacol or tetramethylene glycol from acetone, has already been described (Section **III,77**).

The term **fat** is applied to solid esters of fatty acids with glycerol (glycerides) ; if the fat is liquid at the ordinary temperature, it is conventionally called a **fatty oil**, **vegetable oil** or **animal oil**. The acids which occur most abundantly are palmitic acid $CH_3(CH_2)_{14}COOH$, stearic acid $CH_3(CH_2)_{16}COOH$ and oleic acid $CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$. Upon hydrolysis, fats yield glycerol and the alkali salts of these acids (soaps) :

$$\begin{matrix} CH_2OOCR \\ | \\ CHOOCR \\ | \\ CH_2OOCR \end{matrix} + 3NaOH \longrightarrow \begin{matrix} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{matrix} + 3RCOONa$$

Glyceride — Glycerol — Soap

The free acids are obtained upon acidification. Fats usually consist of mixtures of glycerides. The term **wax** is usually applied to esters of fatty acids with other alcohols such as cetyl alcohol $CH_3(CH_2)_{14}CH_2OH$ and oleyl alcohol $CH_3(CH_2)_7CH=CH(CH_2)_7CH_2OH$.

The cleansing action of soap (sodium or potassium salts of the above-mentioned fatty acids) is connected with the colloidal properties in aqueous solution of the anions of high molecular weight. Such colloidal solutions possess the property of causing other substances (grease, oil and " dirt ") to form emulsions. Another group of substances possessing excellent detergent and lathering properties consists of the sulphates of long chain alcohols, $CH_3(CH_2)_nOSO_3Na$ {common values of n include 11 (lauryl), 15 (cetyl) and 17 (stearyl)}; these alcohols are obtained by the catalytic hydrogenation of the esters of the corresponding acids or of the glycerides themselves. These detergents, marketed under the trade names of *Gardinol, Pentrone, Dreft, Drene, etc.*, possess certain advantages over soap, *e.g.*, they are not affected by dilute acid solutions nor by the presence of alkaline earth salts (*i.e.*, they do not give precipitates with hard water since their calcium and magnesium salts are comparatively soluble).

Some vegetable or fatty oils (*e.g.*, linseed, tung and oiticica oils) when exposed to air in thin layers absorb oxygen and are converted into hard but elastic solids. This change is spoken of as **drying. Drying oils** contain a large proportion of the glycerides of oleic ($CH_3(CH_2)_7CH=CH(CH_2)_7COOH$ or $C_{18}H_{34}O_2$), linoleic ($C_{18}H_{32}O_2$—two ethylenic linkages), linolenic ($C_{18}H_{30}O_2$—three ethylenic linkages) and other unsaturated acids. The reactions involved in the drying of oil films are not completely understood, but oxygen is probably absorbed at the ethylenic linkages and some form of polymerisation results. Linseed oil (obtained from flax seed) is widely used, but the fresh or raw linseed oil dries slowly; the change takes place more rapidly if the oil is previously heated to about 150-200° and mixed with a small amount of certain metallic catalysts, for example, the cobalt, manganese and lead salts of linoleic, oleic and naphthenic acids, known as **driers.** The product is known as " boiled linseed oil." Oil paints are merely suspensions of finely divided pigments (white lead, red lead, lithopone, etc.) in boiled linseed or some other drying oil: a solvent, such as turpentine, is usually added to facilitate the application to surfaces. Varnishes consist of natural or synthetic resins dissolved in a volatile solvent; in oil varnishes, a drying oil is added to increase the elasticity and durability of the film. Synthetic drying oils are now available.

III,135. SAPONIFICATION OF A FAT. SOAP

Place 5 g. of lard (or any fat or fatty oil), 3 g. of potassium hydroxide and 40 ml. of alcohol in a 250 ml. round-bottomed flask, attach a reflux condenser, and boil for about 30 minutes. The reaction is complete when no globules of oil are present when a few drops of the mixture are mixed with a little water. Distil the reaction mixture (Fig. *II, 13,* 3) and recover the alcohol; dissolve the residue in 75 ml. of hot water. Carry out the following experiments with the resulting solution :—

(i) To 25 ml. of the solution add slowly and with stirring a saturated solution of sodium chloride. Filter off the precipitate of soap and wash it with a little saturated sodium chloride solution, and spread it on a watch glass to dry. Test a portion of the product for its lathering properties by rubbing it with water between the hands. Use another portion to determine whether it is soluble in water.

(ii) Mix 10 ml. of the solution with an equal volume of tap water, shake well and observe the result.

(iii) Acidify 20 ml. of the solution with dilute sulphuric acid, filter off the insoluble organic product (set the filtrate aside), wash it with water and perform the following test-tube experiments with it :—

(*a*) Test its solubility in water and compare the result with that in (i).

(*b*) Shake vigorously with a little sodium hydroxide solution. Determine whether the resulting solution possesses lathering properties.

(*c*) Dissolve a small portion in 2–3 ml. of carbon tetrachloride and add a few drops of a solution of bromine in carbon tetrachloride. Observe the bromine is decolourised, thus indicating the presence of an unsaturated acid.

(iv) Acidify the remainder of the solution with dilute sulphuric acid, cool, filter and wash with a little water. Combine the filtrate with that from (iii), just neutralise it with sodium carbonate solution and evaporate to dryness on a water bath in a large evaporating dish. Extract the residue with 15 ml. of absolute alcohol, and filter the alcoholic solution. Evaporate the alcoholic extract on a water bath : the viscous residue consists of crude glycerol. It may be identified by conversion into the tribenzoate (see Section **III,136,*l***).

Drying oils. Place 3 ml. of linseed oil in a test-tube, add about 0·1 g. of litharge and boil the mixture gently for 10 minutes. When cold, pour a little of the product on a watch glass and spread the oil into a thin film with the aid of a small piece of paper. Pour a little of the untreated linseed oil on another watch glass and spread it out as a thin film. Compare the times taken for the films to become dry.

III,136. REACTIONS AND CHARACTERISATION OF POLYHYDRIC ALCOHOLS

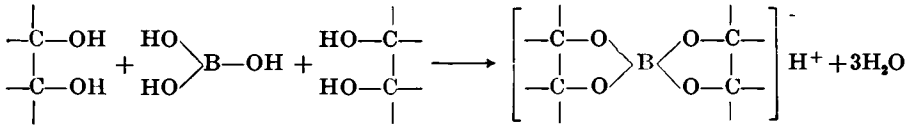
Some characteristic reactions of polyhydric alcohols are given below :

(i) They are colourless viscid liquids (or crystalline solids) freely soluble in water, but insoluble in anhydrous ether.

(ii) Upon heating with a little potassium hydrogen sulphate, they may yield aldehydes (*e.g.*, ethylene glycol yields acetaldehyde ; glycerol gives the irritating odour of acrolein, $CH_2{=}CHCHO$), which can be identified with Schiff's reagent and with dimedone (Section **III,70,*2***).

(iii) Upon adding a few drops of phenolphthalein to a 1 per cent. solution of borax, a pink colouration is produced : the addition of a polyhydric alcohol causes the pink colour to disappear, but it reappears on warming and vanishes again upon cooling.

This reaction is due to the combination of two *cis* hydroxyl groups of the compound with the boric acid to form a much stronger monobasic acid :



(iv) **Periodic acid test.** Periodic acid has a selective oxidising action upon 1 : 2-glycols and upon α-hydroxy aldehydes and ketones (*Malaprade reaction*) :

$$RCHOH.CHOHR' + HIO_4 \longrightarrow RCHO + R'CHO + H_2O + HIO_3$$
$$RCHOH.COR' + HIO_4 \longrightarrow RCHO + R'COOH + HIO_3$$

Add 1 drop (0·05 ml.) of concentrated nitric acid to 2·0 ml. of a 0·5 per cent. aqueous solution of paraperiodic acid (H_5IO_6) contained in a small test-tube and shake well. Then introduce 1 drop or a small crystal of the compound. Shake the mixture for 15 seconds and add 1–2 drops of 5 per cent. aqueous silver nitrate. The immediate production of a *white* precipitate (silver iodate) constitutes a positive test and indicates that the organic compound has been oxidised by the periodic acid. The test is based upon the fact that silver iodate is sparingly soluble in dilute nitric acid whereas silver periodate is very soluble ; if too much nitric acid is present, the silver iodate will not precipitate.

An alternative procedure for the above test is as follows. Mix 2–3 ml. of 2 per cent. aqueous paraperiodic acid solution with 1 drop of dilute sulphuric acid (*ca.* 2·5*N*) and add 20–30 mg. of the compound. Shake the mixture for 5 minutes, and then pass sulphur dioxide through the solution until it acquires a pale yellow colour (to remove the excess of periodic acid and also iodic acid formed in the reaction). Add 1–2 ml. of Schiff's reagent (Section **III,70**) : the production of a violet colour constitutes a positive test.

Crystalline Derivatives

1. **Benzoates.** The preparation of benzoates of polyhydric alcohols may be illustrated by reference to glycerol. They are usually crystalline solids.

Method 1. Place in a test-tube or small flask 1·3 g. of glycerol and 30 ml. of 10 per cent. sodium hydroxide solution ; add gradually, with simultaneous shaking, 1·2 g. of benzoyl chloride. Stopper the vessel, shake for several minutes and allow to stand. Decant the solution from the pasty solid and wash the latter with cold water by decantation. Recrystallise the solid tribenzoate from dilute rectified (or methylated) spirit or from light petroleum, b.p. 40–60° ; the pure compound has m.p. 76°.

Method 2. Add gradually 2·5 ml. of benzoyl chloride to a solution of 0·5 g. of glycerol in 5 ml. of pure pyridine, cooled in ice ; then reflux for 1 hour. Treat the cold mixture with dilute sulphuric acid ; this dissolves the pyridine salt and precipitates the glycerol tribenzoate. Wash it with sodium bicarbonate solution, followed by water, and recrystallise as in Method 1.

Derivatives of higher melting point may be obtained with *p*-nitrobenzoyl chloride ; the experimental details are similar to those given above for benzoyl chloride. 3 : 5-Dinitrobenzoyl chloride (Section **III,27,*1***) may also be used ; glycerol gives unsatisfactory results with this reagent.

2. **α-Naphthyl carbamates (or α-naphthyl urethanes).** Full details are given in Section **III,27,*4***.

The melting points of a few derivatives of selected polyhydric alcohols are collected in the following table.

TABLE III,136. POLYHYDRIC ALCOHOLS

Alcohol	B.P.	Benzoate	*p*-Nitro-benzoate	3:5-Dinitro-benzoate	Phenyl-urethane	α-Naphthyl-urethane	Other Derivatives
2 : 3-Butanediol (1)	182°	76°	—	—	201°	—	—
1 : 2-Propanediol (2)	189	—	127°	—	153	—	—
Ethylene glycol	198	73	141	169°	157	176°	—
1 : 3-Butanediol (3)	208	—	—	—	123	—	—
1 : 3-Propanediol (4)	215	59	119	178	137	164	—
1 : 4-Butanediol (5)	230	82	175	—	183	199	—
1 : 5-Pentanediol (6)	239	—	105	—	176	147	—
Diethylene glycol (7)	244	—	—	149	—	122	—
1 : 6-Hexanediol (8)	250*	—	—	—	—	—	—
Triethylene glycol (9)	285	—	—	—	108	—	—
2-Butyne-1 : 4-diol	145°/15†	—	—	190	131	—	—
Glycerol	190d	76	188	—	180	192	—
Sorbitol	m.p. 110	129	—	—	—	—	Acetate, 99°
Mannitol	m.p. 166	149	—	—	303	—	Acetate, 121‡
Pentaerythritol	m.p. 253	99	—	—	—	—	Acetate, 84

(1) 2 : 3-Butylene glycol. (2) α-Propylene glycol. (3) 1 : 3-Butylene glycol.
(4) Trimethylene glycol. (5) Tetramethylene glycol. (6) Pentamethylene glycol.
(7) ββ′-Dihydroxydiethyl ether. (8) Hexamethylene glycol. (9) Ethylene glycol di-(β-hydroxyethyl) ether.

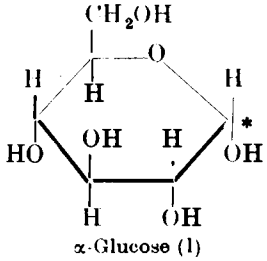
* M.p. 42°. † M.p. 55°.

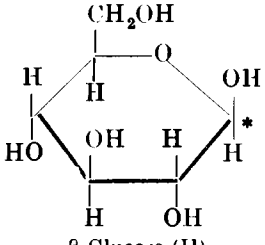
‡ The hexa-acetyl derivative, m.p. 121°, may be prepared as follows. Boil under reflux 1 part of mannitol with 5 parts by weight of acetic anhydride and 1 part of anhydrous sodium acetate or with a little anhydrous zinc chloride for 15-20 minutes, pour into excess of water, stir the mixture until the oil has solidified, and then recrystallise from methylated spirit.

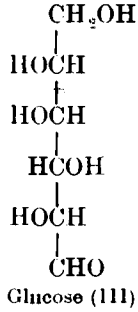
CARBOHYDRATES

Carbohydrates may be divided into **monosaccharides, disaccharides and polysaccharides.** The monosaccharides under certain conditions react as polyhydroxy-aldehydes or polyhydroxy-ketones: two important representatives are glucose $C_6H_{12}O_6$ (an aldose) and fructose (laevulose) $C_6H_{12}O_6$ (a ketose). Upon hydrolysis di- and polysaccharides yield ultimately monosaccharides. Common disaccharides are sucrose, lactose and maltose (all of molecular formula $C_{12}H_{22}O_{11}$), whilst starch, dextrin and cellulose, $(C_6H_{10}O_5)_n$ in which $n > 4$, are typical polysaccharides.

The existence of two forms of glucose and of two isomeric methyl glucosides, as well as other experimental evidence, have led to the adoption of the ring structures (I) and (II):


α-Glucose (I)


β-Glucose (II)

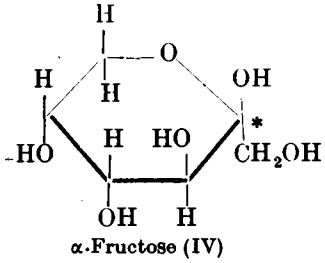

Glucose (III)

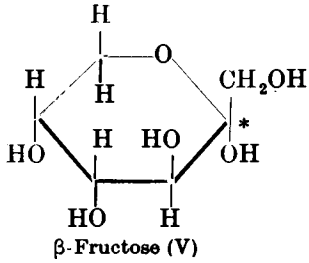
these differ only with regard to the disposition of the H and OH groups about the carbon atoms marked with an asterisk. If the ring be regarded as being in the plane of the paper, α-glucose may have this hydrogen atom above and the OH group below the plane of the paper, whilst β-glucose will have this hydrogen atom below and the OH group above the plane. Under certain conditions the ring opens and glucose reacts as an open chain compound (III). The facility with which the two isomeric forms of glucose pass into one another, in contrast to the stability of the α- and β-methyl glucosides, lends support to the view that both cyclic forms are in equilibrium with a minute amount of the open chain isomeride.

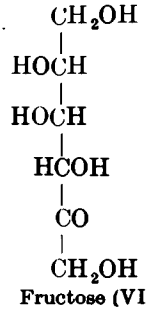
α-Glucose (cyclic) (I) ⇌ Open chain aldehyde (III) ⇌ β-Glucose (cyclic) (II)

It is probable that many of the reactions of glucose in solution are due to the small amount of the open chain aldehyde present. If this reacts in a normal manner with a reagent, the equilibrium is disturbed, most of the cyclic form passes into (III) and ultimately the reaction proceeds to completion.

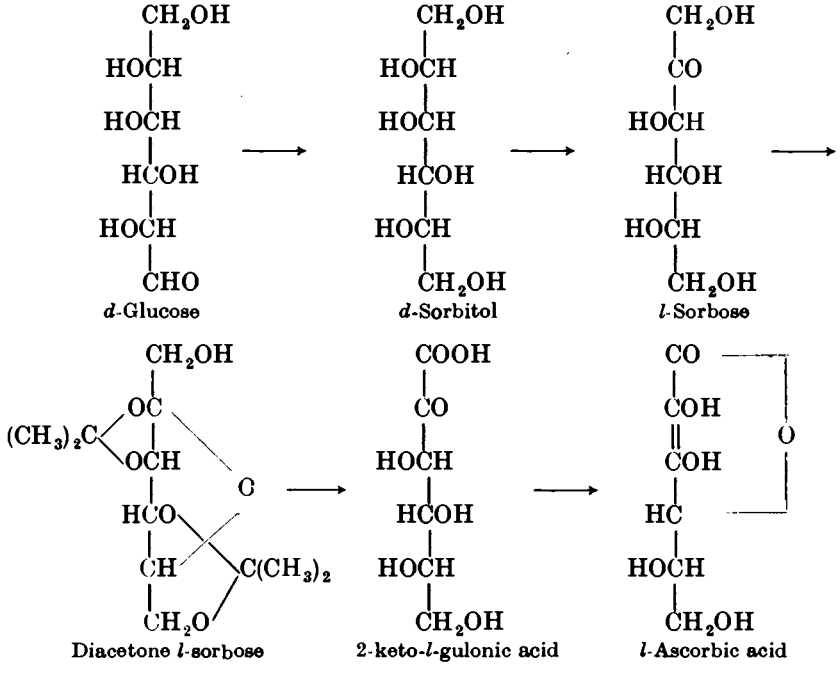
Fructose may be similarly formulated:


α-Fructose (IV)


β-Fructose (V)

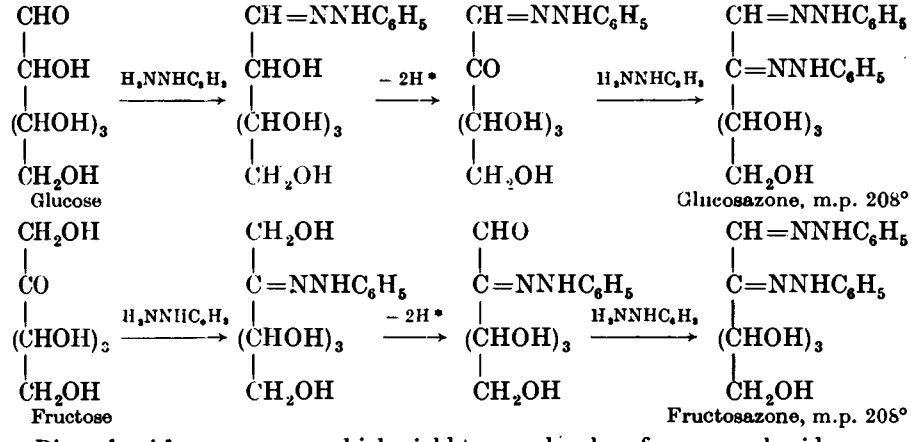

Fructose (VI)

A substance, very closely related to fructose, ***l*-sorbose**, merits mention here as it is an intermediate in the synthesis of *l*-ascorbic acid. *d*-Glucose is converted into the alcohol sorbitol by catalytic (Cu-Cr) hydrogenation, and this upon bacterial oxidation (*Acetobacter xylinum*) gives the 2-hexose, *l*-sorbose. The latter forms a 2 : 3 : 4 : 6-diacetone-*l*-sorbose (condensation of acetone with two pairs of *cis* hydroxyl groups), which is oxidised by potassium permanganate to diacetone-2-keto-*l*-gulonic acid, readily hydrolysed to the free acid, 2-keto-*l*-gulonic acid. The last named upon heating with water is transformed into *l*-ascorbic acid : a better procedure consists in converting the free acid into its methyl ester and heating this with sodium methoxide in methyl alcohol, whereby the sodium salt of *l*-ascorbic acid is formed. The 2-keto-*l*-gulonic acid may be prepared more easily by oxidation of the ketose with nitric acid : preferential oxidation of the primary alcoholic group adjacent to the keto group occurs.



The carbohydrates containing an aldehyde or a keto group (" potential " in cyclic form) react with one molecular proportion of phenylhydrazine in the cold to form the corresponding phenylhydrazone (compare Section **III,74**) ; these are usually soluble in water and consequently of little value for purposes of separation and identification. If, however, they are heated at 100° in the presence of excess (3–4 mols) of phenylhydrazine, the >CHOH in an aldose and the —CH_2OH group in a ketose adjacent to the phenylhydrazone group are apparently oxidised by one molecule of phenylhydrazine into a keto and aldehydo group respectively, which condense with a further molecule of phenylhydrazine to give a di-phenylhydrazone or **osazone**. The osazones are usually yellow, well-defined crystalline compounds and are sparingly soluble in cold water. The characteristic crystalline forms of the osazones of the commonly occurring sugars, when examined under the microscope, may be employed for their identification ; the melting or decomposition points are less satisfactory since these depend to a marked degree upon the rate of heating.

Glucose and fructose give the same osazone. This will be evident from the following schemes representing the reactions which are believed to occur :



Disaccharides are sugars which yield two molecules of monosaccharides upon hydrolysis. The four of greatest practical interest are :

$$\underset{\text{Sucrose}}{C_{12}H_{22}O_{11}} + H_2O \longrightarrow \underset{d\text{-Glucose}}{C_6H_{12}O_6} + \underset{d\text{-Fructose}}{C_6H_{12}O_6}$$

$$\underset{\text{Lactose}}{C_{12}H_{22}O_{11}} + H_2O \longrightarrow \underset{d\text{-Glucose}}{C_6H_{12}O_6} + \underset{d\text{-Galactose}}{C_6H_{12}O_6}$$

$$\underset{\text{Maltose}}{C_{12}H_{22}O_{11}} + H_2O \longrightarrow \underset{d\text{-Glucose}}{C_6H_{12}O_6} + \underset{d\text{-Glucose}}{C_6H_{12}O_6}$$

$$\underset{\text{Cellobiose}}{C_{12}H_{22}O_{11}} + H_2O \longrightarrow \underset{d\text{-Glucose}}{C_6H_{12}O_6} + \underset{d\text{-Glucose}}{C_6H_{12}O_6}$$

The relation of cellobiose to maltose is just the same as that of β-methyl to α-methyl-glucoside. To understand the characteristic reactions of the above disaccharides, all that need be remembered is the manner of union of the monose residues. If union may be regarded as occurring between the " potential" or free aldehyde or the "potential" or free ketone groupings, the resulting disaccharide (*e.g.*, sucrose) has no reducing properties nor does it react with phenylhydrazine. If only one of the " potential " or actual aldehyde groups is concerned, the sugar formed possesses reducing properties, reacts with phenylhydrazine, *etc.* (for example, lactose, maltose and cellobiose).

III,137. α- AND β-GLUCOSE PENTA-ACETATE

Upon heating glucose with excess of acetic anhydride in the presence of a catalyst, all five hydroxyl groups are acetylated ; the resulting penta-acetate can exist in two isomeric forms corresponding to the α- and β-forms of glucose (I) and (II). With zinc chloride as catalyst, the α-glucose penta-acetate is the main product; with sodium acetate, the β-glucose penta-acetate is largely formed.

α-Glucose penta-acetate. Into a 100 ml. round-bottomed or conical flask place 0·5 g. of anhydrous zinc chloride (1) and 12·5 ml. of acetic anhydride : attach a reflux condenser and heat on a boiling water bath for 5–10 minutes. Add slowly 2·5 g. of powdered glucose, shaking the mixture gently during the addition in order to control the vigorous

* This change involves the oxidation of the alcohol grouping of C^2 or C^1 to carbonyl by the action of a second molecule of phenylhydrazine ; the latter is reduced to aniline and ammonia. Alternative explanations of this reaction have been advanced, but these cannot be discussed here (see, however, Section III,139,5).

reaction which ensues. Finally, heat the flask for 1 hour on a boiling water bath. Pour the contents of the flask into 125 ml. of ice water; stir the mixture and cool in ice for 30 minutes. The oil which separates out first will solidify during the stirring. Filter, wash with a little cold water, and recrystallise from methyl alcohol or from methylated spirit until the m.p. is constant; two recrystallisations generally suffice. The pure product melts at 110–111°. The yield is 3·5 g.

Note.

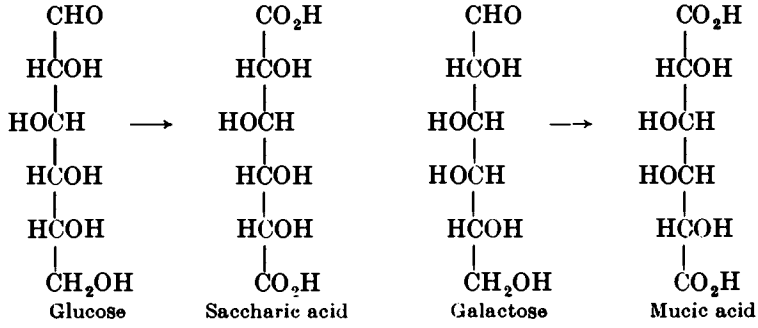
(1) Zinc chloride is extremely deliquescent and it must therefore be introduced into the flask as rapidly as possible. Place a small stick of zinc chloride in a glass mortar, powder rapidly, and weigh out the required quantity.

β-Glucose penta-acetate. Grind together in a dry porcelain or glass mortar 4 g. of anhydrous sodium acetate (Section **II,50,9**) and 5 g. of dry glucose and place the powdered mixture in a 200 ml. round-bottomed flask. Add 25 ml. of acetic anhydride, attach a reflux condenser and heat on a water bath until a clear solution is obtained (about 30 minutes: shake the mixture from time to time). Continue the heating for a further 2 hours. Pour the reaction mixture into 250 ml. of ice-cold water in a beaker. Break up the solid lumps and allow to stand with occasional stirring for about 1 hour. Filter the crystals at the pump, wash well with water, and recrystallise from methylated spirit (or from methyl or ethyl alcohol) until the m.p. is 131–132°; two recrystallisations are usually necessary. The yield is 7 g.

Conversion of β- into α-glucose penta-acetate. Add 0·5 g. of anhydrous zinc chloride rapidly to 25 ml. of acetic anhydride in a 200 ml. round-bottomed flask, attach a reflux condenser, and heat on a boiling water bath for 5–10 minutes to dissolve the solid. Then add 5 g. of the pure β-glucose penta-acetate, and heat on a water bath for 30 minutes. Pour the hot solution into 250 ml. of ice water, and stir vigorously in order to induce crystallisation of the oily drops. Filter the solid at the pump, wash with cold water, and recrystallise from methylated spirit or from methyl alcohol. Pure α-glucose penta-acetate, m.p. 110–111°, will be obtained. Confirm its identity by a mixed m.p. determination.

III,138. MUCIC ACID

Vigorous oxidation of a monosaccharide (*e.g.*, with dilute nitric acid) produces carboxyl groups at both ends of the chain. Thus galactose gives the sparingly soluble mucic acid; glucose affords the soluble saccharic acid, which is best isolated as the sparingly soluble acid potassium salt.



Disaccharides, *e.g.*, lactose, which yield galactose upon hydrolysis, will also give the sparingly-soluble mucic acid but in poorer yield. This reaction may be employed for the differentiation between certain disaccharides: lactose $\longrightarrow$ mucic + saccharic acids; sucrose $\longrightarrow$ saccharic acid only; maltose $\longrightarrow$ saccharic acid only.

Dissolve 10 g. of lactose (1) in 100 ml. of nitric acid, sp. gr. 1·15, in an evaporating dish and evaporate in a fume cupboard until the volume has been reduced to about 20 ml. The mixture becomes thick and pasty owing to the separation of mucic acid. When cold, dilute with 30 ml. of water, filter at the pump and set the filtrate (*A*) aside. Wash the crude acid with cold water. Purify the mucic acid by dissolving it in the minimum volume of dilute sodium hydroxide solution and reprecipitating with dilute hydrochloric acid: do not allow the temperature to rise above 25°. Dry the purified acid (about 5 g.) and determine the m.p. Mucic acid melts with decomposition at 212–213°.

Note.

(1) A much better yield is obtained if galactose is employed. Lactose is generally preferred, however, as it is much cheaper.

COGNATE PREPARATION

Saccharic acid. Use the filtrate (*A*) from the above oxidation of lactose or, alternatively, employ the product obtained by evaporating 10 g. of glucose with 100 ml. of nitric acid, sp. gr. 1·15, until a syrupy residue remains and then dissolving in 30 ml. of water. Exactly neutralise at the boiling point with a concentrated solution of potassium carbonate, acidify with acetic acid, and concentrate again to a thick syrup. Upon the addition of 50 per cent. acetic acid, acid potassium saccharate separates out. Filter at the pump and recrystallise from a small quantity of hot water to remove the attendant oxalic acid. It is necessary to isolate the saccharic acid as the acid potassium salt since the acid is very soluble in water. The purity may be confirmed by conversion into the silver salt (Section **III,103**) and determination of the silver content by ignition.

III,139. REACTIONS AND CHARACTERISATION OF CARBOHYDRATES

Mono- and di-saccharides are colourless solids or syrupy liquids, which are freely soluble in water, practically insoluble in ether and other organic solvents, and neutral in reaction. Polysaccharides possess similar properties, but are generally insoluble in water because of their high molecular weights. Both poly- and di-saccharides are converted into monosaccharides upon hydrolysis.

(i) **Molisch's test.** This is a general test for carbohydrates. Place 5 mg. of the substance in a test-tube containing 0·5 ml. of water and mix it with 2 drops of a 10 per cent. solution of α-naphthol in alcohol or in chloroform. Allow 1 ml. of concentrated sulphuric acid to flow down the side of the inclined tube (it is best to use a dropper pipette) so that the acid forms a layer beneath the aqueous solution without mixing with it.

If a carbohydrate is present, a red ring appears at the common surface of the liquids: the colour quickly changes on standing or shaking, a dark purple solution being formed. Shake and allow the mixture to stand for 2 minutes, then dilute with 5 ml. of water. In the presence of a carbohydrate, a dull-violet precipitate will appear immediately.

For practice, the student should apply the test to glucose, lactose, sucrose, starch and paper fibres.

(ii) **Barfoed's reagent.** This reagent may be used as a general test for monosaccharides. Heat a test-tube containing 1 ml. of the reagent and 1 ml. of a dilute solution of the carbohydrate in a beaker of boiling water. If red cuprous oxide is formed within 2 minutes, a monosaccharide is present. Disaccharides on prolonged heating (about 10 minutes) may also cause reduction, owing to partial hydrolysis to monoses.

Barfoed's reagent is prepared by dissolving 13·3 g. of crystallised neutral copper acetate in 200 ml. of 1 per cent. acetic acid solution. The reagent does not keep well.

For practice, the student should apply the test to glucose and lactose.

(iii) **Fehling's solution.** Place 5 ml. of Fehling's solution {prepared by mixing equal volumes of Fehling's solution No. 1 (copper sulphate solution) and solution No. 2 (alkaline tartrate solution—see Section **III,70,**(ii)} in a test-tube and heat to gentle boiling. Add a solution of 0·1 g. of the carbohydrate in 2 ml. of water and continue to boil gently for a minute or two, and observe the result. A yellow or red precipitate of cuprous oxide indicates the presence of a reducing sugar. An alternative method of carrying out the test is to add the hot Fehling's solution dropwise to the boiling solution of the carbohydrate; in the presence of a reducing sugar the blue colour will disappear and a yellow precipitate, changing to red, thrown down.

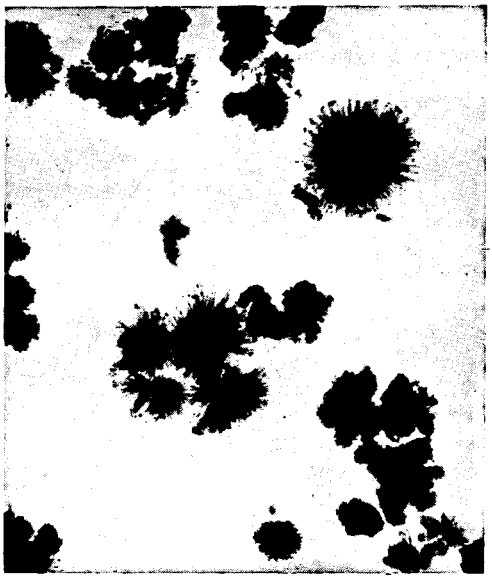
Of the common disaccharides sucrose does not reduce Fehling's solution. If the cane sugar is hydrolysed by boiling it with dilute acid and the solution is neutralised with aqueous sodium hydroxide, the reduction of Fehling's solution occurs readily.

(iv) **Benedict's solution.** This is a modification of Fehling's solution and consists of a single test solution which does not deteriorate appreciably on standing. To 5 ml. of Benedict's solution add 0·4 ml. of a 2 per cent. solution of the carbohydrate, boil for 2 minutes and allow to cool spontaneously. If no reducing sugar is present, the solution remains clear; in the presence of a reducing sugar, the solution will contain cuprous oxide. The test may also be carried out according to the experimental details given under (iii).

Benedict's solution is prepared as follows. Dissolve 86·5 g. of crystallised sodium citrate ($2Na_3C_6H_5O_7,11H_2O$) and 50 g. of anhydrous sodium carbonate in about 350 ml. of water. Filter, if necessary. Add a solution of 8·65 g. of crystallised copper sulphate in 50 ml. of water with constant stirring. Dilute to 500 ml. The resulting solution should be perfectly clear; if it is not, pour it through a fluted filter paper.

For practice, the student should apply tests (iii) and (iv) to glucose, lactose, maltose and sucrose.

GLUCOSAZONE

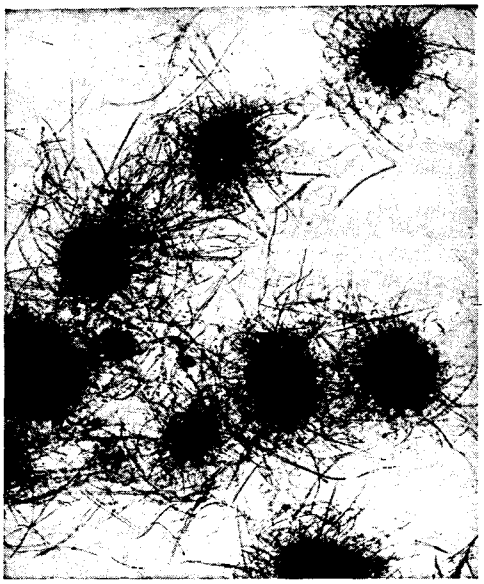


GALACTOSAZONE

ARABINOSAZONE

XYLOSAZONE

Fig. *111, 139,* 1.



LACTOSAZONE

MALTOSAZONE

CELLOBIOSAZONE

SORBOSAZONE

Fig. *111*, *139*, 1.

Characterisation of Sugars

The melting points (more accurately termed the decomposition points) of sugars and some of their derivatives, *e.g.*, osazones, are not so definite as those of other classes or organic compounds : these vary with the rate of heating and the differences between individual members are not always large. There are, however, a number of reactions and derivatives which will assist in the characterisation of the simple sugars normally encountered by the student in his training in qualitative organic analysis.

1. **Osazone formation.** Certain sugars may be identified by the length of time required to form osazones upon treatment with phenylhydrazine under standard experimental conditions. Monosaccharides give precipitates at 100° within 20 minutes. The disaccharides maltose and lactose give no osazone at 100° even after 2 hours, but osazones are obtained on cooling after 10–15 minutes heating. With sucrose an osazone commences to separate after about 30 minutes, due to gradual hydrolysis into glucose and fructose, but no osazone is produced on cooling after heating for 10–15 minutes.

Place 0·20 g. of the carbohydrate, 0·40 g. of pure *white* phenylhydrazine hydrochloride (*e.g.*, of A.R. quality), 0·60 g. of crystallised sodium acetate and 4·00 ml. of water in a dry test-tube. (Weigh the quantities with an accuracy of 0·01 g.) Stopper the tube *loosely* with a cork, and stand or clamp it upright in a beaker containing boiling water. Note the time of immersion and the time when the osazone first separates. Shake the tube occasionally (without removing it from the boiling water) in order to prevent supersaturation. The precipitate separates quite suddenly : duplicate experiments should agree within 0·5 minute. Note whether the precipitate is white (mannose), yellow or orange yellow, and whether it is crystalline or " oily."

The approximate times of osazone formation in minutes are given in Table **III,139.** The product from mannose is the simple hydrazone and is practically white. Arabinose osazone separates first as an oil, whilst that from galactose is highly crystalline. Lactose and maltose give no precipitate from hot solution.

For practice, the student should prepare the osazones from glucose and fructose. He should also use the same technique for lactose and maltose, but the solution should be cooled after boiling for 10–15 minutes. The resulting osazones should be examined under the microscope : this is most simply done by withdrawing a small quantity of the crystalline suspension with a dropper pipette on to a microscope slide, and viewing under the microscope. It may be necessary to recrystallise the osazone in order to obtain the best results. The precipitate should be filtered off on a small filter paper, washed with a little cold water, and then recrystallised from hot water or from 60 per cent. alcohol or from dilute pyridine. The crystal forms should be compared with those given in Fig. *III, 139,* 1 (plate facing this page).* The crystal forms of the osazones are more trustworthy for identification purposes than the melting points.

* The photographs of the osazones were kindly supplied by Thomas Kerfoot and Co. Ltd., of Vale of Bardsley, Ashton-under-Lyne, the well-known manufacturers of sugars.

2. **Acetates.** Complete acetylation of all the hydroxyl groups is desirable in order to avoid mixtures. In some cases, the completely acetylated sugars may be obtained in the α- and β-forms depending upon the catalyst, *e.g.*, zinc chloride or sodium acetate, that is employed in the acetylation. The experimental details for acetylation may be easily adapted from those already given for α- and β-glucose penta-acetates (Section **III,137**).

3. ***p*-Nitrophenylhydrazones.** This reagent has been used in the characterisation of a number of monosaccharides.

Heat 0·25 g. of the compound with 3 ml. of alcohol, add 0·25 g. of *p*-nitrophenylhydrazine, and heat the suspension until the reaction appears complete. The *p*-nitrophenylhydrazone soon separates. Filter, preferably after standing overnight, wash with a little cold alcohol, and then recrystallise from alcohol.

4. **Benzoates.** Benzoyl chloride has a very limited application as a reagent in the sugar series, but it is useful for the preparation of a crystalline derivative of glucose and of fructose.

In a 50–100 ml. conical flask place a solution of 0·5 g. of glucose in 5 ml. of water, 12–15 ml. of 10 per cent. sodium hydroxide solution and 1 ml. of benzoyl chloride, cork tightly, and shake until the odour of benzoyl chloride has disappeared and a crystalline (frequently sticky) solid has separated. Filter off the solid, wash it with a little water, and recrystallise it from ethyl or *n*-butyl alcohol. (If the product is sticky, it should be removed, and spread on a porous tile before recrystallisation.) Glucose pentabenzoate has m.p. 179°. Fructose pentabenzoate, m.p. 78-79°, may be similarly prepared.

The following simple test distinguishes fructose from all other carbohydrates. Upon heating a little fructose with dilute cobalt chloride solution, cooling and treating with a little ammonia solution, a violet to purple colour is developed; the colour gradually fades and must be observed immediately after the addition of the ammonia solution. Green cobalt hydroxide is formed with all other carbohydrates.

5. **Methylphenylosazones.** *as*-Methylphenylhydrazine does not form osazones with aldoses presumably because the base or more probably the methylphenylhydrazonium ion $[C_6H_5NCH_3NH_3]^+$ will oxidise a $-CH_2OH$ but not a $>CHOH$ group: it readily forms osazones with ketoses, thus providing an excellent reagent for fructose.

Dissolve 0·2 g. of fructose in 10 ml. of water, add 0·6 g. of *as*-methylphenylhydrazine and sufficient rectified spirit to give a clear solution. Since the fructose may not be quite pure, warm the mixture slightly, allow to stand, preferably overnight, so that any insoluble hydrazones may separate; if present, remove them by filtration. Add 4 ml. of 50 per cent. acetic acid to the filtrate; it will become yellow in colour. Heat the solution on a water bath for 5–10 minutes, and allow to stand in the dark until crystallisation is complete; it may be necessary to "scratch" the walls of the vessel to induce crystallisation. Filter the crystals and wash with water, followed by a little ether. Recrystallise the orange-coloured methylphenylosazone from benzene: m.p. 152°.

The properties of a number of sugars are collected in Table **III,139**; the specific rotations in water are included for reference purposes.

Carbohydrate	M.P.*	$\alpha_D^{20°}$ In Water	Osazone		Other Derivatives
			M.P.	Time of Formation (Minutes)	
†D-Glucose (hydrated)	90°				Penta-acetate, α- 112°, β- 132;
D-Glucose (anhydrous)	146°	+ 52°	205°	4	pentabenzoate, 179
D-Ribose	95	− 21·5	166	—	—
D-Fructose	104	− 92	205	2	Penta-acetate, α- 70, β- 109; pentabenzoate, 79
L-Rhamnose (hydrated)	105				
L-Rhamnose (anhydrous)	125	+ 9	190	9	Penta-acetate, 99
L-Lyxose	106	+ 13·5	163	—	—
D-Galactose (hydrated)	120				Penta-acetate, α- 95, β- 142;
D-Galactose (anhydrous)	170	+ 82	201	15–19	mucic acid, 213
D-Mannose	132	+ 14·5	205	0·5	Penta-acetate, α- 74, β- 115
D-Xylose	145	+ 19	164	7	Penta-acetate, α- 59, β- 126
L-Arabinose	160	+105	166	9	Penta-acetate, α- 94, β- 86
L-Sorbose	161	− 43	162	4	—
Maltose (hydrated)	100				
Maltose (anhydrous)	165	+130	206	—	Octa-acetate, α- 125, β- 160
Sucrose	185	+ 66·5	205	30	Octa-acetate, 69
Gentiobiose	190	+ 9·5	162	—	Octa-acetate, α- 189, β- 193
Lactose (hydrated)	203				Octa-acetate, α- 152, β- 90;
Lactose (anhydrous)	223	+ 52·5	200	—	mucic acid, 213
Cellobiose	225	+ 35	198	—	Octa-acetate, α- 230. β- 192

* The melting points of carbohydrates (sugars) are not usually sharp and they are perhaps best expressed as decomposition points.

† The small capital letter prefix refers to configuration, related to D-glyceraldehyde, and not to the direction of optical rotation. The sign of optical rotation is expressed as (+) and (−) or as *d* and *l* or by the words *dextro* and *laevo*. Thus we have D-(−)-fructose and L-(+)-arabinose.

Notes on the Identification of Polysaccharides

Most polysaccharides are insoluble or sparingly soluble in cold water, insoluble in cold alcohol and ether, and rarely possess melting points. Only inulin melts at about 178° (dec.) after drying at 130°.

Starch. A few centigrams rubbed to a thin cream with cold water and then gradually stirred into 100 ml. of boiling water dissolve to give a nearly clear solution. This gives a deep blue colouration with a dilute solution of iodine in potassium iodide solution, temporarily decolourised by heat or by traces of free alkali, but restored on cooling or upon acidifying. It is hydrolysed by boiling with dilute hydrochloric acid to give products (largely glucose) which reduce Fehling's solution.

Cellulose. This is insoluble in water, hot and cold. It dissolves in a solution of Schweitzer's reagent (precipitated cupric hydroxide is washed free from salts and then dissolved in concentrated ammonia solution), from which it is precipitated by the addition of dilute acids. Cellulose is not hydrolysed by dilute hydrochloric acid.

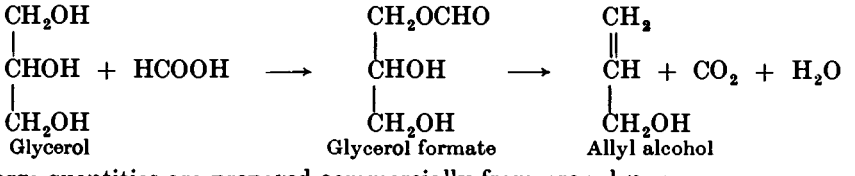
Inulin. This polysaccharide melts with decomposition at about 178°. It is insoluble in cold but dissolves readily in hot water giving a clear solution which tends to remain supersaturated. It does not reduce Fehling's solution. Inulin gives no colouration with iodine solution.

Glycogen. It dissolves easily in water to an intensely opalescent solution ; the opalescence is not destroyed by filtration, but is removed by the addition of acetic acid. Glycogen gives a wine colouration with iodine solution ; the colouration disappears on heating and reappears on cooling. The compound does not reduce Fehling's solution : upon boiling with dilute acid glucose is produced and the resulting solution, when neutralised, therefore reduces Fehling's solution.

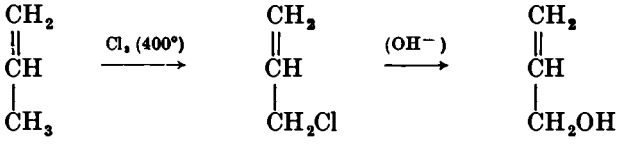
UNSATURATED ALIPHATIC COMPOUNDS

III,140. ALLYL ALCOHOL

Allyl alcohol may be prepared by heating glycerol with formic acid:



Large quantities are prepared commercially from propylene:



To a 1-litre distilling flask, provided with a thermometer reaching to within 1–2 cm. of the bottom, attach a condenser set for downward distillation: fit a 500 ml. distilling flask to the lower end of the condenser by means of a cork and connect the side arm of the distilling flask to a wash bottle containing concentrated sodium hydroxide solution to dissolve and decompose any acrolein formed in the subsequent reaction. Place 400 g. of glycerol, 175 g. (146 ml.) of commercial 85 per cent. formic acid and a few fragments of porous porcelain in the distilling flask. Heat the mixture *rapidly* over a burner. Carbon dioxide is evolved and a liquid distils. When the temperature reaches 195° (after 30–45 minutes), change the receiver for another distilling flask of equal size. Continue the heating until the temperature rises to 260°: the main reaction occurs at 225–235° and about 190 ml. of distillate are obtained. Allow the contents of the flask to cool to about 115°, and introduce a further 125 g. (105 ml.) of commercial 85 per cent. formic acid. Heat the flask rapidly as before and collect the fraction distilling at 195–260° (about 125 ml.). Allow the reaction mixture to cool again to about 115°, add a third portion of 125 g. (105 ml.) of formic acid, and repeat the distillation: about 90 ml. passes over at 195–260° and the residue in the flask is about 50 ml.

Treat the combined distillates of b.p. 195–260° with anhydrous potassium carbonate to neutralise the little formic acid present and to salt out the allyl alcohol. Distil the latter through a fractionating column and collect the fraction of b.p. up to 99° separately; this weighs 210 g. and consists of 70 per cent. allyl alcohol. To obtain anhydrous allyl alcohol, use either of the following procedures:—

(i) Reflux the alcohol with successive quantities of anhydrous potassium carbonate * until the carbonate no longer becomes sticky but remains finely-divided and "flows" freely. Decant from the desiccant and distil. Allyl alcohol of 98–99 per cent. purity passes over at 94–97°. Considerable quantities of the alcohol are lost mechanically in the drying process.

* Anhydrous calcium sulphate may also be used, but the process is unnecessarily expensive.

(ii) Mix the alcohol with one quarter of its volume of carbon tetrachloride or of ethylene dichloride and distil slowly through an efficient fractionating column. Collect the low boiling point mixture of carbon tetrachloride (or ethylene chloride), allyl alcohol and water, dry it with anhydrous potassium carbonate and return it to the flask. Repeat the process several times until only a little water passes over. Finally distil the mixture completely through the column and collect the following fractions :—(*a*) up to 90° ; (*b*) 90–95° ; and (*c*) 95·5–97° : fraction (*c*) is pure allyl alcohol. Dry fractions (*a*) and (*b*), and refractionate : an additional quantity of pure allyl alcohol, b.p. 95·5–97°, is thus obtained.

III,141. CROTONALDEHYDE

Acetaldehyde condenses in the presence of a little sodium sulphite or sodium hydroxide solution to aldol. The latter eliminates water upon distillation at atmospheric pressure, but more efficiently in the presence of a trace of iodine, which acts as a catalyst, to yield crotonaldehyde :

$$\underset{\text{Acetaldehyde}}{CH_3CHO} + HCH_2CHO \xrightarrow{OH^-} \underset{\text{Aldol}}{CH_3CH(OH)CH_2CHO} \xrightarrow{-H_2O} \underset{\text{Crotonaldehyde}}{CH_3CH{=}CHCHO}$$

Crotonaldehyde can be produced so cheaply on a commercial scale that its preparation in the laboratory is rarely undertaken. It is, however, included here as an illustration of the preparation of an unsaturated aliphatic aldehyde.

If acetaldehyde is warmed with a concentrated solution of an alkali hydroxide, it is converted into a resinous product resulting from repeated aldol condensations between aldol, crotonaldehyde and acetaldehyde.

In a 1-litre three-necked flask, equipped with a dropping funnel, mechanical stirrer and a thermometer and cooled in a bath of ice and salt, place 85 g. (109 ml.) of freshly distilled acetaldehyde (Section **III,65**). When the temperature has fallen to −5°, add 25 ml. of 15 per cent. sodium sulphite solution, with stirring, during 1 hour. The temperature rises to about + 10°, and the liquid increases in viscosity and density. Aldol has $d_{4^\circ}^{20^\circ}$ of 1·103, so that the progress of the condensation may be followed by a determination of the volume of the reaction mixture. Extract the aldol with two 75 ml. portions of ether, and remove the ether on a water bath. Transfer the residue to a Claisen flask with fractionating side arm (Figs. *II*, *24*, 2–5), add 0·1 g. of iodine and distil slowly. A little water passes over first, followed by a constant boiling point mixture, containing 80 per cent. of crotonaldehyde, at 84°. The yield of the latter is 45 g. Pure crotonaldehyde boils at 102°.

III,142. ββ-DIMETHYLACRYLIC ACID

This reaction illustrates the conversion of the —$COCH_3$ group into the —COOH group by means of a hypohalite :

$$\underset{\text{Mesityl oxide}}{(CH_3)_2C{=}CHCOCH_3} + 3KOCl \longrightarrow (CH_3)_2C{=}CHCOOK + CHCl_3 + 2KOH$$

$$2(CH_3)_2C{=}CHCOOK + H_2SO_4 \longrightarrow \underset{\text{ββ-Dimethylacrylic acid}}{2(CH_3)_2C{=}CHCOOH} + K_2SO_4$$

Fit a 1-litre three-necked flask with two double surface condensers and a glycerine-sealed stirrer (Fig. *II*, *7*, 10). Place 25 g. (29 ml.) of mesityl oxide (Section **III,79**), 50 ml. of dioxan and a cold (10°) solution

of 100 g. of potassium hypochlorite in 750 ml. of water (1) in the flask, and stir the mixture. Heat is evolved in the reaction and after about 5 minutes chloroform commences to reflux. As soon as the reaction becomes very vigorous, stop the stirrer and cool the flask with the water from the reflux condenser so that the chloroform refluxes gently; after 20–30 minutes, when the reaction has subsided, resume the stirring and continue it until the temperature of the mixture has fallen to that of the laboratory (2–3 hours). Decompose the slight excess of hypochlorite by the addition of sodium bisulphite (about 1 g.), *i.e.*, until a test-portion no longer liberates iodine from potassium iodide solution.

Replace one of the reflux condensers by a dropping funnel and add 50 per cent. sulphuric acid (about 50 ml.) with stirring and cooling until the solution is acid to Congo red paper. Extract the cold solution with eight 50 ml. portions of ether (2) and shake the mixture well during each extraction. Dry the combined ethereal extracts with a little anhydrous magnesium or calcium sulphate, and remove the ether and chloroform slowly on a water bath. Distil the residue from a Claisen flask with fractionating side arm (Figs. *II*, *24*, 2–4) under diminished pressure and collect the acid at 100–106°/20 mm.; this fraction solidifies on cooling and melts at 60–65°. The yield is 13 g. Recrystallise from hot water (1 g. of acid in 10 ml. of water), cool the solution in ice for 2–3 hours, filter and dry overnight in a vacuum desiccator. Alternatively, recrystallise from light petroleum, b.p. 60–80°. Pure ββ-dimethylacrylic acid has m.p. 68°.

Notes.

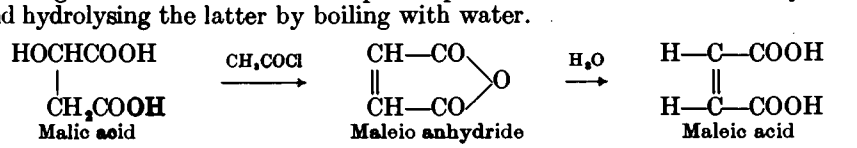
(1) The potassium hypochlorite solution may be prepared from the calcium hypochlorite marketed under the name "High Test Hypochlorite" or "H.T.H." * and containing not less than 65 per cent. of available calcium hypochlorite. Dissolve 125 g. of "H.T.H." in 500 ml. of warm water contained in a 1·5 litre round-bottomed flask, and add a warm solution of 87·5 g. of potassium carbonate and 25 g. of potassium hydroxide in 250 ml. of water. Stopper the flask and shake vigorously until the semi-solid gel first formed becomes fluid. Filter on a large Buchner funnel, wash with 100 ml. of water, and suck as dry as possible. The filtrate (about 750 ml.) contains about 100 g. of potassium hypochlorite. Alternatively, but less satisfactorily, fresh bleaching powder (*ca.* 35 per cent. calcium hypochlorite) may be used. The potassium hypochlorite solution is prepared by treating a warm (50°) solution of bleaching powder (in proportion of 100 g. in 400 ml. of water) with a warm solution of potassium carbonate and a little potassium hydroxide (70 g. K_2CO_3 + 20 g. KOH in 300 ml. of water), stirring vigorously and filtering.

$$Ca(OCl)_2 + K_2CO_3 \longrightarrow CaCO_3 + 2KOCl$$

(2) A continuous ether extractor (see Figs. *II*, *44*, 1–2) gives more satisfactory results.

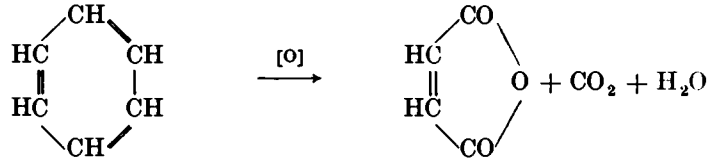
III,143. MALEIC AND FUMARIC ACIDS

Maleic acid may be prepared by warming malic acid with acetyl chloride, distilling the mixture under atmospheric pressure to isolate maleic anhydride, and hydrolysing the latter by boiling with water.

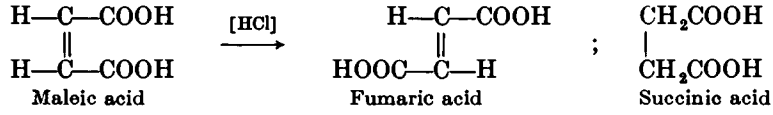


* Supplied by the Matheson Alkali Works, U.S.A.

Commercially, maleic anhydride is prepared more cheaply by the catalytic vapour phase oxidation (in the presence of vanadium pentoxide at about 400°) of benzene with atmospheric oxygen :



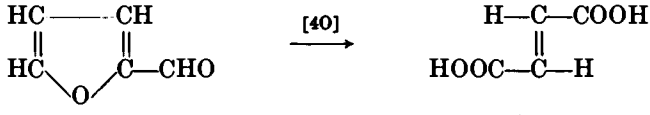
Upon heating with hydrochloric acid, maleic acid, m.p. 144°, is converted into fumaric acid, m.p. 287° :



Maleic acid — Fumaric acid — Succinic acid

Both acids yield succinic acid, m.p. 185°, upon catalytic reduction (see Section **III,150**), thus establishing their structures. Maleic and fumaric acids are examples of compounds exhibiting ***cis - trans* isomerism (or geometric isomerism)**. Maleic acid has the *cis* structure since *inter alia* it readily yields the anhydride (compare Section **III,93**). Fumaric acid possesses the *trans* structure ; it does not form an anhydride, but when heated to a high temperature gives maleic anhydride.

Fumaric acid is conveniently prepared by the oxidation of the inexpensive furfural with sodium chlorate in the presence of a vanadium pentoxide catalyst :



Furfural — Fumaric acid

A. **Maleic acid.** Assemble the apparatus shown in Fig. *III, 28*, 1. Place 45 g. of dry malic acid in the 200–250 ml. distilling flask and cautiously add 63 g. (57 ml.) of pure acetyl chloride. Warm the flask gently on a water bath to start the reaction, which then proceeds exothermically. Hydrogen chloride is evolved and the malic acid passes into solution. When the evolution of gas subsides, heat the flask on a water bath for 1–2 hours. Rearrange the apparatus and distil. A fraction of low boiling point passes over first and the temperature rises rapidly to 190° ; at this point run out the water from the condenser. Continue the distillation and collect the maleic anhydride at 195–200°. Recrystallise the crude maleic anhydride from chloroform (compare Section **III,93**) ; 22 g. of pure **maleic anhydride**, m.p. 54°, are obtained.

To obtain maleic acid, evaporate the maleic anhydride with one half of its weight of water on a water bath : remove the last traces of water by leaving in a desiccator over concentrated sulphuric acid. The resulting maleic acid has m.p. 143° and is quite pure (1). It may be recrystallised, if desired, from acetone- light petroleum (b.p. 60–80°) and then melts at 144° (1).

Note.

(1) The melting point of pure maleic acid depends to a marked degree upon the rate of heating, and values between 133° and 143–144° may be observed. Slow heating (about 20 minutes) gives a value of 133–134° ; with more rapid heating

(about 10 minutes), the m.p. is 139–140°. If the acid is immersed in a bath at 140° or is placed upon the electric m.p. apparatus (Fig. *II*, *11*, 4) at 140°, it melts sharply at 143°. The low melting points obtained by slow heating are evidently due to the formation of maleic anhydride and/or fumaric acid, which depress the m.p.

B. **Conversion of maleic acid into fumaric acid.** Dissolve 10 g. of maleic acid in 10 ml. of warm water, add 20 ml. of concentrated hydrochloric acid and reflux gently (provide the flask with a reflux condenser) for 30 minutes. Crystals of fumaric acid soon crystallise out from the hot solution. Allow to cool, filter off the fumaric acid, and recrystallise it from hot *N*-hydrochloric acid. The m.p. in a sealed capillary tube is 286–287°.

C. **Fumaric acid from furfural.** Place in a 1-litre three-necked flask, fitted with a reflux condenser, a mechanical stirrer and a thermometer, 112·5 g. of sodium chlorate, 250 ml. of water and 0·5 g. of vanadium pentoxide catalyst (1). Set the stirrer in motion, heat the flask on an asbestos-centred wire gauze to 70–75°, and add 4 ml. of 50 g. (43 ml.) of technical furfural. As soon as the vigorous reaction commences (2) *but not before*, add the remainder of the furfural through a dropping funnel, inserted into the top of the condenser by means of a grooved cork, at such a rate that the vigorous reaction is maintained (25–30 minutes). Then heat the reaction mixture at 70–75° for 5–6 hours (3) and allow to stand overnight at the laboratory temperature. Filter the crystalline fumaric acid with suction, and wash it with a little cold water (4). Recrystallise the crude fumaric acid from about 300 ml. of *N*-hydrochloric acid, and dry the crystals (26 g.) at 100°. The m.p. in a sealed capillary tube is 282–284°. A further recrystallisation raises the m.p. to 286–287°.

Notes.

(1) The **vanadium pentoxide catalyst is prepared** as follows: Suspend 5 g. of pure ammonium vanadate in 50 ml. of water and add slowly 7·5 ml. of pure concentrated hydrochloric acid. Allow the reddish-brown, semi-colloidal precipitate to settle (preferably overnight), decant the supernatant solution, and wash the precipitate several times by decantation. Finally, suspend the precipitate in 75 ml. of water and allow it to stand for 3 days. This treatment renders the precipitate granular and easy to filter. Filter the precipitate with suction, wash it several times with cold 5 per cent. sodium chloride solution to remove hydrochloric acid. Dry the product at 120° for 12 hours, grind it in a mortar to a fine powder, and heat again at 120° for 12 hours. The yield of catalyst is about 3·5 g.

(2) When the vigorous reaction commences, the temperature rises to about 105° and remains at this temperature for some time. The main quantity of furfural should not be added until the vigorous reaction has started: if this precaution is ignored, an explosion may result.

(3) A water bath may be used for this purpose.

(4) A small quantity (*ca.* 3 g.) of fumaric acid may be recovered from the filtrate by heating it on a water bath with 15 ml. of concentrated hydrochloric acid, evaporating to about 150 ml., and then cooling with running water. The fumaric acid which separates is recrystallised from *N*-hydrochloric acid.

III,144. CROTONIC ACID AND VINYLACETIC ACID

Crotonic acid may be prepared by condensing acetaldehyde with malonic acid in pyridine solution in the presence of a trace of piperidine (**Doebner reaction**; see discussion following Section **IV,123**).

$$CH_3CHO + H_2C(CO_2H)_2 \longrightarrow CH_3CH{=}CHCO_2H + CO_2 + H_2O$$

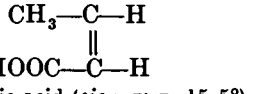
The commercial method consists in the oxidation of crotonaldehyde, which is itself prepared from acetaldehyde (see Section III,141) :

$$2CH_3CHO \overset{OH^-}{\rightleftharpoons} \underset{\text{Aldol}}{CH_3CH(OH)CH_2CHO} \overset{H^+}{\longrightarrow} \underset{\text{Crotonaldehyde}}{CH_3CH{=}CHCHO} \overset{[O]}{\longrightarrow} \underset{\text{Crotonic acid}}{CH_3CH{=}CHCO_2H}$$

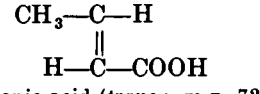
Vinylacetic acid is obtained by the hydrolysis of allyl cyanide with concentrated hydrochloric acid :

$$\underset{\text{Allyl cyanide}}{CH_2{=}CHCH_2CN} + HCl + 2H_2O \longrightarrow \underset{\text{Vinylacetic acid}}{CH_2{=}CHCH_2CO_2H} + NH_4Cl$$

Crotonic acid exists in *cis* and *trans* forms (compare maleic and fumaric acids) :



Isocrotonic acid (*cis* ; m.p. 15·5°)



Crotonic acid (*trans* ; m.p. 72°)

The acid prepared as above is the *trans* isomer ; isocrotonic acid is produced by special methods.

Crotonic acid is an example of an **αβ-unsaturated acid**, whilst vinylacetic acid is a **βγ-unsaturated acid.** Upon heating the latter with a solution of an alkali hydroxide at 100° or with sulphuric acid, it passes almost completely into the former. Actually an equilibrium mixture is produced containing 98 per cent. of crotonic acid :

$$\underset{\beta\gamma\text{-unsaturated acid (b.p. 163°)}}{CH_2{=}CHCH_2COOH} \overset{OH^-}{\rightleftharpoons} \underset{\alpha\beta\text{-unsaturated acid (m.p. 72°, b.p. 189°)}}{CH_3CH{=}CHCOOH}$$

A. Crotonic Acid

Mix together in a 250 ml. flask carrying a reflux condenser and a calcium chloride drying tube 25 g. (32 ml.) of freshly-distilled acetaldehyde with a solution of 59·5 g. of dry, powdered malonic acid (Section **III,157**) in 67 g. (68·5 ml.) of dry pyridine to which 0·5 ml. of piperidine has been added. Leave in an ice chest or refrigerator for 24 hours. Warm the mixture on a steam bath until the evolution of carbon dioxide ceases. Cool in ice, add 60 ml. of 1 : 1 sulphuric acid (by volume) and leave in the ice bath for 3–4 hours. Collect the crude crotonic acid (*ca.* 27 g.) which has separated by suction filtration. Extract the mother liquor with three 25 ml. portions of ether, dry the ethereal extract, and evaporate the ether ; the residual crude acid weighs 6 g. Recrystallise from light petroleum, b.p. 60–80° ; the yield of crude crotonic acid, m.p. 72°, is 20 g.

B. Vinylacetic Acid

Allyl cyanide. Into a 1·5 litre three-necked flask (1), provided with a mercury-sealed stirrer and two long double surface condensers, place 293 g. (210 ml.) of freshly-distilled allyl bromide, b.p. 70–71° (Section **III, 35**) and 226 g. of dry cuprous cyanide (Section **II,50,3**, Method 1). Remove the mercury-sealed stirrer and replace it by a tightly fitting

cork. Warm the flask on a water bath so that the allyl bromide refluxes. Immediately the vigorous reaction commences (after 15–30 minutes), remove the water bath and cool the flask in a bath of ice and water; the two double surface condensers will prevent any loss of product. When the reaction subsides, introduce the mercury-sealed stirrer and heat the mixture, with stirring, on the water bath for 1 hour. Remove the condensers and arrange the apparatus for distillation: close one neck with a cork. Heat the flask in an oil or butyl phthalate bath, and distil the allyl cyanide with stirring (2). Redistil and collect the pure allyl cyanide at 116–121°. The yield is 140 g.

Vinylacetic acid. Place 134 g. (161 ml.) of allyl cyanide (3) and 200 ml. of concentrated hydrochloric acid in a 1-litre round-bottomed flask attached to a reflux condenser. Warm the mixture cautiously with a small flame and shake from time to time. After 7–10 minutes, a vigorous reaction sets in and the mixture refluxes; remove the flame and cool the flask, if necessary, in cold water. Ammonium chloride crystallises out. When the reaction subsides, reflux the mixture for 15 minutes. Then add 200 ml. of water, cool and separate the upper layer of acid. Extract the aqueous layer with three 100 ml. portions of ether. Combine the acid and the ether extracts, and remove the ether under atmospheric pressure in a 250 ml. Claisen flask with fractionating side arm (compare Fig. *II*, *13*, 4): continue the heating on a water bath until the temperature of the vapour reaches 70°. Allow the apparatus to cool and distil under diminished pressure (compare Fig. *II*, *20*, 1); collect the fraction (*a*) distilling up to 71°/14 mm. and (*b*) at 72–74°/14 mm. (chiefly at 72·5°/14 mm.). A dark residue (about 10 ml.) and some white solid (? crotonic acid) remains in the flask. Fraction (*b*) weighs 100 g. and is analytically pure vinylacetic acid. Fraction (*a*) weighs about 50 g. and separates into two layers: remove the water layer, dry with anhydrous sodium sulphate and distil from a 50 ml. Claisen flask with fractionating side arm; a further 15 g. of reasonably pure acid, b.p. 69–70°/12 mm., is obtained.

Notes.

(1) The preparation may be carried out on half or quarter scale in a 500 ml. three-necked flask.

(2) When the volume of liquid in the flask is small, it is advisable to arrange the apparatus for distillation under reduced pressure (water pump) in order to completely separate the allyl cyanide from the solid residue. The final tarry residue may be removed by treatment with concentrated nitric acid, followed by water.

(3) The preparation may be conducted on a quarter or half scale in a 500 ml. flask with equally satisfactory results.

Cognate Preparation

β-*n*-Hexylacrylic Acid (αβ-Nonenoic Acid)

This preparation is another example of the condensation of an aldehyde with malonic acid and pyridine to yield ultimately an αβ-unsaturated acid (**Doebner reaction**). It is included here because, unlike the acids prepared from many of the lower aliphatic aldehydes, the product consists largely (about 95 per cent.) of the αβ-isomeride and only about 5 per cent. of the βγ-isomeride is present:

$$\underset{\textit{n}\text{-Heptaldehyde}}{CH_3(CH_2)_5CHO} + \underset{\text{Malonic acid}}{H_2C(CO_2H)_2} \xrightarrow{C_5H_5N} \underset{\alpha\beta\text{-Nonenoic acid}}{CH_3(CH_2)_5CH{=}CHCO_2H} + CO_2 + H_2O$$

Dissolve 57 g. of dry malonic acid in 92·5 ml. of dry pyridine contained in a 500 ml. round-bottomed flask, cool the solution in ice, and add 57 g. (70 ml.) of freshly-distilled *n*-heptaldehyde (oenanthol) with stirring or vigorous shaking. After a part of the aldehyde has been added, the mixture rapidly sets to a mass of crystals. Insert a cotton wool (or calcium chloride) tube into the mouth of the flask and allow the mixture to stand at room temperature for 60 hours with frequent shaking. Finally, warm the mixture on a water bath until the evolution of carbon dioxide ceases (about 8 hours) and then pour into an equal volume of water. Separate the oily layer and shake it with 150 ml. of 25 per cent hydrochloric acid to remove pyridine. Dissolve the product in benzene, wash with water, dry with anhydrous magnesium sulphate, and distil under reduced pressure. Collect the $\alpha\beta$-nonenoic acid at 130–132°/2 mm. The yield is 62 g.

III,145. SORBIC ACID

Sorbic acid is prepared by the condensation of crotonaldehyde with malonic acid in the presence of pyridine at 100° **(Doebner reaction)**:

$$\underset{\text{Crotonaldehyde}}{CH_3CH{=}CHCHO} + \underset{\text{Malonic acid}}{H_2C(CO_2H)_2} \xrightarrow{C_5H_5N} \underset{\text{Sorbic acid}}{CH_3CH{=}CHCH{=}CHCO_2H} + CO_2 + H_2O$$

It contains a conjugated system of double bonds.

Place 40 g. (46·5 ml.) of crotonaldehyde (b.p. 101–103°), 60 g. of dry malonic acid (Section **III,157**) and 60 g. (61 ml.) of dry pyridine (b.p. 113–115°) in a 500 ml. round-bottomed flask, attach a reflux condenser, and heat on a water bath for 3 hours. At the end of this period the vigorous evolution of carbon dioxide will have ceased. Cool the mixture in ice and cautiously acidify it by the addition of a solution of 21·3 ml. of concentrated sulphuric acid in 50 ml. of water with shaking. Most of the sorbic acid separates out immediately; a more complete separation is obtained by cooling the solution in ice for 3–4 hours. Filter the acid at the pump and wash it with 5 ml. of ice-cold water. Recrystallise from about 125 ml. of boiling water; the maximum recovery of purified acid is achieved by leaving the solution in an ice chest or a refrigerator overnight and then filtering. The yield of sorbic acid, m.p. 134°, is 20 g.

III,146. DIALLYL (HEXADIENE-1,5)

This unsaturated hydrocarbon is easily prepared by the action of sodium upon allyl iodide or bromide:

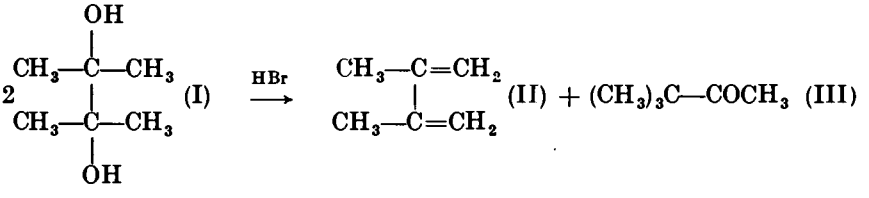
$$\underset{\text{Allyl iodide}}{2CH_2{=}CHCH_2I} + 2Na \longrightarrow \underset{\text{Diallyl}}{CH_2{=}CHCH_2CH_2CH{=}CH_2} + 2NaI$$

Place 56 g. of clean sodium, cut into small pieces, in a 500 ml. round-bottomed flask fitted with two 25 or 30 cm. double surface condensers in series. Weigh out 136 g. (72 ml.) of freshly distilled allyl iodide, b.p. 99–101° (Section **III,39**). Introduce about one quarter of the allyl iodide through the condensers. Warm the flask gently until the sodium *commences* to melt and immediately remove the flame. A vigorous reaction sets in and a liquid refluxes in the condensers. Add

the remainder of the allyl iodide in small portions over a period of 2 hours. Allow the mixture to cool during 3 hours and arrange the flask for distillation (compare Fig. *II*, *13*, 3). Distil from an oil or butyl phthalate bath maintained at 90–100° when most of the hydrocarbon will pass over; finally raise the temperature of the bath to 150° in order to recover the product as completely as possible. The distillate weighs 26 g. and is almost pure diallyl. Redistil from a 50 ml. Claisen flask with fractionating side arm and containing a little sodium; all the liquid boils at 59–60°.

III,147. 2 : 3-DIMETHYL-1 : 3-BUTADIENE

Anhydrous pinacol (I) is catalytically decomposed by aqueous hydrobromic acid into dimethylbutadiene (II) and pinacolone (III); separation is effected by distillation through an efficient fractionating column:



In a 1-litre round-bottomed flask, surmounted by a modified Hempel fractionating column (Fig. *II*, *15*, 5) filled with $\frac{1}{8}''$ or $\frac{1}{4}''$ glass or porcelain rings (1), place 177 g. of anhydrous pinacol (Section **III,77**), 5 ml. of constant boiling point hydrobromic acid, and a few fragments of porous porcelain. Attach a condenser and a receiver to the column. Heat the flask gently in an air bath (compare Fig. *II*, *5*, 3) and circulate cold water through the " cold finger ": the rate of distillation should be 20–30 drops per minute. Collect the distillate until the temperature at the top of the column is 95° (60–70 minutes). Separate the upper non-aqueous layer, wash it twice with 50 ml. portions of water, add 0·25 g. of hydroquinone as an inhibitor, and dry it overnight with 7–8 g. of anhydrous calcium chloride. Transfer to a 500 ml. flask and distil through the same column (or through a Widmer column). Collect the following fractions: (*a*) 69–70·5° (70 g.), (*b*) 70·5–105° (7 g.), and (*c*) 105–106° (35 g.). Fraction (*a*) is pure dimethylbutadiene, (*b*) is an intermediate fraction and (*c*) is pinacolone.

Dimethylbutadiene may be kept for a limited period in an ice box or in a refrigerator; it is advisable to add about 0·2 g. of hydroquinone as an inhibitor.

Note.

(1) Any efficient fractionating column may be used (see Section **II, 17**).

III,148. DIMETHYLETHYNYL CARBINOL

This is an example of an acetylenic alcohol. It is prepared from acetone by the following series of reactions:

$$CH_3COCH_3 + NaNH_2 \longrightarrow (CH_3COCH_2)Na + NH_3$$

$$(CH_3COCH_2)Na + C_2H_2 \longrightarrow (CH_3)_2C(C{\equiv}CH)ONa$$

$$(CH_3)_2C(C{\equiv}CH)ONa + H_2SO_4 \longrightarrow (CH_3)_2C(OH)—C{\equiv}CH + NaHSO_4$$

Fit a 1-litre round-bottomed flask with a three-holed stopper carrying a separatory funnel, a mechanical stirrer and a gas outlet tube leading to a fume cupboard. Place 500 ml. of anhydrous ether and 78 g. of finely-ground sodamide (Section **II,50,*8***) in the flask and surround it with a freezing mixture of ice and salt. Stir the mixture vigorously and add 116 g. (147 ml.) of dry acetone (1) dropwise during a period of 1·5–2 hours. Pass a slow current of acetylene (from a cylinder and dried with anhydrous calcium chloride) through the flask for 2 hours in order to sweep out the ammonia; make sure that the temperature of the freezing mixture does not rise above —10°, and add Dry Ice (solid carbon dioxide) if necessary. Replace the three-holed stopper by one with two holes bearing an inlet tube reaching to the bottom of the flask (connected to a cylinder of acetylene) and a stopcock. Wire the two-holed stopper securely into the mouth of the flask. Place the flask in an ice-salt mixture and mount the whole in a shaking machine (compare Figs. *II*, 7, 14) and shake vigorously for 10 hours (2); maintain the mixture under a pressure of 10 lb. of acetylene as indicated by the gauge on the cylinder. Release the pressure every half hour by means of the stopcock in order to sweep out any ammonia formed from small amounts of previously unreacted sodamide.

Pour the reaction mixture cautiously into 400 g. of crushed ice and acidify it in the cold by the addition of a solution prepared by adding 55 ml. of concentrated sulphuric acid to 150 ml. of water and then cooling to 0°. Separate the ether layer and extract the aqueous layer twice with 50 ml. portions of ether. Dry the combined ethereal solutions over 50 g. of anhydrous potassium carbonate and distil the filtered solution through a Widmer column (Figs. *II*, *17*, 1 and *II*, *24*, 4). Collect separately the fraction boiling up to 103°, and the dimethylethynyl carbinol at 103–107° Discard the high boiling point material. Dry the fraction of low boiling point with anhydrous potassium carbonate and redistil. The total yield is 75 g.

Notes.

(1) The acetone should be dried over anhydrous potassium carbonate or anhydrous calcium sulphate.

(2) The shaking period need not be continuous. The passage of acetylene may be interrupted, but the cold reaction mixture must be kept in an ice box during the intervening period.

COGNATE PREPARATION

Methylethylethynyl carbinol. Use 144 g. (179 ml.) of dry methyl ethyl ketone, and other quantities as above. The yield is 60 g., b.p. 119-123°.

III,149. 10-UNDECYNOIC ACID

Undecylenic acid (or 10-undecenoic acid) (I), a comparatively inexpensive commercial product obtained from castor oil, reacts with bromine in dry carbon tetrachloride to give 10 : 11-dibromoundecoic acid (II), which upon heating with a concentrated solution of potassium hydroxide yields 10-undecynoic acid (III):

$$CH_2{=}CH(CH_2)_8CO_2H\ (I) \xrightarrow{Br_2} CH_2BrCHBr(CH_2)_8CO_2H\ (II) \xrightarrow{KOH} CH{\equiv}C(CH_2)_8CO_2H\ (III)$$

The position of the triple bond is established by oxidation of the latter by means of alkaline potassium permanganate solution to sebacic acid, $HO_2C(CH_2)_8CO_2H$, m.p. 133°.

Purify commercial undecylenic acid by distillation of, say, 250 g. under diminished pressure and collect the fraction, b.p. 152–154°/6 mm.; this has a freezing point of 23°. Dissolve 108 g. of the purified undecylenic acid in 285 ml. of dry carbon tetrachloride (1) in a 1-litre three-necked flask provided with a mercury-sealed stirrer, a dropping funnel and a reflux condenser. Cool the flask in a freezing mixture of ice and salt, stir the solution and add 96 g. (31 ml.) of dry bromine (Section **II,49,*8***) during a period of 1 hour: allow the mixture to gradually warm up to the temperature of the laboratory. Arrange the flask for distillation (compare Fig. *II*, *41*, 1, but with stirrer in central neck), remove the carbon tetrachloride by heating on a water bath, and pour the residue into a large evaporating dish. Upon standing 1–2 days (more rapidly when left in a vacuum desiccator over silica gel), the dibromo acid crystallises completely. The yield is quantitative.

Transfer the solid dibromo acid to a 2-litre round-bottomed Pyrex flask attached to a reflux condenser, add a solution of 263 g. of potassium hydroxide in 158 ml. of water, and heat in an oil bath at 150–160° for 8 hours. Considerable frothing occurs, but this is reduced by the addition of small quantities (about 0·1 g.) of solid "Pentrone-T" (largely sodium oleyl sulphonate) from time to time. Allow the mixture to stand overnight, add 1500 ml. of water, shake until all the solid dissolves, and acidify with dilute sulphuric acid to Congo red. A solid cake of acid separates on the surface of the liquid after standing for several hours. Extract with four 250 ml. portions of ether, dry with anhydrous sodium or magnesium sulphate, and remove the ether on a water bath. Transfer the residue to a 250 ml. Claisen flask and distil cautiously under diminished pressure using a free flame. A little ether and water pass over first and the temperature rises rapidly to 175°/15 mm. Collect separately the fractions (*a*) b.p. 177–182°/15 mm. (52 g.) and (*b*) 182–200°/15 mm. (15 g.). The flask contains a large residue, which is discarded. Fraction (*a*) solidifies completely on cooling and has m.p. 37–41°; upon recrystallisation from light petroleum, b.p. 60–80°, 34 g. of pure 10-undecynoic acid, m.p. 41–42°, are obtained. Fraction (*b*) solidifies to a slightly "sticky" solid: upon recrystallisation from light petroleum, b.p. 60–80°, a "sticky" solid separates, which, after spreading upon a porous tile, becomes colourless and has m.p. 41–42° (3 g.).

Note.

(1) Dry carbon tetrachloride may be prepared by distillation of the commercial product and rejection of the first 20 per cent. of the distillation.

Oxidation of 10-undecynoic acid to sebacic acid. Dissolve 2·00 g. of the acid, m.p. 41–42°, in 50 ml. of water containing 0·585 g. of pure anhydrous sodium carbonate. Saturate the solution with carbon dioxide and add 0·1*N* potassium permanganate solution (about 1500 ml.) slowly and with constant stirring until the pink colour remains for half an hour; the addition occupies about 3 hours. Decolourise the solution with a little sulphur dioxide and filter off the precipitated acid through a

weighed sintered glass crucible. Upon standing for 24 hours a further crop of acid separates. Filter this through the same crucible and dry in a vacuum desiccator over concentrated sulphuric acid. The yield of acid is 1·46 g. This has m.p. 133° and the m.p. is not depressed upon admixture with pure sebacic acid. In determining the total yield of sebacic acid, allowance must be made for the amount dissolved in the 1500 ml. of solution.

III,150. CATALYTIC REDUCTION WITH ADAMS' PLATINUM OXIDE CATALYST

Adams' platinum oxide catalyst is readily prepared from chloroplatinic acid or from ammonium chloroplatinate, and is employed for catalytic hydrogenation at pressures of one atmosphere to several atmospheres and from room temperature to about 90°. Reduction is usually carried out with rectified spirit or absolute alcohol as solvents. In some cases (*e.g.*, the reduction of benzene, toluene, xylene, mesitylene, cymene and diphenyl *), the addition to the absolute alcohol solution of 2–5 per cent. of the volume of rectified spirit which has been saturated with hydrogen chloride increases the effectiveness of the catalyst; under these conditions chlorobenzene, bromobenzene, *o*-, *m*- and *p*-bromotoluenes, *p*-dichloro- and *p*-dibromo-benzene are reduced completely but the halogens are simultaneously eliminated. Other solvents which are occasionally employed include glacial acetic acid, ethyl acetate, ethyl acetate with 17 per cent. acetic acid or 8 per cent. of alcohol. In the actual hydrogenation the platinum oxide PtO_2,H_2O is first reduced to an active form of finely-divided platinum, which is the real catalyst: allowance must be made for the consumption of hydrogen in the process.

PREPARATION OF ADAMS' PLATINUM OXIDE CATALYST

Method 1. **From ammonium chloroplatinate.** Place 3·0 g. of ammonium chloroplatinate and 30 g. of A.R. sodium nitrate (*1*) in Pyrex beaker or porcelain casserole and heat gently at first until the rapid evolution of gas slackens, and then more strongly until a temperature of about 300° is reached. This operation occupies about 15 minutes, and there is no spattering. Maintain the fluid mass at 500–530° for 30 minutes, and allow the mixture to cool. Treat the solid mass with 50 ml. of water. The brown precipitate of platinum oxide (PtO_2,H_2O) settles to the bottom. Wash it once or twice by decantation, filter through a hardened filter paper on a Gooch crucible, and wash on the filter until practically free from nitrates. Stop the washing process immediately the precipitate tends to become colloidal (2): traces of sodium nitrate do not affect the efficiency of the catalyst. Dry the oxide in a desiccator, and weigh out portions of the dried material as required.

Method 2. **From chloroplatinic acid.** Dissolve 3·5 g. of the purest commercial chloroplatinic acid (3) in 10 ml. of water contained in a 250 ml. Pyrex beaker or porcelain casserole, and add 35 g. of A.R. sodium nitrate (1). Evaporate the mixture to dryness by heating gently over a Bunsen flame whilst stirring with a glass rod. Then raise the temperature

* Diphenyl is reduced comparatively slowly to di*cyclo*hexyl at atmospheric pressure; a pressure of 3–5 atmospheres is recommended (use the apparatus shown in Fig. *VI*, *4*, 1).

to 350-370° within about 10 minutes: fusion will occur accompanied by the evolution of brown oxides of nitrogen and the gradual separation of a precipitate of brown platinum oxide. If foaming occurs, stir the mixture more vigorously and direct an additional flame at the top of the reaction mixture, if necessary. If the burner beneath the beaker is removed when frothing commences, the top of the fused mass solidifies and material may be carried over the sides of the vessel. After 15 minutes, when the temperature has reached about 400°, the evolution of gas decreases considerably. Continue the heating until at the end of 2 minutes the temperature is 500–550°; at this stage the evolution of oxides of nitrogen has practically ceased and there is a gentle evolution of gas. Maintain the temperature at this point (best with the full force of a Bunsen burner) for about 30 minutes, by which time fusion is complete. Allow the mass to cool (the Pyrex beaker may crack), add 50 ml. of water, and proceed as in *Method 1.*

Method 3. **From platinum metal or platinum residues.** Dissolve the platinum metal or platinum residues in *aqua regia*, evaporate just to dryness several times with concentrated hydrochloric acid, dissolve the final residue in a little water and precipitate as ammonium chloroplatinate with excess of saturated ammonium chloride solution. Filter and dry the precipitate at 100°. Then proceed according to *Method 1.*

Notes.

(1) The use of an equivalent quantity of A.R. potassium nitrate is said to produce a more active catalyst.

(2) It is advisable to test a small portion of the filtrate for platinum by acidifying with hydrochloric acid and adding a few drops of stannous chloride solution: a yellow or brown colour develops according to the quantity of platinum present. The yellow colour is soluble in ether, thus rendering the test more sensitive. If platinum is found, treat the filtrate with excess of formaldehyde and sodium hydroxide solution and heat; platinum black separates on standing and may be filtered and worked up with other platinum residues (see *Method 3*).

(3) That supplied by Johnson, Matthey and Co. Ltd. gives satisfactory results.

SIMPLE APPARATUS FOR HYDROGENATION AT ATMOSPHERIC PRESSURE

The apparatus is shown in Fig. *III, 150,* 1. The bottle *B* has a capacity of 2·5 litres and *A* is a narrow-mouthed 2-litre graduated cylinder. All rubber tubing is of the heavy-wall type ("pressure" tubing) and is "wired on" to the glass by means of copper wire ligatures; the rubber stoppers in *A* and *B* are likewise fixed firmly in position by copper wires. The glass tube carrying the stopcock *3* is securely attached to the cylinder *A* in any convenient manner (copper wire, etc.). The rubber "pressure" tubing *C* is about 1 metre long. To charge the measuring cylinder with hydrogen, fill it first almost completely with water (the glass tube *F* is within 5 mm. of the top) and adjust the level of the water in the bottle *B* so that it is just above the lower tubulure. Close stopcocks *1, 2* and *3.* By means of rubber "pressure" tubing connect a hydrogen cylinder, provided with a needle valve control, to *D.* Open the screw clip *E* and pass a *slow* stream of hydrogen through the T-piece. Open taps *1* and *2* and adjust the screw clip *E* so that hydrogen passes slowly into *A*; the

displaced water enters *B*. When the level of the water in *A* is near to the 2000 ml. mark, open the screw clip *E* and simultaneously close the stopcocks *1* and *2*: shut off the hydrogen supply at the cylinder. Now open stopcocks *1* and *3* and thus refill the cylinder *A* almost completely

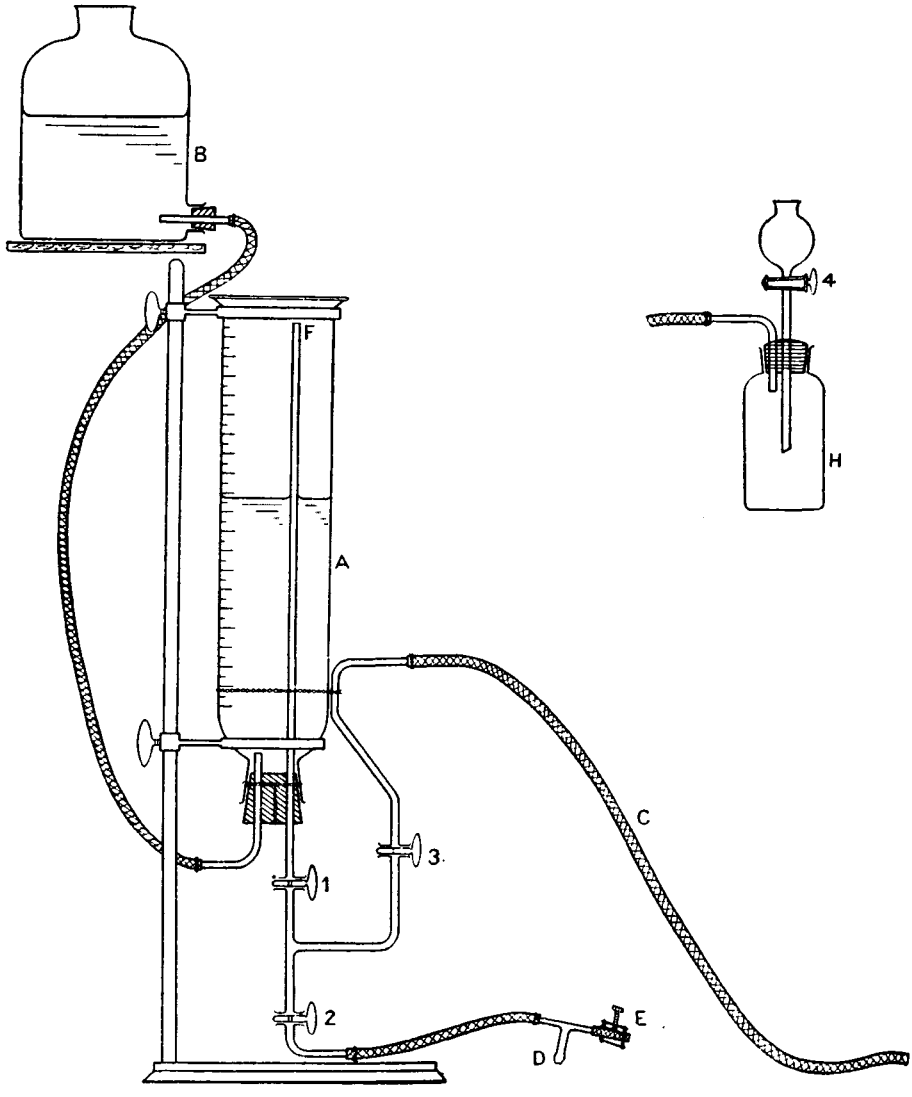


Fig. *III*, *150*, 1.

with water; allow the hydrogen to run to waste. Repeat the process four or five times to ensure the complete elimination of any air present in *A*. Finally, charge the cylinder *A* with hydrogen; stopcocks *1*, *2* and *3* must then be kept closed.

The hydrogenation is conveniently conducted in a wide-mouthed bottle *H* of 250 ml. capacity, provided with a " head " carrying a 50 ml.

funnel and fitted into the flask by means of a ground glass joint. The funnel permits of the addition of solvents or solutions and also provides an outlet for displacing the air in the bottle. Test the apparatus for leakages in the following manner. Lubricate the ground joint with a suitable inert grease (see Section **II,59**) and fix the " head " tightly into the bottle by means of short lengths of rubber tubing over it and held by means of copper wire ligatures round the neck of the bottle. Clamp the bottle in the shaking machine (see Fig. *II*, *7*, 5) and attach the rubber tubing *C*; this should be loosely clamped near the centre to prevent undue strain on the glass. Open stopcocks *1*, *3* and *4* and displace the air from the bottle *H* with hydrogen. Close the stopcock *4* from time to time; this will assist the displacement of the air and will also permit the detection of a leak in the ground glass joint. Recharge the cylinder *A* with hydrogen; close stopcock *3* during this process. Open taps *1* and *3*, close tap *2*, equalise the levels in *A* and *B*, record the volume of hydrogen and return *B* to the position shown in the figure. Set the shaking machine in motion and observe the volume of hydrogen in *A* after 30–60 minutes. If the volume remains unchanged, there is no leak in the apparatus.

The hydrogenation bottle *J* depicted in Fig. *III*, *150*, 2 may also be used; it incorporates a magnetic stirrer (compare Fig. *II*, *7*, 15) in lieu of a shaking machine and therefore has many obvious advantages. The mode of use is similar to that described for bottle *H*.

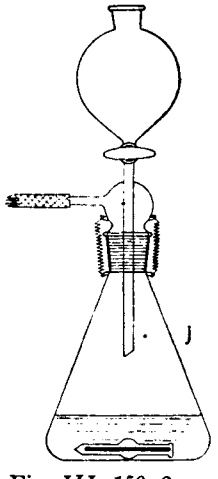


Fig. *III*, *150*, 2.

REDUCTION OF MALEIC ACID TO SUCCINIC ACID

Place 0·1 g. of the catalyst in the hydrogenation vessel and then introduce a solution of 5·9 g. of pure maleic acid (Section **III,143**) in 75 ml. of absolute alcohol. Make sure that the catalyst is completely covered by the solution, since an explosion may occur when hydrogen is admitted if traces of the platinum oxide stick to the walls of the bottle. Lubricate the stopper with an inert grease (compare Section **II,59**) and insert it into the vessel; fix it securely in position by means of two short lengths of rubber tubing passing over the top of the stopper and held tightly against the neck of the bottle by means of copper wire ligatures. Connect the hydrogenation vessel *H* to the supply of hydrogen in the cylinder *A* by means of a length of rubber " pressure " tubing and firmly clamp the bottle in the shaking machine. Displace the air from the connecting tubes and from the bottle by closing stopcock *2*, opening stopcocks *1*, *3* and *4*, and passing about 1500 ml. of hydrogen slowly from the reservoir; alternately close and open tap *4* from time to time in order to assist the displacement and also to detect any leaks in the ground glass joint. Finally, close taps *3* and *4*, and recharge reservoir *A* so that it contains about 2 litres of hydrogen. Open taps *1* and *3*. Equalise the water levels in *A* and *B*, open tap *4* momentarily and record the reading on *A*; raise *B* to its original position (as in Fig. *III*, *150*, 1). Set the

shaking machine in motion; observe the barometric pressure and the temperature of the water in *B*. After 2 hours no further change in volume occurs and the theoretical volume of hydrogen is absorbed. Record the exact volume after equalising the levels in *A* and *B*. Filter the reaction product through two filter papers supported on a Buchner or similar funnel, and evaporate the alcoholic solution to dryness on a water bath. The residue (5·9 g.) has m.p. 184°; the m.p. is unaffected after crystallisation from 25 ml. of hot water or upon admixture with an authentic sample of succinic acid.

REDUCTION OF CINNAMIC ACID TO DIHYDROCINNAMIC ACID

Use 0·1 g. of the platinum oxide catalyst and 11·4 g. of pure cinnamic acid dissolved in 100 ml. of absolute alcohol. The theoretical volume of hydrogen is absorbed after 7–8 hours. Filter off the platinum, and evaporate the filtrate on a water bath. The resulting oil solidifies on cooling to a colourless acid, m.p. 47–48° (11·2 g.). Upon recrystallisation from light petroleum, b.p. 60–80°, pure dihydrocinnamic acid, m.p. 48–49°, is obtained.

ETHYL ACETOACETATE

Ethyl acetoacetate may be prepared by the action of sodium upon dry ethyl acetate and decomposition of the resulting sodio compound with dilute acetic acid. Most samples of ethyl acetate contain some ethyl alcohol and it is usually assumed that sodium ethoxide is the condensing agent :

$$CH_3CO{-}OC_2H_5 + HCH_2COOC_2H_5 + Na^+(OC_2H_5)^-$$
$$\longrightarrow Na^+\{CH_3COCHCOOC_2H_5\}^- + C_2H_5OH$$
$$\xrightarrow[CH_3COOH]{\text{Dilute}} CH_3COCH_2COOC_2H_5 + (CH_3COO)^-Na^+$$

Acetoacetic ester is the classical example of a **tautomeric substance**, which at room temperature exists as an equilibrium mixture of the *keto* and *enol* forms containing approximately 93 per cent. of the keto form :

$$\underset{\text{Keto form (93 \%)}}{CH_3COCH_2COOC_2H_5} \rightleftharpoons \underset{\text{Enol form (7 \%)}}{CH_3C(OH)=CHCOOC_2H_5}$$

The sodio derivative, which is prepared by mixing alcoholic solutions of the ester and of sodium ethoxide, condenses with alkyl halides to yield mono-alkyl C-substituted products, for example :

$$CH_3COCH_2COOC_2H_5 + C_2H_5ONa + CH_3CH_2CH_2Br$$
$$\longrightarrow \underset{\text{Ethyl } n\text{-propylacetoacetate}}{CH_3COCHCOOC_2H_5 + C_2H_5OH + NaBr}$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad CH_2CH_2CH_3$$

These substances, as well as the parent compound, are β-keto esters and undergo hydrolytic cleavage in two directions. One type of cleavage, **ketonic hydrolysis**, is effected by the action of dilute caustic alkali in the cold, followed by acidification and boiling ; the free acetoacetic acid produced has a carboxyl and carbonyl group on the same carbon atom and therefore readily undergoes decarboxylation to yield a ketone, for example :

$$\underset{\quad |\quad\quad\quad}{CH_3COCHCOOC_2H_5} \xrightarrow[NaOH]{\text{Dilute}} \underset{\quad |\quad\quad\quad}{CH_3COCHCOONa} \xrightarrow{H_2SO_4} \underset{\quad |\quad\quad\quad}{CH_3COCHCOOH}$$
$$CH_2CH_2CH_3 \qquad\qquad CH_2CH_2CH_3 \qquad\qquad CH_2CH_2CH_3$$

$$\xrightarrow{\text{Heat}} \underset{\text{Methyl } n\text{-butyl ketone}}{CH_3COCH_2CH_2CH_2CH_3} + CO_2$$

With concentrated alkali, fission occurs at the position adjacent to the carbonyl group to give acetic acid and a mono-substituted acetic acid : the process is termed **acid hydrolysis.**

$$CH_3COCHRCOOC_2H_5 \xrightarrow[(OH^-)]{2H_2O} CH_3COOH + RCH_2COOH$$

This method of synthesising acids is rarely used since better yields are obtained with ethyl malonate (Section III,155).

The mono-alkyl C-substituted derivatives of ethyl acetoacetate upon treatment with sodium ethoxide and another molecule of alkyl halide afford the di-alkyl C-substituted products

$$CH_3COCRR'COOC_2H_5 ;$$

these upon ketonic hydrolysis give ketones of the general formula

$$CH_3COCHRR'$$

and upon acid hydrolysis yield dialkyl derivatives of acetic acid

$$RR'CHCOOH.$$

The formation of ethyl acetoacetate is an example of a general reaction known as the **acetoacetic ester condensation** in which an ester having hydrogen on the α-carbon atom condenses with a second molecule of the same ester or with another ester (which may or may not have hydrogen on the α-carbon atom) in the presence of a basic catalyst (sodium, sodium ethoxide, sodamide, sodium triphenylmethide) to form a β-keto-ester. The *mechanism* of the reaction may be illustrated by the condensation of ethyl acetate with another molecule of ethyl acetate by means of sodium ethoxide.*

$$CH_3—COOC_2H_5 + \bar{O}C_2H_5 \rightleftharpoons \bar{C}H_2—COOC_2H_5\ (I) + HOC_2H_5 \qquad (1)$$

$$CH_3—\overset{\overset{O^{\delta-}}{\circlearrowleft}}{\underset{\underset{OC_2H_5}{|}}{C^{\delta+}}} + \bar{C}H_2—COOC_2H_5 \rightleftharpoons CH_3—\overset{\overset{O^-}{\circlearrowleft}}{\underset{\underset{OC_2H_5}{\circlearrowleft}}{C}}—CH_2COOC_2H_5\ (II)$$

$$\rightleftharpoons CH_3—\overset{\overset{O}{\|}}{C}—CH_2—COOC_2H_5\ (III) + \bar{O}C_2H_5 \qquad (2)$$

$$CH_3—\overset{\overset{O}{\|}}{C}—CH_2—COOC_2H_5 + \bar{O}C_2H_5 \rightleftharpoons CH_3—\overset{\overset{O}{\|}}{\bar{C}}—CH—COOC_2H_5\ (IV) + C_2H_5OH \qquad (3)$$

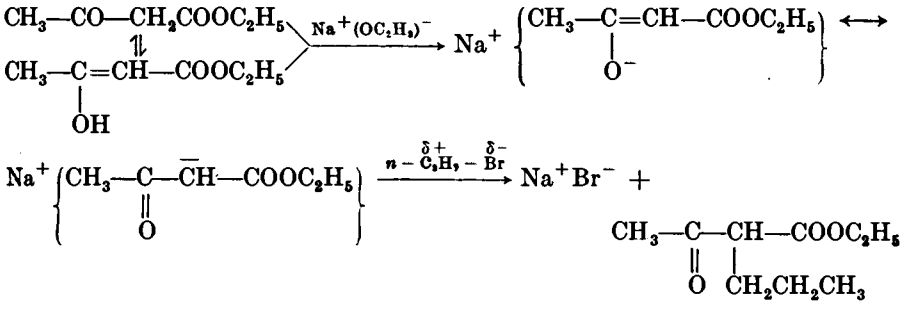
The first step is the interaction of the basic catalyst with the ester to produce the carbanion (I) ; the carbanion so formed then attacks the carbonyl carbon of a second molecule of ester to produce the anion (II), which is converted to ethyl acetoacetate (II) by the ejection of an ethoxide ion. Finally (III) reacts with ethoxide ion to produce acetoacetic ester anion (IV). This and other anions are mesomeric ; thus (IV) may be written :

$$Na^+\left\{CH_3—\overset{\overset{O}{\circlearrowleft}}{\underset{\|}{C}}—\bar{C}H—COOC_2H_5\right\} \longleftrightarrow Na^+\left\{CH_3—\overset{\overset{O^-}{|}}{C}=CH—COOC_2H_5\right\}$$

The equilibrium of the last step (3), which is not actually part of the condensation mechanism, is far to the right because of the greater basic strength of the ethoxide ion as compared to (IV), and this largely assists the forward reactions in (1) and (2). The reaction mixture contains the sodium derivative of the keto-ester, and the free ester is obtained upon acidification.

* When sodium is employed as the condensing agent, the effective reagent is still sodium ethoxide. The sodium reacts with a trace of alcohol present in the ester to give a small amount of sodium ethoxide ; once the reaction commences, alcohol is generated and reacts with sodium to give more of the sodium ethoxide. Highly purified ethyl acetate does not condense in the presence of sodium.

It may be pointed out that C-alkylation of ethyl acetoacetate is readily accounted for by the mesomeric nature of the carbanion (IV), as will be evident from the following* :



Only esters containing two α-hydrogen atoms (ethyl acetate, propionate, *n*-butyrate, etc.) can be condensed with the aid of sodium alkoxides. For esters with one α-hydrogen atom, such as ethyl *iso*butyrate, the more powerful base sodium triphenylmethide $Ph_3C^-Na^+$ leads to condensation with the formation of ethyl α-*iso*butyryl*iso*butyrate :

$$(CH_3)_2CH—COOC_2H_5 + CH(CH_3)_2—COOC_2H_2 \overset{Ph_3C^-}{\rightleftharpoons} (CH_3)_2CH—CO—C(CH_3)_2—COOC_2H_5 + C_2H_5OH$$

Ketonic hydrolysis with a mixture of sulphuric and acetic acids of the ethyl *iso*butyryl*iso*butyrate yields di-*iso*-propyl ketone :

$$(CH_3)_2CH—CO—C(CH_3)_2—COOC_2H_5 \longrightarrow (CH_3)_2CH—CO—CH(CH_3)_2 + CO_2 + C_2H_5OH$$

The acetoacetic ester condensation (involving the acylation of an ester by an ester) is a special case of a more general reaction termed the **Claisen condensation.** The latter is the condensation between a carboxylic ester and an ester (or ketone or nitrile) containing an α-hydrogen atom in the presence of a base (sodium, sodium alkoxide, sodamide, sodium triphenylmethide, etc.). If R—H is the compound containing the α- or active hydrogen atom, the Claisen condensation may be written :

$$R—H + R'—CO—OR'' \longrightarrow R—CO—R' + R''—OH$$

i.e., it is a base-catalysed acylation of an active hydrogen compound by means of an ester as acylating agent. Examples include acetylacetone (Section **VI,1**), benzoylacetone (Section **VI,2**) and ethyl phenyloxalacetate (Section **IX,8**).

III,151. ETHYL ACETOACETATE

Into a 1-litre round-bottomed flask, fitted with a double surface condenser, place 250 g. (277 ml.) of dry ethyl acetate (1) and 25 g. of clean sodium wire (2). Warm the flask on a water bath in order to start the reaction. Once the reaction commences, it proceeds vigorously and cooling of the flask may be necessary in order to avoid loss of ethyl

* Alternatively, it may be assumed that the basic ethoxide ion attacks a hydrogen atom of the activated CH_2 group to yield the carbanion directly :

$$CH_3—CO—CH_2—COOC_2H_5 + Na^+ + \bar{O}C_2H_5 \rightleftharpoons Na^+ \{CH_3—CO—\bar{C}H—COOC_2H_5\} + C_2H_5OH$$

acetate through the condenser. When the vigorous action is over, warm the reaction mixture on a water bath until the sodium is completely dissolved (about 1·5 hours). Cool the resulting clear red solution and make it *slightly* acid to litmus paper by the addition of 138 ml. of 50 per cent. acetic acid. Saturate the liquid with salt, separate the upper layer of ester and dry it with anhydrous calcium chloride or anhydrous magnesium sulphate. Distil under reduced pressure (compare Fig. *II*, *20*, 1) (3) from a Claisen flask with fractionating side arm (Figs. *II*, *24*, 2-5). After a fore-run of ethyl acetate, collect the ethyl acetoacetate at 76–80°/18 mm. (or 86–90°/30 mm. or 72–76°/14 mm. or 69–73°/12 mm.). The yield is 55 g.

Notes.

(1) It is important to use dry ethyl acetate, but it should contain 2–3 per cent. of alcohol. The so-called absolute or anhydrous ethyl acetate of commerce is satisfactory. Experimental details for the purification of 95–97 per cent. ethyl acetate are given in Section **II,47,***19*.

(2) Sodium wire, produced with a sodium press (Fig. *II*, *47*, 1), is first collected in sodium-dried ether, the necessary quantity removed, rapidly dried between filter paper, and transferred to the flask. Thin shavings of sodium, although less satisfactory may also be employed, but it is important to avoid undue exposure of the sodium to the atmosphere which produces a surface film of sodium hydroxide.

(3) Ethyl acetoacetate decomposes slightly (with the formation of dehydracetic acid $C_8H_8O_4$) when distilled at atmospheric pressure. The extent of decomposition is reduced if the distillation is conducted rapidly. The b.p. is 180°/760 mm. and a 6° fraction should be collected. Normal pressure distillation is not recommended if a pure product is desired.

Purification of Commercial Ethyl Acetoacetate

This is an alternative experiment to the actual preparation of the ester and will give the student practice in conducting a distillation under diminished pressure. Commercial ethyl acetoacetate generally contains *inter alia* some ethyl acetate and acetic acid; these are removed in the following procedure.

Place 50 g. of technical ethyl acetoacetate in a separatory funnel and shake it with small volumes of saturated sodium bicarbonate solution until effervescence ceases, then with 10 ml. of water, and dry it with 5 g. of anhydrous magnesium sulphate or anhydrous calcium chloride. Decant the solution through a fluted filter paper (or through a small plug of cotton wool) into a 100 ml. Claisen flask, and distil under diminished pressure. Use the apparatus shown in Fig. *II*, *20*, 1 and read Sections **II,19** and **II,20** for full experimental details. The boiling points of ethyl acetoacetate under various pressures are: 71°/12 mm.; 73°/15 mm.; 78°/18 mm.; 82°/20 mm.; 88°/30 mm.; 92°/40 mm.; 97°/60 mm.; and 100°/80 mm. When the pressure is steady, deduce the boiling point from the above data and collect the ester over an interval of 4°, *i.e.*, 2° on either side of the boiling point of the pure ester. Weigh the yield of product.

Reactions of Ethyl Acetoacetate

The experiments enumerated below illustrate the tautomeric character of ethyl acetoacetate.

(i) Dissolve 1 ml. of the ester in 4 ml. of ethyl alcohol and add 2 drops of aqueous ferric chloride solution. A deep violet-red colouration is

produced. Similar colourations are produced by many hydroxy compounds (*e.g.*, phenols) and in consequence this may be regarded as evidence for the presence of the enol form. Pour the solution into about 100 ml. of water in a conical flask, mix well, and add bromine water dropwise from a burette with vigorous shaking until the solution just becomes colourless. Upon standing the violet-red ferric chloride colouration soon reappears with gradually increasing intensity. The colour may be discharged again by bromine and will reappear on standing.

The bromine adds on at the ethylenic linkage to form the dibromo compound (I), which easily loses hydrogen bromide to give the mono-bromo keto ester (II):

$$CH_3C(OH)=CHCOOC_2H_5 \xrightarrow{Br_2} CH_3C(OH)BrCHBrCOOC_2H_5\ (I) \xrightarrow{-HBr} CH_3COCHBrCOOC_2H_5\ (II)$$

The enol form is thus temporarily removed from the solution and the ferric chloride colouration produced by the enol form consequently disappears and the solution becomes colourless. Some of the unchanged keto form of the ester then passes into the enol form in order to restore the original equilibrium and the ferric chloride colouration therefore reappears.

(ii) Shake 1 ml. of ethyl acetoacetate with 10 ml. of an ammoniacal solution of cupric sulphate; the latter may be prepared by adding 1 : 1-ammonia solution to Fehling's solution No. 1 (Section **III,70**) until the initial precipitate disappears. Shake in a corked test-tube for several minutes: a bluish-green precipitate of the cupric derivative of the enol form separates. The precipitate dissolves when the mixture is shaken with chloroform, thus proving that it is not a normal ionised salt.

(iii) Treat 2 ml. of the ester with 0·5 ml. of a freshly-prepared, saturated sodium bisulphite solution and shake. A gelatinous precipitate of the bisulphite addition compound of the keto form separates within 10 minutes.

(iv) Dissolve 0·2 g. of semicarbazide hydrochloride and 0·3 g. of crystallised sodium acetate in a few drops of water, add 5 drops of ethyl acetoacetate and enough ethyl alcohol, drop by drop, to give a homogeneous solution. Warm on a water bath at 70–80° for 10 minutes, then cool in ice, and, if necessary, scratch the walls of the tube with a glass rod. Filter off the semicarbazone at the pump, and recrystallise it from ether. Determine its m.p. (130°).

Cognate Preparation

ETHYL *ISO*BUTYRYL*ISO*BUTYRATE

Triphenylmethylsodium (sodium triphenylmethide). Prepare a 1·5 per cent. sodium amalgam from 15 g. of sodium and 985 g. of mercury (Section **II,50,** 7). Place a mixture of 1000 g. of the amalgam and 74 g. of triphenylchloromethane (Section **IV,203**) in a 2-litre Pyrex glass-stoppered bottle and add 150 ml. of sodium-dried ether. Grease the glass stopper with a little lubricant (*e.g.*, with " Lubriseal "), insert it firmly, clamp the bottle in a mechanical shaker and shake. The reaction is strongly exothermic: cool the bottle with wet rags and stop the shaking from time to time, if necessary. A characteristic red colour appears after

about 10 minutes' shaking. After shaking for four to six hours, *cool the bottle to room temperature*, remove it from the shaker, wire the stopper down and allow the mixture to stand undisturbed overnight; sodium chloride and particles of mercury settle to the bottom.

Separate the ether solution of sodium triphenylmethide as follows. Remove the glass stopper and replace it immediately by a tightly-fitting two-holed cork carrying a short glass tube that protrudes about 1 cm. into the bottle, and a long glass tube bent into an inverted U shape. Connect the bottle through a drying train to a cylinder of nitrogen and the other arm of the U tube to a 2-litre conical flask (as in Fig. *III*, *151*, 2) which has previously been filled with nitrogen. Seal all corks with a coating of paraffin wax. Open the stopcock of the dropping funnel slightly and force the ether solution of triphenylmethylsodium slowly and steadily into the nitrogen-filled flask by means of a small pressure of nitrogen from the cylinder. By carefully adjusting the depth of the siphon tube in the bottle, all but 50–75 ml. of the clear ether solution may be removed.

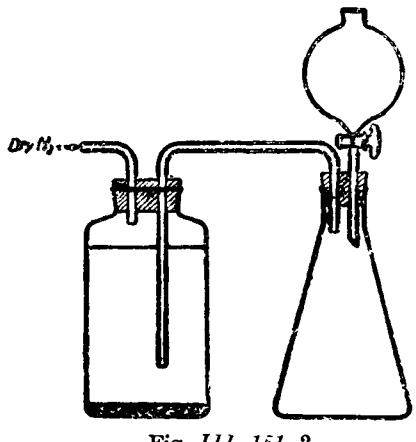


Fig. *III*, *151*, 2.

If pure triphenylchloromethane and freshly prepared sodium amalgam are used, the yield of sodium triphenylmethide should be almost quantitative but is usually 0·15 mol per litre (1). The reagent should be used as soon as possible after its preparation.

Note.

(1) The solution may be analysed approximately as follows. Remove 25 ml. of the ether solution and run it into 25 ml. of water contained in a small separatory funnel; shake. Run off the aqueous layer into a 250 ml. conical flask and extract the ether layer with two 25 ml. portions of water. Titrate the combined aqueous extracts with 0·1*N* sulphuric acid, using methyl red as indicator.

Ethyl *iso*butyryl*iso*butyrate. Add 24·6 g. (28·3 ml.) of ethyl *iso*butyrate, b.p. 110–111°, to the solution of *ca.* 0·21 mol of sodium triphenylmethide in approximately 1400 ml. of ether contained in the 2-litre conical flask. Stopper the flask, shake well to effect complete mixing, and keep at room temperature for 60 hours. Acidify the reaction mixture by adding, with shaking, 15 ml. of glacial acetic acid, and then extract with 100 ml. of water. Wash the ethereal solution with 50 ml. portions of 10 per cent. sodium carbonate solution until free from excess acid, dry over anhydrous magnesium sulphate, and distil off the ether on a steam bath. Distil the residue under reduced pressure from a Claisen flask with fractionating side arm (Figs. *II*, *24*, 4–5). Collect the ethyl *iso*butyryl *iso*butyrate at 95–96°/18 mm.; the yield is 15 g. The b.p. at atmospheric pressure is 201–202°.

Ketonic hydrolysis to di-*iso*-propyl ketone. Mix 15 g. of the ester with 30 ml. of glacial acetic acid, 10 ml. of water and 10 ml. of concentrated sulphuric acid, and reflux in a flask connected by a ground glass joint

to a reflux condenser equipped with a bubble counter (compare Fig. *III*, *72*, 1). When evolution of carbon dioxide ceases, dilute the cooled solution with 180 ml. of water, add 100 ml. of ether and render alkaline to phenolphthalein with 20 per cent. sodium hydroxide solution. Separate the ether layer, extract the aqueous layer with two 50 ml. portions of ether, dry the combined ether layer and extracts with anhydrous magnesium sulphate, distil off the ether and fractionate the residue. The yield of di-*iso*-propyl ketone, b.p. 123–124°, is 7 g.

III,152. ETHYL *n*-PROPYLACETOACETATE AND METHYL *n*-BUTYL KETONE

Fit a 2-litre three-necked flask (1) with an efficient double surface condenser and a separatory funnel; close the central neck with a tightly fitting stopper. The apparatus must be perfectly dry. Place 34·5 g. of clean sodium, cut into small pieces (2), in the flask and clamp the flask by the wide central neck. Measure out 1 litre of "super-dry" ethyl alcohol (Section **II,47,5**) (3) and place about 500 ml. in the separatory funnel; insert cotton wool (or calcium chloride) guard tubes at the top of the condenser and the separatory funnel respectively. Place a large bowl beneath the flask and have a large wet towel in readiness to control the vigour of the subsequent reaction. Run in about 200 ml. of the absolute alcohol on to the sodium (4); a vigorous reaction takes place. If the alcohol refluxes violently in the condenser, cool the flask by wrapping it in the wet towel and also, if necessary, run a stream of cold water over it. As soon as the reaction moderates somewhat, introduce more alcohol to maintain rapid, but controllable, refluxing. In this manner most of the sodium reacts rapidly and the time required to produce the solution of sodium ethoxide is considerably reduced. Finally add the remainder of the alcohol and reflux the mixture on a water bath until the sodium has reacted completely. Remove the stopper in the central neck and introduce a mercury-sealed stirrer (compare Fig. *II*, *7*, 11, *a*). Add 195 g. (190 ml.) of pure ethyl acetoacetate, stir the solution, and heat to gentle boiling; then run in 205 g. (151 ml.) of *n*-propyl bromide (Section **III,35**) over a period of about 60 minutes. Continue the refluxing and stirring until a sample of the solution is neutral to moist litmus paper (6–10 hours); the reaction is then complete.

Cool the mixture and decant the solution from the sodium bromide: wash the salt with two 20 ml. portions of absolute alcohol and add the washings to the main solution. Distil off the alcohol, which contains the slight excess of *n*-propyl bromide used in the condensation, through a short fractionating column from a water bath. The residue (*A*) of crude ethyl *n*-propylacetoacetate may be used directly in the preparation of methyl *n*-butyl ketone. If the fairly pure ester is required, distil the crude product under diminished pressure and collect the fraction boiling at 109–113°/27 mm. (183 g.) (*B*).

To prepare methyl *n*-butyl ketone, add the crude ester (*A*) or the redistilled ethyl *n*-propylacetoacetate (*B*) to 1500 ml. of a 5 per cent solution of sodium hydroxide contained in a 4-litre flask equipped with a mechanical stirrer. Continue the stirring at room temperature for

4 hours; by this time the mono-substituted acetoacetic ester is completely hydrolysed and passes into solution. Transfer the mixture to a large separatory funnel, allow to stand and remove the small quantity of unsaponified material which separates as an upper oily layer. Place the aqueous solution of sodium *n*-propylacetoacetate in a 3-litre round-bottomed flask provided with a cork fitted with a small separatory funnel and a wide bent delivery tube connected to a condenser set for downward distillation (compare Fig. *III, 35,* 1). Add 150 ml. of 50 per cent. sulphuric acid (sp. gr. 1·40) slowly through the separatory funnel with shaking; a vigorous evolution of carbon dioxide occurs. When the latter has subsided, heat the reaction mixture slowly to the boiling point and distil slowly until the total volume is reduced by about one half; by this time all the methyl *n*-butyl ketone should have passed over. The distillate contains the ketone, ethyl alcohol and small quantities of acetic and *n*-valeric acids. Add small portions of solid sodium hydroxide to the distillate until it is alkaline and redistil the solution until 80-90 per cent has been collected; discard the residue.

Separate the ketone layer from the water, and redistil the latter until about one third of the material has passed over. Remove the ketone after salting out any dissolved ketone with potassium carbonate (5). Wash the combined ketone fractions four times with one third the volume of 35–40 per cent. calcium chloride solution in order to remove the alcohol. Dry over 15 g. of anhydrous calcium chloride; it is best to shake in a separatory funnel with 1–2 g. of the anhydrous calcium chloride, remove the saturated solution of calcium chloride as formed, and then allow to stand over 10 g. of calcium chloride in a dry flask. Filter and distil. Collect the methyl *n*-butyl ketone at 126–128°. The yield is 71 g.

Notes.

(1) A 2-litre round-bottomed flask provided with the adapter illustrated in Fig. *II, 1,* 8, *d* may also be used. For preparations on one half or one quarter of this scale, a 1000 or 500 ml. flask equipped with an efficient double surface condenser will give reasonably good results.

(2) The surface layer on lumps of sodium is removed with a large knife, the clean sodium is *rapidly* weighed out on a few large filter papers and immediately transferred to a beaker containing sodium-dried ether. The sodium may then be removed at leisure, cut into small pieces and transferred to the flask.

(3) If the absolute alcohol of commerce is used, the yield is appreciably diminished.

(4) The addition of the alcohol to the sodium, although attended by a very vigorous reaction which must be carefully controlled, is preferable to the reverse procedure of adding the sodium in small pieces to the alcohol. The latter method is longer and has the further disadvantage that it necessitates frequent handling and exposure to the air of small pieces of sodium.

(5) A more complete recovery of the ketone from the aqueous solution may be obtained by repeated distillation of the aqueous layer until no appreciable amount of ketone is found in the distillate. The procedure outlined is, however, quite satisfactory.

COGNATE PREPARATION

Ethyl *n*-butylacetoacetate and methyl *n*-amyl ketone. Use 34·5 g. of sodium, 1 litre of "super-dry" absolute ethyl alcohol, 195 g. of redistilled ethyl acetoacetate, and 225 g. (177 ml.) of dry *n*-butyl bromide (Sections **III,35** and **III,37**). This yields 280 g. of crude or 200 g. of pure ethyl *n*-butylacetoacetate, b.p. 112-116°/16 mm. Upon hydrolysis 105 g. of methyl *n*-amyl ketone, b.p. 149–151°, are isolated.

DIETHYL MALONATE

Ethyl malonate can be conveniently prepared by neutralising a solution of monochloroacetic acid with sodium bicarbonate, then heating with potassium cyanide to form sodium cyanoacetate :

$$CH_2ClCOONa + KCN \longrightarrow CH_2(CN)COONa + KCl$$

Upon warming the crude sodium cyanoacetate with ethyl alcohol and sulphuric acid, ethyl malonate is produced. Two mechanisms of the reaction have been proposed :—

(i) The cyano group is hydrolysed giving malonic acid and the latter is esterified :

$$CH_2(CN)COONa \xrightarrow{\text{Hydrolysis}} CH_2(COOH)_2 \xrightarrow{\text{Esterification}} CH_2(COOC_2H_5)_2$$

(ii) The original carboxyl group is esterified, the cyano group adds on alcohol to form an imino ester, and the latter is hydrolysed by water :

$$N{\equiv}CCH_2COONa \xrightarrow[C_2H_5OH]{H^+} N{\equiv}CCH_2COOC_2H_5 \xrightarrow[C_2H_5OH]{H^+}$$

$$HN{=}C(OC_2H_5)CH_2COOC_2H_5 \xrightarrow{H_2O} O{=}C(OC_2H_5)CH_2COOC_2H_5$$

Imino ester — Ethyl malonate

Malonic ester, like acetoacetic ester (Section **III,151**), when treated with an equivalent of sodium ethoxide, forms a mono-sodium derivative, which is of great value in synthetical work. The simplest formulation of the reaction is to regard it as an attack of the basic ethoxide ion on a hydrogen atom in the CH_2 group ; the hydrogen atoms in the CH_2 group are activated by the presence of the two adjacent carbethoxyl groups :

$$C_2H_5OOC{-}CH_2{-}COOC_2H_5 + \bar{O}C_2H_5 \rightleftharpoons C_2H_5OOC{-}\bar{C}H{-}COOC_2H_5\ (I) + HOC_2H_5$$

The carbanion (I) is a resonance hybrid (mesomeric anion) to which there are contributions carrying the negative charge on either carbon or oxygen :

$$C_2H_5O{-}C(O^-){=}CH{-}C(=O){-}OC_2H_5 \longleftrightarrow C_2H_5O{-}C(=O){-}CH^-{-}C(=O){-}OC_2H_5$$

$$\longleftrightarrow C_2H_5O{-}C(=O){-}CH{=}C(O^-){-}OC_2H_5$$

The sodio compound may be written $[CH(COOC_2H_5)_2]^-Na^+$, and it must always be borne in mind that the anion is mesomeric. The system reacts smoothly with an alkyl halide to give a C-substituted malonic ester, evidently through the carbanion (I) :

$$C_4H_9{}^{\alpha}Br + [CH(COOC_2H_5)_2]^-Na^+ \longrightarrow C_4H_9{}^{\alpha}CH(COOC_2H_5)_2 + Na^+Br^-$$

n-Butyl bromide — Ethyl *n*-butylmalonate

The mono-alkyl malonic ester may be hydrolysed by alcoholic potassium hydroxide to the corresponding alkyl-malonic acid :

$$C_4H_9{}^{\alpha}CH(COOC_2H_5)_2 \xrightarrow[\text{then acidification}]{\text{Conc. KOH solution,}} C_4H_9{}^{\alpha}CH(COOH)_2$$

n-Butylmalonic acid

and the latter (which has two carboxyl groups on the same carbon atom) upon heating above the m.p., undergoes smooth decarboxylation to yield the monocarboxylic acid :

$$C_4H_9{}^{\alpha}CH(COOH)_2 \xrightarrow{\text{Heat}} \underset{n\text{-Caproic acid}}{CH_3CH_2CH_2CH_2CH_2COOH}$$

If only the monocarboxylic acid is required, the ester after hydrolysis with potash may be strongly acidified with sulphuric acid and the mixture heated under reflux ; the mineral acid promotes decarboxylation at a temperature just above 100°. The net result is the replacement of the halogen atom of the alkyl halide by —CH_2COOH ; thus in the above example :

$$(CH_3CH_2CH_2CH_2)Br \xrightarrow[\text{synthesis}]{\text{Malonic ester}} (CH_3CH_2CH_2CH_2)CH_2COOH$$

The monosubstituted malonic ester still possesses an activated hydrogen atom in its CH group ; it can be converted into a sodio derivative (the anion is likewise mesomeric) and this caused to react with an alkyl halide to give a C-disubstituted malonic ester. The procedure may accordingly be employed for the synthesis of dialkylmalonic and dialkylacetic acids :

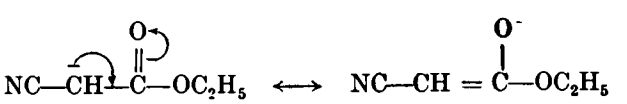
$$RCH(COOC_2H_5)_2 \xrightarrow{Na^+(OC_2H_5)^-} Na^+[RC(COOC_2H_5)_2]^- \xrightarrow{R\,X} RR'(COOC_2H_5)_2$$
$$\xrightarrow[\text{etc.}]{KOH,} RR'(COOH)_2 \xrightarrow{\text{Heat}} RR'CHCOOH + CO_2$$

Where R and R′ are identical, the dialkylmalonic ester may be prepared in one operation by treating 1 mol of ethyl malonate with 2 mols each of sodium ethoxide and the alkyl halide (usually bromide or iodide).

Ethyl cyanoacetate (Section **III,131**) is sometimes preferable to diethyl malonate for the synthesis of acids. It forms a sodio derivative with sodium ethoxide :

$$NC—CH_2—COOC_2H_5 + Na^+ + OC_2H_5 \rightleftharpoons Na^+[NC—CH—COOC_2H_5]^- + C_2H_5OH$$

The anion is mesomeric (or is a resonance hybrid) :



Alkylation of the sodio derivative affords the C-substituted cyanoacetic ester, which when heated with dilute acid gives the mono-substituted acetic acid.

$$\underset{\underset{CN}{|}}{CH_2—COOC_2H_5} \xrightarrow[;RX]{Na^+(OC_2H_5)^-} \underset{\underset{CN}{|}}{RCH—COOC_2H_5} \xrightarrow[\text{hydrolysis}]{\text{Acid}} RCH_2—COOH + CO_2$$

III,153. DIETHYL MALONATE

Carry out this preparation in the fume cupboard. Dissolve 100 g. of chloroacetic acid (Section **III,125**), contained in a large porcelain basin or casserole, in 200 ml. of water. Warm the solution to about 50°, using a 200° thermometer as a stirring rod. Introduce 90 g. of pure, powdered sodium bicarbonate in small quantities at a time with stirring ; maintain the temperature at 50–60° until effervescence ceases. Now add 80 g. of pure, finely-powdered potassium cyanide (or an equivalent quantity of sodium cyanide), stir the mixture without further warming until the

somewhat vigorous reaction is complete. Evaporate the solution, preferably on an electrically heated hot plate, with vigorous and constant stirring, until the temperature rises to 130–135°. Protect the hand by a glove during this operation ; arrange that the glass window of the fume cupboard is between the dish and the face during the period of heating. Stir the mass occasionally whilst the mixture cools and, immediately it solidifies, break up the solid mass coarsely in a mortar and transfer it to a 1-litre round-bottomed flask. Add 40 ml. of absolute ethyl alcohol and attach a reflux condenser to the flask. Introduce through the condenser during 10 minutes in small portions and with frequent shaking, a cold mixture of 160 ml. of absolute ethyl alcohol and 160 ml. of concentrated sulphuric acid ; some hydrogen chloride may be evolved during the final stages of the addition. Heat the flask on a water bath for 1 hour. Cool rapidly under the tap with shaking to prevent the formation of a solid mass of crystals. Add 200 ml. of water, filter at the pump, wash the undissolved salts with about 75 ml. of ether, shake up with the filtrate and transfer to a separatory funnel. Separate the upper layer, and extract the aqueous solution twice with 50 ml. portions of ether. Place the combined ethereal extracts in a separatory funnel and shake *cautiously* with concentrated sodium carbonate solution until the latter remains alkaline and no more carbon dioxide is evolved. Dry the ethereal solution over anhydrous magnesium or calcium sulphate.

Remove the ether using the apparatus shown in Fig. *II, 13,* 4 except that a 200 ml. Claisen flask replaces the distilling flask depicted in the diagram. Distil the residual ester under diminished pressure (Fig. *II, 20,* 1) and collect the ethyl malonate at 92–94°/16 mm. The yield is 105 g.

The b.p. under atmospheric pressure is 198–199°, but is attended by slight decomposition.

III,154. ETHYL *n*-BUTYLMALONATE

Prepare a solution of sodium ethoxide from 34·5 g. of clean sodium and 1-litre of " super-dry " ethyl alcohol (Section **II,47,5**) (1) in a 2-litre three-necked flask following the experimental conditions given under *Ethyl* n-*Propylacetoacetate* (Section **III,152**) (2). When the sodium ethoxide solution, which is vigorously stirred, has cooled to about 50°, add 247·5 g. (234·5 ml.) of redistilled diethyl malonate slowly through the separatory funnel ; to the resulting clear solution introduce gradually (60–90 minutes) 205·5 g. (161·5 ml.) of redistilled *n*-butyl bromide (Sections **III,35** and **III,37**). Reaction occurs almost immediately and much heat is evolved ; if the reaction becomes violent, cool the flask by directing a stream of cold water over it. Reflux the reaction mixture on a water bath until it is neutral to moist litmus (about 2 hours). Connect the flask by means of a wide delivery tube to a condenser set for distillation (compare Fig. *II, 41,* 1 but with a mercury-sealed stirrer in the central neck) and distil off as much of the alcohol as possible (about 600 ml.) by heating on a water bath. Cool the contents of the flask to about 20°, add 600 ml. of water and shake well. Separate the upper layer of crude ester, dry it with anhydrous magnesium sulphate, and distil from a Claisen flask under reduced pressure (Fig. *II, 20,* 1). A low

boiling point fraction passes over first, followed by ethyl *n*-butylmalonate at 130–135°/20 mm. The yield is 285 g. The distillation may also be conducted under normal pressure ; the b.p. of the ester is 235–240°.

Notes.

(1) With commercial absolute ethyl alcohol, the yield is reduced to about 225 g.

(2) The preparation may be carried out on one third of the above scale in a 1-litre flask with hand shaking replacing mechanical stirring. The yield is slightly lower.

COGNATE PREPARATION

Ethyl *n*-propylmalonate. Use 34·5 g. of sodium and 345 g. (440 ml.) of " super-dry " ethyl alcohol, 240 g. (227·5 ml.) of ethyl malonate and 185 g. (136·5 ml.) of *n*-propyl bromide (Section **III,***35*). The yield of ethyl *n*-propylmalonate, b.p. 218–225°, mainly 219·5–221·5°, is 220 g.

III,155. *n*-CAPROIC ACID (*from Ethyl* n-*Butylmalonate*)

Into a 2-litre, three-necked flask, fitted with a separatory funnel, a mechanical stirrer and a reflux condenser, place a hot solution of 200 g. of potassium hydroxide in 200 ml. of water. Stir the solution and add slowly 200 g. of ethyl *n*-butylmalonate (Section **III,154**). A vigorous reaction occurs and the solution refluxes. When all the ester has been added, boil the solution gently for 2–3 hours, *i.e.*, until hydrolysis is complete : a test portion should dissolve completely in water. Dilute with 200 ml. of water and distil off 200 ml. of liquid in order to ensure the complete removal of the alcohol formed in the hydrolysis (1) ; it is best to connect the flask by means of a wide delivery tube to a condenser set for downward distillation (compare Fig. *II*, *41*, 1 but with a mercury-sealed stirrer in the centre neck). Replace the separatory funnel and the reflux condenser.

To the cold residue in the flask add, through the separatory funnel, a cold solution of 320 g. (174 ml.) of concentrated sulphuric acid in 450 ml. of water : add the acid slowly with stirring in order to prevent excessive foaming. The solution becomes hot. Reflux the mixture for 3-4 hours and allow to cool. Separate the upper layer of the organic acid and extract the aqueous portion with four 150 ml. portions of benzene (2). Combine the acid layer with the benzene extracts, wash it with 25 ml. of water, and dry with anhydrous magnesium sulphate. Distil off the benzene through a short fractionating column until the vapours reach a temperature of about 100°. Transfer the residue to a Claisen flask with a fractionating side arm (the latter should be well lagged and, preferably, electrically heated) and distil from an air bath. Collect the *n*-caproic acid at 200–206°. The yield is 80 g.

If desired, the distillation may be conducted under reduced pressure. The boiling points under various pressures are 99°/10 mm. and 111°/20 mm. ; a 3° fraction should be collected.

Notes.

(1) It is essential to remove the alcohol completely, otherwise some ethyl *n*-caproate, b.p. 168°, is formed which will contaminate the final product.

(2) Better results are obtained if a continuous extraction apparatus (*e.g.* Fig. *II*, *44*, 2) is employed. Ether may also be used as the solvent.

COGNATE PREPARATIONS

***n*-Valeric acid.** Ethyl *n*-propylmalonate (Section **III,156**) may be similarly converted into *n*-valeric acid, b.p. 183–185° (compare Sections **III,83** and **III,84**); the yield is 75 per cent. of the theoretical.

Pelargonic acid (*n*-Nonoic acid), $CH_3(CH_2)_7COOH$. Equip a 1-litre, three-necked flask with a reflux condenser, a mercury-sealed stirrer, a dropping funnel and a thermometer. Place 23 g. of sodium, cut in small pieces, in the flask, and add 500 ml. of anhydrous *n*-butyl alcohol (1) in two or three portions: follow the experimental details given in Section **III,152** for the preparation of a solution of sodium ethoxide. When the sodium has reacted completely, allow the solution to cool to 70–80° and add 160 g. (152 ml.) of redistilled ethyl malonate rapidly and with stirring. Heat the solution to 80–90°, and place 182·5 g. (160 ml.) of *n*-heptyl bromide (compare experimental details in Section **III,37**) in the dropping funnel. Add the bromide slowly at first until precipitation of sodium bromide commences, and subsequently at such a rate that the *n*-butyl alcohol refluxes gently. Reflux the mixture until it is neutral to moist litmus (about 1 hour).

Transfer the entire reaction mixture, including the precipitated sodium bromide and the small volume of water used to rinse the reaction flask, to a 3-litre flask. Add a solution of 140 g. of pure potassium hydroxide in an equal quantity of water slowly and with shaking. Attach a reflux condenser to the flask, introduce a few fragments of porous porcelain and heat the mixture cautiously, with occasional shaking, until refluxing commences. Heat to gentle refluxing until hydrolysis is complete (about 5 hours, *i.e.*, until a test portion is completely miscible with excess of water). Immediately equip the flask for steam distillation as in Fig. *II*, *41*, 3 and steam distil the mixture until no more *n*-butyl alcohol passes over. Treat the residue cautiously with 270 ml. of concentrated hydrochloric acid whilst shaking gently, and reflux the mixture for 1 hour; if sodium chloride separates as a solid cake, take care during the heating that the flask does not crack. When cold, transfer the mixture to a separatory funnel and remove the oil to a 750 ml. round-bottomed flask. Heat it under an air-cooled reflux condenser in an oil bath at 180° until the evolution of carbon dioxide ceases (about 2 hours) (2). Decant the oil into a Claisen flask with fractionating side arm (the latter should be well lagged) and distil under reduced pressure. Collect the pelargonic acid at 140–142°/12 mm. The yield is 115 g.

$$CH_2(COOC_2H_5)_2 + C_7H_{15}{}^{\alpha}Br + C_4H_9{}^{\alpha}ONa \longrightarrow C_7H_{15}{}^{\alpha}CH(COOC_2H_5)_2 + C_4H_9{}^{\alpha}OH + NaBr$$

$$C_7H_{15}{}^{\alpha}CH(COOC_2H_5)_2 \xrightarrow{KOH} C_7H_{15}{}^{\alpha}CH(COOK)_2 \xrightarrow[\text{heat}]{HCl,} C_7H_{15}{}^{\alpha}CH_2COOH + CO_2$$

Notes.

(1) This is conveniently prepared by drying commercial *n*-butyl alcohol with anhydrous potassium carbonate or anhydrous calcium sulphate, distilling through a column, and collecting the fraction, b.p. 117–118°.

(2) An additional small quantity of pelargonic acid may be obtained by treating the solid residue with 50 ml. of concentrated hydrochloric acid.

III,156. *n*-PROPYLMALONIC ACID

Dissolve 156 g. of pure potassium hydroxide in 156 ml. of water in a 1·5 litre round-bottomed flask and add 500 ml. of rectified spirit to produce a homogeneous solution. Introduce 220 g. of ethyl *n*-propylmalonate (Section **III,154**) slowly and with shaking. Attach a vertical double surface condenser and reflux the mixture for 3 hours; hydrolysis is then complete, *i.e.*, a test portion dissolves completely in excess of water. Distil off as much alcohol as possible on a water bath, and dissolve the residue in a comparatively small volume of water. Cool the solution in a large beaker surrounded by ice; add dilute sulphuric acid slowly from a suitably supported dropping funnel, whilst stirring vigorously with a mechanical stirrer, until the solution is acid to Congo red paper. Extract the solution with three 150 ml. portions of ether, dry the ethereal extract with anhydrous magnesium or sodium sulphate, and distil off the ether on a water bath. Spread the syrupy residue in thin layers upon large clock glasses (1); after 2–3 days, filter off the crystals at the pump, using light petroleum, b.p. 40–60°, to facilitate the transfer from the clock glasses to the sintered glass filter funnel. Spread the crystals on a porous tile to remove traces of oily impurities; the crude *n*-propylmalonic acid has m.p. 95–96°. Spread the filtrate and washings on large clock glasses as before and filter off the solid which crystallises after 1 day. Repeat the process until no further crystals are obtained. Recrystallise all the crystals from hot benzene. The yield of pure *n*-propylmalonic acid, m.p. 96°, is 110 g.

Note.

(1) An alternative procedure is to leave the syrupy residue in a vacuum desiccator over anhydrous calcium chloride and silica gel, and to filter off the successive crops of crystals as they separate. These are washed with light petroleum, b.p. 40–60°, spread on a porous tile and recrystallised.

Cognate Preparations

***n*-Butylmalonic acid.** This acid may be similarly prepared from *Ethyl* n-*Butylmalonate* (Section **III,154**) and melts at 102° after recrystallisation from benzene.

SOME ALIPHATIC DICARBOXYLIC ACIDS

Malonic acid may be prepared from chloroacetic acid by the following series of reactions (compare *Diethyl Malonate*, Section III,153) :—

$$ClCH_2COOH \xrightarrow{Na_2CO_3} ClCH_2COONa \xrightarrow[KCN]{NaCN\ or} CNCH_2COONa$$

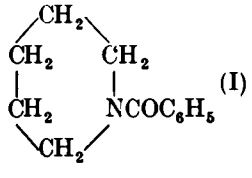
$$\xrightarrow[NaOH\ aq.]{Hydrolysis,} CH_2(COONa)_2 \xrightarrow{CaCl_2} CH_2(COO)_2Ca \xrightarrow{HCl} CH_2(COOH)_2$$

Glutaric acid ($n = 3$), **pimelic acid** ($n = 5$) and **suberic acid** ($n = 6$) may be obtained from the corresponding dibromides. These are converted by aqueous-alcoholic potassium or sodium cyanide into the dinitriles, and the latter are smoothly hydrolysed by 50 per cent. sulphuric acid into the dicarboxylic acids :

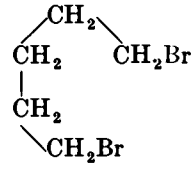
$$Br(CH_2)_nBr \xrightarrow{KCN} NC(CH_2)_nCN \xrightarrow{H_2SO_4} HOOC(CH_2)_nCOOH + (NH_4)_2SO_4$$

Trimethylene dibromide (Section III,35) is easily prepared from commercial trimethylene glycol, whilst hexamethylene dibromide (1 : 6-dibromohexane) is obtained by the red P - Br_2 reaction upon the glycol ; 1 : 6-hexanediol is prepared by the reduction of diethyl adipate (sodium and alcohol ; lithium aluminium hydride ; or copper-chromium oxide and hydrogen under pressure). Pentamethylene dibromide (1 : 5-dibromopentane) is readily produced by the red P-Br_2 method from the commercially available 1 : 5 pentanediol or tetrahydropyran (Section III,37). Pentamethylene dibromide is also formed by the action of phosphorus pentabromide upon benzoyl piperidine (I) (from benzoyl chloride and piperidine) :

$$C_5H_{11}N + C_6H_5COCl \xrightarrow{NaOH} C_5H_{10}NCOC_6H_5\ (I) + NaCl + H_2O$$



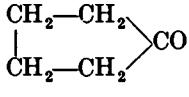
(I) $\xrightarrow{PBr_5}$



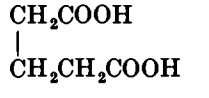
$+ C_6H_5CN$ (II) $+ POBr_3$

The benzonitrile (II) is removed by treatment with concentrated sulphuric acid.

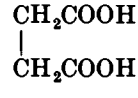
The oxidation of *cyclo*pentanone (Section III,73) with dilute nitric acid gives glutaric acid accompanied by some succinic acid ; the latter is removed as the sparingly-soluble barium salt :



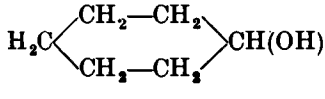
$\xrightarrow[HNO_3]{Dilute}$



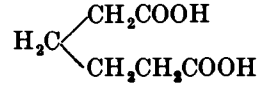
+



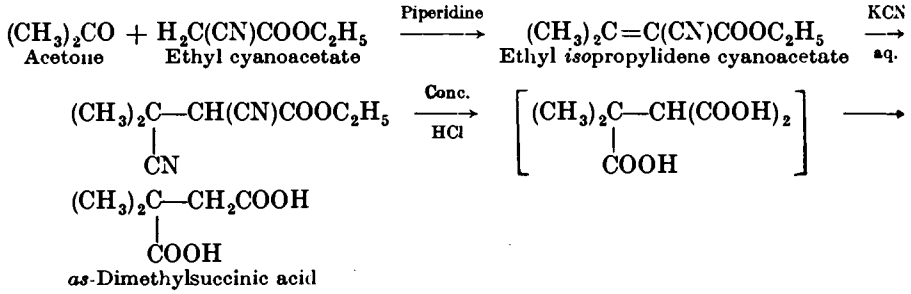
Adipic acid is conveniently prepared by the oxidation of *cyclo*hexanol (or *cyclo*hexanone) with concentrated or with 50 per cent. nitric acid :



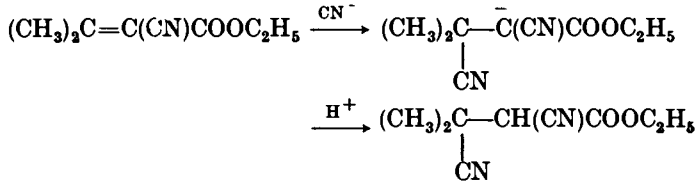
$\xrightarrow[HNO_3]{Conc.}$



The preparation of ***as*-dimethylsuccinic acid** according to the following scheme has a number of points of interest :



The formation of ethyl *iso*propylidene cyanoacetate is an example of the **Knoevenagel reaction** (see Discussion before Section **IV,123**). With higher ketones a mixture of ammonium acetate and acetic acid is an effective catalyst ; the water formed is removed by azeotropic distillation with benzene. The essential step in the reaction with aqueous potassium cyanide is the addition of the cyanide ion to the β-end of the αβ-double bond :



III,157. MALONIC ACID

Conduct the preparation in the fume cupboard. Dissolve 250 g. of redistilled chloroacetic acid (Section **III,125**) in 350 ml. of water contained in a 2·5 litre round-bottomed flask. Warm the solution to about 50°, neutralise it by the cautious addition of 145 g. of anhydrous sodium carbonate in small portions ; cool the resulting solution to the laboratory temperature. Dissolve 150 g. of sodium cyanide powder (97–98 per cent. NaCN) in 375 ml. of water at 50–55°, cool to room temperature and add it to the sodium chloroacetate solution ; mix the solutions rapidly and cool in running water to prevent an appreciable rise in temperature. When all the sodium cyanide solution has been introduced, allow the temperature to rise ; when it reaches 95°, add 100 ml. of ice water and repeat the addition, if necessary, until the temperature no longer rises (1). Heat the solution on a water bath for an hour in order to complete the reaction. Cool the solution again to room temperature and slowly dissolve 120 g. of solid sodium hydroxide in it. Heat the solution on a water bath for 4 hours. Evolution of ammonia commences at 60–70° and becomes more vigorous as the temperature rises (2). Slowly add a solution of 300 g. of anhydrous calcium chloride in 900 ml. of water at 40° to the hot sodium malonate solution ; mix the solutions well after each addition. Allow the mixture to stand for 24 hours in order to convert the initial cheese-like precipitate of calcium malonate into a coarsely crystalline form. Decant the supernatant solution and wash the solid by decantation four times with 250 ml. portions of cold water. Filter at the pump,

suck the calcium malonate as dry as possible, and dry in the air or in an electrically-heated oven at 40–50° ; the yield is 450 g.

Place the dry calcium malonate in a 2-litre round-bottomed flask, which is surrounded by a freezing mixture of ice and salt. Place 400 ml. of alcohol-free ether (3) in the flask and stir the mixture vigorously with a mechanical stirrer. Add 450 ml. of concentrated hydrochloric acid (4) gradually through a dropping funnel with bent stem. Remove the ether layer, and extract the aqueous solution five times with 150 ml of ether. Much more satisfactory extraction of the acid is achieved by the use of a continuous extractor (Figs. *II*, *44*, 1 and *II*, *44*, 2) and this procedure is recommended. Dry the ethereal solution with anhydrous sodium or magnesium sulphate and distil off the ether on a water bath. The residue (malonic acid) crystallises and, after drying in the air, melts between 132° and 134° according to the purity of the chloroacetic acid originally employed. The yield is 215 g. This acid is sufficiently pure for most purposes, but if it is required perfectly pure it may be crystallised from benzene - ether containing 5 per cent. of light petroleum (b.p. 60–80°) : the m.p. of the pure acid is 136°.

Notes.

(1) If the reaction is allowed to become too vigorous, hydrogen cyanide is liberated and some glycolate is formed.

(2) Most of the ammonia is evolved in about 1 hour. The vapour should be tested periodically for the presence of ammonia with mercurous nitrate paper.* If traces are still present after 3–4 hours, the solution should be steam distilled for 30 minutes.

(3) If the ether contains alcohol, some esterification of the acid may occur during the extraction period.

(4) One ml. of concentrated hydrochloric acid is required for each gram of calcium malonate ; the volume should be adjusted in accordance with the yield of the calcium salt.

III,158. GLUTARIC ACID (*from Trimethylene Dicyanide*)

In a 2-litre round-bottomed flask, equipped with a double surface condenser, place 60 g. of trimethylene dicyanide (Section **III,114**) and 900 g. of 50 per cent. sulphuric acid (by weight). Reflux the mixture for 10 hours and allow to cool. Saturate the solution with ammonium sulphate and extract with four 150 ml. portions of ether ; dry the ethereal extracts with anhydrous sodium or magnesium sulphate. Distil off the ether on a water bath ; the residual glutaric acid (69 g.) crystallises on cooling and has m.p. 97–97·5°. Upon recrystallisation from chloroform, or benzene, or benzene mixed with 10 per cent. by weight of ether, the m.p. is 97·5–98°.

Cognate Preparations

Suberic acid. Prepare hexamethylene dibromide from hexamethylene glycol (Section **III,15**) according to the procedure described in Section **III,35**). Convert the 1 : 6-dibromohexane, b.p. 114–115°/12 mm., into hexamethylene dicyanide, b.p. 178–180°/15 mm., by refluxing it with a 20–25 per cent. excess of aqueous - alcoholic sodium cyanide solution (compare Section **III,114**), distilling off the liquid under diminished

* See A. I. Vogel, *A Text-Book of Macro and Semimicro Qualitative Inorganic Analysis*, Fourth Edition, 1954, Longmans, Green & Co. Ltd.

pressure whilst heating on a water bath, adding water to the residue, and exhaustively extracting with ether: upon evaporating the ether, and distilling the residue under diminished pressure, the dinitrile is obtained.

Heat a mixture of hexamethylene dicyanide with 15 times its weight of 50 per cent. sulphuric acid by weight under reflux for 10 hours. The acid crystallises out on cooling. Filter off the suberic acid upon a sintered glass funnel, and recrystallise it from acetone: m.p. 141–142°. The yield is 90 per cent. of the theoretical.

Pimelic acid. This may be prepared from 1 : 5-pentanediol or tetrahydropyran, through the dibromide (Sections **III,35** and **III,37**) and dinitrile exactly as described for *Suberic Acid.* An alternative method for the preparation of 1 : 5-dibromopentane, together with full details of the subsequent steps, is given in the following Section.

III,159. PIMELIC ACID (*from Benzoyl Piperidine*)

Benzoyl piperidine. In a 1-litre three-necked flask, equipped with a mechanical stirrer, separatory funnel and a thermometer, place 85 g. (99 ml.) of redistilled piperidine (b.p. 105–108°) and a solution of 53 g. of sodium hydroxide in 400 ml. of water. Stir the mixture and introduce during the course of 1 hour 140 g. (115·5 ml.) of redistilled benzoyl chloride: maintain the temperature at 35–40°, Cool to room temperature and extract the benzoyl piperidine with ether. Wash the ethereal solution with a little water to remove any dissolved sodium hydroxide, and dry with anhydrous potassium carbonate. Remove the ether on a water bath and distil the residue under diminished pressure (Fig. *II, 20,* 1). Collect the benzoyl piperidine at 184–186°/15 mm.; it is an almost colourless viscous liquid and crystallises on standing in colourless needles m.p. 46°. The yield is 170 g.

Pentamethylene dibromide (1 : 5-Dibromopentane). Place 126 g. of benzoyl piperidine in a 500 ml. Claisen flask. Cool in ice and add 182 g. (64 ml.) of phosphorus tribromide (Section **II,49,*9***). Introduce slowly, whilst the flask is cooled in ice, 121 g. (39 ml.) of dry bromine (Section **II,49,*8***); shake the flask after each addition of bromine. Connect the flask for distillation under reduced pressure (Fig. *II, 20,* 1). Heat the Claisen flask very gently in an air bath (Fig. *II., 5,* 3) for 30 minutes and then distil so that the liquid passes over very slowly during 1 hour. Remove the air bath and distil with a free flame until no more liquid passes over and a yellow solid (PBr_5) collects in the condenser. Pour the distillate with vigorous stirring into 400 g. of crushed ice and allow to stand in order to decompose the phosphorus oxybromide (1). Dissolve the oil which separates in 600 ml. of light petroleum, b.p. 40–60° (2), which has previously been treated with small portions of concentrated sulphuric acid until the latter remained colourless. Wash the extract with sodium carbonate solution until the latter remains alkaline then wash with a little water. Shake in a separatory funnel with 10 ml. portions of concentrated sulphuric acid until the acid remains practically colourless. Wash the light petroleum extract successively with water, sodium carbonate solution, and water, and dry with anhydrous calcium chloride or anhydrous calcium sulphate. Remove the light petroleum

under atmospheric pressure and distil the residue under reduced pressure. Collect the pentamethylene dibromide at 98–100°/13 mm. The yield is 97 g.

Notes.

(1) The decomposition of the phosphorus oxybromide may also be conducted in a 1-litre three-necked flask charged with 400 g. of finely crushed ice and fitted with a reflux condenser and mechanical stirrer.

(2) The following is a modification of the process described and gives quite satisfactory results. Wash the crude mixture of benzonitrile and dibromopentane with sodium carbonate solution until the latter remains alkaline, and then with water. Distil it under reduced pressure and collect the fraction boiling up to 120°/18 mm. Dissolve this in twice its volume of light petroleum, b.p. 40–60°, which has previously been shaken with small volumes of concentrated sulphuric acid until the acid remains colourless. Shake the solution with 5 per cent. of its volume of concentrated sulphuric acid, allow to settle, and run off the sulphuric acid layer; repeat the extraction until the acid is colourless or almost colourless. Wash successively with water, sodium carbonate solution and water, dry over anhydrous calcium chloride or calcium sulphate, and distil off the solvent. Distil the residue under diminished pressure and collect the 1 : 5-dibromopentane at 98-100°/13 mm.

Pentamethylene dicyanide (1 : 5-Dicyanopentane). In a 500 ml. round-bottomed flask, equipped with a reflux condenser, place a solution of 29 g. of potassium cyanide (or the equivalent quantity of powdered sodium cyanide) in 30 ml. of warm water and add a solution of 45 g. of pentamethylene dibromide in 75 ml. of rectified spirit. Reflux the mixture on a water bath for 8 hours. Remove the solvent under diminished pressure, using a water bath. Extract the residue 4–5 times with 100 ml. portions of ether, dry the combined ethereal extracts with anhydrous calcium chloride or anhydrous calcium sulphate, and distil off the ether under atmospheric pressure. Distil the residue under diminished pressure and collect the pentamethylene dicyanide at 168–170°/15 mm. The yield is 18 g.

Pimelic acid. Heat a mixture of 18 g. of pentamethylene dicyanide and 250 g. of 50 per cent. sulphuric acid by weight in a 750 ml. round-bottomed flask under reflux for 9 hours. Most of the pimelic acid separates from the cold reaction mixture. Filter off the crystalline acid upon a sintered glass funnel. Saturate the filtrate with ammonium sulphate and extract it with three 50 ml. portions of ether. Dissolve the residue on the filter (which is slightly discoloured, but is fairly pure pimelic acid) in the combined ethereal extracts, dry with anhydrous sodium or magnesium sulphate, and remove the ether by distillation. Recrystallise the residual solid acid from benzene containing 5 per cent. of ether. The yield of pure pimelic acid, m.p. 105-106°, is 22 g.

III,160. GLUTARIC ACID (*from* cyclo*Pentanone*)

Fit a 3-litre round-bottomed flask with a long reflux condenser and a dropping funnel (1). Place a mixture of 400 ml. of concentrated nitric acid and 600 ml. of water in the flask and heat nearly to boiling. Allow 100 g. (116 ml.) of *cyclo*pentanone (Section **III,73**) to enter the hot acid dropwise, taking care that the first few drops are acted upon by the acid, otherwise an explosion may occur; the addition is complete in 1 hour. Much heat is evolved in the reaction so that the flame beneath the flask must be considerably lowered. Owing to the evolution of nitrous fumes, the reaction should be carried out in the fume cupboard or the fumes

should be passed into a water trap (Fig. *II*, *8*, 1, *c*). Transfer to a large evaporating dish and evaporate the solution to dryness on a water bath: an oil is obtained, which solidifies on cooling (m.p. 80–85°) and consists of a mixture of glutaric acid (*ca.* 85 per cent.) and succinic acid (*ca.* 15 per cent.) (2). Dissolve the mixture in 100 ml. of concentrated ammonia solution (sp. gr. 0·88) and 100 ml. of water, boil to expel the excess of ammonia, and add a slight excess of 40 per cent. barium chloride solution. Filter off the precipitate of barium succinate. Strongly acidify the filtrate with dilute hydrochloric acid and extract with five 100 ml. portions of ether (or until no more glutaric acid is obtained upon evaporating the final ethereal extract) (3). Dry the combined ethereal extracts with anhydrous sodium or magnesium sulphate, and distil off the ether. Recrystallise the cold residue from benzene. The yield of pure glutaric acid, m.p. 97°, is 70 g.

Notes.

(1) The corks are badly attacked by the nitric acid and must be renewed in each run. An asbestos stopper, prepared as described in Section III, **161**, can be used repeatedly.

(2) An alternative method of separation consists in treating the dry residue several times with a warm mixture of benzene and ether. The residual solid (about 20 g.) is moderately pure succinic acid, m.p. 183–184°. Upon evaporating the benzene - ether extract, and recrystallising the residue from chloroform or from benzene, about 70 g. of glutaric acid, m.p. 95–96°, are obtained.

(3) A continuous extractor (Fig. *II*, *44*, 2) gives the best results and is recommended.

III,161. ADIPIC ACID

Into a 3-litre three-necked flask, fitted with a dropping funnel, a mechanical stirrer (1) and a long reflux condenser, place 1900 ml. (2700 g.) of concentrated nitric acid, sp. gr. 1·42. Since oxides of nitrogen are evolved in the subsequent oxidation, the reaction should be carried out in a fume cupboard, or the oxides of nitrogen are led by a tube from the top of the condenser to a water trap (Fig. *II*, *8*, 1, *c*). Heat the nitric acid to boiling, set the stirrer in motion, add a few drops of *cyclo*hexanol and make certain that these are acted upon by the acid before adding more; an explosion may result if *cyclo*hexanol is allowed to accumulate in the acid. Once the reaction has started, add 500 g. of *cyclo*hexanol through the dropping funnel at such a rate that all is introduced in 4–5 hours; if the addition of the secondary alcohol is too slow, the corks (2), which are attacked by nitrous fumes, may have to be replaced before the operation is complete. Keep the reaction mixture at the boiling point during the addition of the *cyclo*hexanol and for a further period of about 15 minutes in order to complete the oxidation. Pour the warm reaction mixture into a beaker; upon cooling, the adipic acid crystallises. Filter on a large sintered glass funnel, and wash with 200 ml. of cold water. Recrystallise the crude acid from 700 ml. of concentrated nitric acid; filter and wash as above. The yield of recrystallised adipic acid, m.p. 152°, is 400 g. (3).

Notes

(1) If mechanical stirring is omitted, a 5 or 6 litre flask should be used. Here it is essential that the mixture be vigorously boiled.

(2) Corks are badly attacked and must be renewed in each run. It is preferable to employ **asbestos - sodium silicate stoppers**, which can be used repeatedly,

and are prepared as follows. Cut thin asbestos paper in strips about 2·5 cm. wide moisten these with water glass solution, and wind the strips round the end of a condenser, etc., until a stopper of the correct size is formed. Assemble the apparatus, coat the stoppers with water glass, and allow to harden overnight.

(3) The scale of this preparation may be considerably reduced, if desired, by obvious modifications of the apparatus.

III,162. *as*-DIMETHYLSUCCINIC ACID

Into a 500 ml. round-bottomed flask, provided with a double surface condenser, place 50 g. (63 ml.) of pure, dry acetone, 50 g. (47 ml.) of ethyl cyanoacetate (Section **III,131**) and 0·5 g. of piperidine. Allow to stand for 60 hours and heat on a water bath for 2 hours. Treat the cold reaction mixture with 100 ml. of ether, wash with dilute hydrochloric acid, then with water, and dry over anhydrous sodium or magnesium sulphate. Distil under diminished pressure and collect the ethyl ***iso*propylidene cyanoacetate** (ethyl **α-cyano-ββ-dimethylacrylate**) at 114–116°/14 mm.(1). The yield is 39 g.

Dissolve 20 g. of the cyano ester in 100 ml. of rectified spirit and add a solution of 19·2 g. of pure potassium cyanide in 40 ml. of water. Allow to stand for 48 hours, then distil off the alcohol on a water bath. Add a large excess of concentrated hydrochloric acid and heat under reflux for 3 hours. Dilute with water, saturate the solution with ammonium sulphate, and extract with four 75 ml. portions of ether. Dry the combined ethereal extracts with anhydrous sodium or magnesium sulphate, and distil off the ether. Recrystallise the residual acid from excess concentrated hydrochloric acid, and dry in the air. The yield of pure *as*-dimethylsuccinic acid, m.p. 141–142°, is 12 g.

Note.

(1) Higher (including *cyclo*aliphatic) ketones may be condensed with ethyl cyanoacetate under the following conditions. Mix 0·50 mol of ethyl cyanoacetate, 0·55–0·70 mol of the ketone, 0·02 mol of piperidine and 50 ml. of dry benzene, and heat under reflux for 12–24 hours in an apparatus incorporating an automatic water separator (Fig. *III*, *126*, 1 ; compare Fig. *III*, *57*, 2). Piperidine may be replaced by a catalyst composed of 7·7 g. (0·1 mol) of ammonium acetate and 24 g. (0·4 mol) of glacial acetic acid. Wash the cold reaction mixture with three 25 ml. portions of 10 per cent. sodium chloride solution, and remove the benzene on a water bath under reduced pressure. Transfer the residue to a 1-litre bottle containing a solution of 65 g. of sodium bisulphite in 250 ml. of water and shake mechanically for 2–6 hours. Dilute the turbid solution, which contains the sodium bisulphite addition compound, with 400 ml. of water, and extract the ethyl cyanoacetate with three 50 ml. portions of benzene. Cool the bisulphite solution in ice, and add dropwise, with mechanical stirring, an ice-cold solution of 28 g. of sodium hydroxide in 110 ml. of water. Extract the regenerated unsaturated ester at once with four 25 ml. portions of benzene, wash the extracts with 50 ml. of 1 per cent. hydrochloric acid, and dry with anhydrous magnesium sulphate. Filter and distil from a Claisen flask with fractionating side arm under reduced pressure ; the benzene may be conviently removed by distilling at atmospheric pressure until the temperature rises to 90°. Diethyl ketone yields ethyl **α-cyano-ββ-diethylacrylate** {ethyl (1-ethylpropylidene)-cyanoacetate}, b.p. 123–125°/12 mm. or 96–97°/3 mm. ; di-*n*-propyl ketone gives ethyl **α-cyano-ββ-di-*n*-propylacrylate** {ethyl (1-propylbutylidene)-cyanoacetate}, b.p. 136–137°/11 mm. or 116–117°/4 mm. The yield is 60–70 per cent.

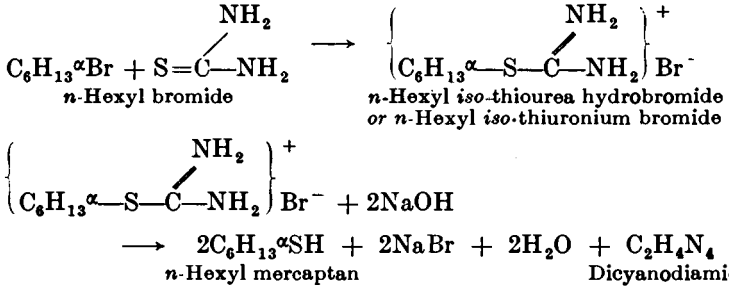
The appropriate succinic acid can be prepared by condensation of the unsaturated cyano ester with alcoholic potassium cyanide.

ALIPHATIC SULPHUR COMPOUNDS

Mercaptans (or thio-alcohols or thiols), the sulphur analogues of the alcohols, were formerly prepared by the interaction of an alkyl halide and sodium hydrosulphide in alcoholic solution :

$$RBr + NaSH \longrightarrow RSH + NaBr$$

A better method involves the interaction of an alkyl bromide and thiourea to form an alkyl *iso*-thiourea, followed by hydrolysis of the latter with sodium hydroxide solution, for example :



The lower members have remarkably disagreeable odours, but the offensive odour diminishes with increasing carbon content until it almost disappears at about $C_{10}H_{21}{}^{\alpha}SH$, *n*-dodecyl (lauryl) mercaptan.

The **alkyl sulphides or thioethers**, the sulphur analogues of the ethers, are conveniently obtained by boiling alkyl halides with anhydrous sodium sulphide in alcoholic solution, for example :

$$\underset{n\text{-Propyl bromide}}{2C_3H_7{}^{\alpha}Br} + Na_2S \longrightarrow \underset{n\text{-Propyl sulphide}}{(C_3H_7{}^{\alpha})_2S} + 2NaBr$$

$$\underset{n\text{-Hexyl bromide}}{2C_6H_{13}{}^{\alpha}Br} + Na_2S \longrightarrow \underset{n\text{-Hexyl sulphide}}{(C_6H_{13}{}^{\alpha})_2S} + 2NaBr$$

The **dialkyl disulphides** may be prepared by the oxidation of an alkaline solution of a mercaptan with iodine, for example :

$$2C_2H_5SNa + I_2 \longrightarrow (C_2H_5)_2S_2 + 2NaI$$

$$\underset{\text{Di-}n\text{-butyl disulphide}}{2C_4H_9{}^{\alpha}SNa + I_2 \longrightarrow (C_4H_9{}^{\alpha})_2S_2} + 2NaI$$

Xanthates (or xanthogenates), *e.g.*, CS(OR)SK, are formed by the reaction between carbon disulphide and an alcoholic solution of potassium hydroxide, for example :

$$S=C=S + KOC_2H_5 \longrightarrow \underset{\text{Potassium ethyl xanthogenate}}{S=C(SK)OC_2H_5}$$

The xanthates react with alkyl halides to give the **di-esters of dithiocarbonic acid** $\{O=C(SH)_2 \rightleftharpoons S=C(SH)OH\}$, for example :

$$\underset{\text{Potassium ethyl xanthate}}{S=C(SK)OC_2H_5} + C_2H_5I \longrightarrow \underset{\text{Ethyl S-ethyl xanthate}}{S=C(SC_2H_5)OC_2H_5} + KI$$

$$S=C(SK\ OC_2H_5 + \underset{n\text{-Butyl iodide}}{C_4H_9{}^{\alpha}I} \longrightarrow \underset{\text{Ethyl S-}n\text{-butyl xanthate}}{S=C(SC_4H_9{}^{\alpha})OC_2H_5} + KI$$

III,163. *n*-HEXYL MERCAPTAN (*n*-HEXYL THIOL)

Into a 500 ml. bolt-head or three-necked flask, equipped with a glycerine-sealed stirrer (Fig. *II*, 7, 10) and a reflux condenser, place 62·5 g. (53·5 ml.) of *n*-hexyl bromide (Section **III,37**) and a solution of 38 g. of thiourea (Section **III,134**) in 25 ml. of water. Connect a tube from the top of the condenser leading to an inverted funnel (Fig. *II*, *8*, 1, *a*) just immersed in potassium permanganate solution in order to prevent the escape of unpleasant odours. Stir the mixture vigorously and heat under reflux for 2 hours; the mixture becomes homogeneous after about 30 minutes and the additional heating ensures the completeness of the reaction. Add a solution of 30 g. of sodium hydroxide in 300 ml. of water and reflux, with stirring, for a further 2 hours; during this period the mercaptan separates since it is largely insoluble in the alkaline medium. Allow to cool and separate the upper layer of almost pure *n*-hexyl mercaptan (35 g.). Acidify the aqueous layer with a cold solution of 7 ml. of concentrated sulphuric acid in 50 ml. of water, and extract it with 75 ml. of ether. Combine the ethereal extract with the crude thiol, dry with anhydrous magnesium or sodium sulphate, and remove the ether on a water bath. Distil the residue using an air bath (Fig. *II*, *5*, 3) and collect the *n*-hexyl mercaptan at 150–152°. The yield is 37·5 g.

Cognate Preparation

***n*-Butyl mercaptan.** Use 51 g. (40 ml.) of *n*-butyl bromide (Sections **III,35** and **III,37**), 38 g. of thiourea and 25 ml. of water. Reflux, with stirring, for 3 hours; the mixture becomes homogeneous after 1 hour. Allow to cool and separate the upper layer of the mercaptan (*A*). Acidify the aqueous layer with a cold solution of 7 ml. of concentrated sulphuric acid in 50 ml. of water, cool and saturate with salt; remove the upper layer of *n*-butyl mercaptan (*B*) and combine it with (*A*). Extract the aqueous liquid with 75 ml. of ether, dry the ethereal extract with anhydrous sodium or calcium sulphate, and distil off the ether from a water bath through a fractionating column (compare Fig. *II*, *15*, 3). Combine the residue with (*A*) and (*B*), and distil. Collect the *n*-butyl mercaptan at 97–99°. The yield is 24 g.

General remarks on the preparation of mercaptans. The above method is of quite general application. If the bromide is inexpensive, the extraction with ether may be omitted, thus rendering the preparation of thiols a comparatively easy and not unduly unpleasant operation. The following mercaptans may be prepared in yields of the same order as those for *n*-butyl and *n*-hexyl mercaptans: ethyl, b.p. 35–36°; *n*-propyl, b.p. 66–67°; *iso*propyl, b.p. 51-52°; *iso*butyl, b.p. 87-88°; *n*-amyl, b.p. 124–125°; *n*-heptyl, b.p. 175–176°; *n*-octyl, b.p. 198–200° or 98–100°/22 mm.; *n*-nonyl, b.p. 220–222° or 98–100°/15 mm.; *n*-decyl, b.p. 96–97°/5 mm. or 114°/13 mm.; *n*-undecyl, b.p. 103–104°/3 mm.; *n*-dodecyl, b.p. 111-112°/3 mm. or 153-155°/24 mm.; *n*-tetradecyl, b.p. 176-180°/22 mm.; benzyl, b.p. 195°.

III,164. DI-*n*-PROPYL SULPHIDE

Place 56 g. of finely-powdered, anhydrous sodium sulphide (" fused " sodium sulphide) and 100 ml. of rectified spirit in a 500 ml. round-bottomed flask equipped with a reflux condenser. To the boiling mixture

add 46 g. (34 ml.) of *n*-propyl bromide (Section **III,35**) slowly and reflux for 6 hours. Distil off the alcohol on a water bath, and add a large excess of water to the distillate. Separate the upper layer of crude sulphide, wash it with three 40 ml. portions of 5 per cent. sodium hydroxide solution, then with water until the washings are neutral, and dry over anhydrous calcium chloride or anhydrous calcium sulphate. Distil from a 50 ml. Claisen flask and collect the *n*-propyl sulphide at 141–143°. The yield is 20 g. If the sulphide is required perfectly pure, it should be redistilled from a little sodium.

COGNATE PREPARATION

Di-*n*-hexyl sulphide. Use 83 g. (71 ml.) of *n*-hexyl bromide (Section **III,37**), 56 g. of finely-powdered, anhydrous sodium sulphide and 100 ml. of rectified spirit. Reflux on a water bath for 20 hours. Distil off the alcohol from a water bath ; very little sulphide is obtained upon adding excess of water to the distillate. Add excess of water to the residue in the flask and separate the upper layer of crude *n*-hexyl sulphide. Purify as for *n*-propyl sulphide, but distil under reduced pressure. Collect the *n*-hexyl sulphide at 113–114°/4 mm. The yield is 45 g.

III,165. DIETHYL DISULPHIDE

Fit a 500 ml. three-necked flask with a mechanical stirrer and a double surface condenser. Cool the flask in ice, introduce 38·5 g. (46 ml.) of ethyl mercaptan and 175 ml. of 15 per cent. sodium hydroxide solution, and stir the mixture. When all the mercaptan has reacted, add with constant stirring, 67·5 g. of iodine gradually (during about 2 hours) by momentarily removing the rubber stopper from the third neck of the flask and replacing it immediately the iodine has been introduced. After each addition the iodine gradually disappears and an oily layer forms on the surface of the liquid. Stir the mixture (1) for a further 2·5 hours and allow to stand for 2 hours : transfer to a separatory funnel. Remove the colourless upper layer and extract the aqueous layer with ether. Combine the ethereal extract with the upper layer, wash it with one third of its volume of 15 per cent. sodium hydroxide solution, then twice with water, partially dry it with anhydrous calcium chloride, and remove the ether on a water bath. The resulting colourless liquid usually has a slight odour of mercaptan. Wash it three times with one third of its volume of 5 per cent. sodium hydroxide solution, followed by water until free from alkali, and then dry with anhydrous calcium chloride or anhydrous calcium sulphate. Distil, using an air bath, and collect the diethyl disulphide at 151–152°. The yield is 27 g.

Note.

(1) The mixture should be colourless, otherwise difficulty will be experienced in the subsequent purification of the product. If the reaction mixture is coloured by iodine (due to volatilisation of some of the mercaptan), add just sufficient ethyl mercaptan to decolourise it.

COGNATE PREPARATION

Di-*n*-butyl disulphide. Use 45 g. (53·5 ml.) of *n*-butyl mercaptan (Section **III,163**), 135 ml. of 15 per cent. sodium hydroxide solution and

55 g. of iodine. The iodine may be dissolved in 40 per cent. potassium iodide solution, if desired. Wash the *colourless* upper layer (see *Note 1* above) three times with one third of its volume of 5 per cent. sodium hydroxide solution, then with water until free from alkali, dry over anhydrous calcium chloride or anhydrous calcium sulphate, and distil under reduced pressure. Collect the di-*n*-butyl disulphide at 84°/3 mm. The yield is 35 g. The b.p. under atmospheric pressure is 230–231°.

III,166. POTASSIUM ETHYL XANTHATE

Into a 500 ml. round-bottomed flask, fitted with a reflux condenser, place 42 g. of potassium hydroxide pellets and 120 g. (152 ml.) of absolute ethyl alcohol. Heat under reflux for 1 hour. Allow to cool and decant the liquid from the residual solid into another dry 500 ml. flask; add 57 g. (45 ml.) of A.R. carbon disulphide slowly and with constant shaking. Filter the resulting almost solid mass, after cooling in ice, on a sintered glass funnel at the pump, and wash it with two 25 ml. portions of ether (sp. gr. 0·720), followed by 25 ml. of anhydrous ether. Dry the potassium ethyl xanthate in a vacuum desiccator over silica gel. The yield is 74 g. If desired, it may be recrystallised from absolute ethyl alcohol, but this is usually unnecessary.

Cognate Preparation

Potassium *n*-butyl xanthate. Use 100 g. (123·5 ml.) of dry *n*-butyl alcohol, 18 g. of potassium hydroxide pellets, and 36 g. (28·5 ml.) of A.R. carbon disulphide. The yield of pure, dry potassium *n*-butyl xanthate $CS(OC_4H_9^{\alpha})SK$, is 42 g.

III,167. ETHYL S-ETHYL XANTHATE

Place 32 g. of potassium ethyl xanthate (Section **III,166**) and 50 ml. of absolute ethyl alcohol in a 500 ml. round-bottomed flask provided with a double surface condenser. Add 32 g. (16·5 ml.) of ethyl iodide. No reaction appears to take place in the cold. Heat on a water bath for 3 hours: a reaction sets in within 15 minutes and the yellow reaction mixture becomes white owing to the separation of potassium iodide. Add about 150 ml. of water, separate the lower layer, and wash it with water. Dry it with anhydrous calcium chloride or anhydrous calcium sulphate and distil from a 50 ml. Claisen flask. Collect the ethyl S-ethyl xanthate at 196–198°. The yield is 23 g.

Cognate Preparation

Ethyl S-*n*-butyl xanthate. Use 32 g. of potassium ethyl xanthate, 37 g. (23 ml.) of *n*-butyl iodide (Section **III,40**) and 50 ml. of absolute ethyl alcohol. Reflux on a water bath for 3 hours. Pour into 150 ml. of water, saturate with salt (in order to facilitate the separation of the upper layer), remove the upper xanthate layer, wash it once with 25 ml. of saturated salt solution, and dry with anhydrous calcium chloride or anhydrous calcium sulphate. Distil from a 50 ml. Claisen flask under reduced pressure. Collect the pale yellow ethyl S-*n*-butyl xanthate at 90–91°/4 mm. The yield is 34 g.

III,168. REACTIONS AND CHARACTERISATION OF MERCAPTANS (THIOLS)

Mercaptans RSH (also thioethers or sulphides R'SR'' and disulphides R'SSR'') are generally liquids and possess unpleasant odours.

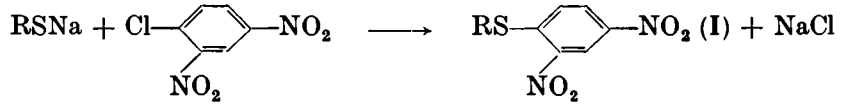
Upon fusion with caustic alkali (for experimental details, see Section **IV,33,*1***) and acidification of the aqueous extract, hydrogen sulphide is evolved (detected by lead acetate paper). This test is given by all organic compounds of divalent sulphur (RSH, R'SR'' and R'SSR'').

Alkyl mercaptans are partly soluble in solutions of caustic alkalis, but their salts are hydrolysed in dilute aqueous solution back to the free mercaptans. Thiophenols are soluble in alkali hydroxide solutions. Upon treatment with sodium, hydrogen is evolved.

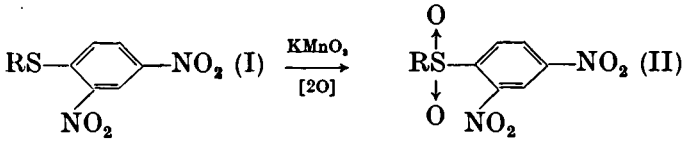
Crystalline Derivatives of Thiols

Of the crystalline derivatives of thiols, those formed with 3 : 5-dinitrobenzoyl chloride are not very satisfactory since they have, in general lower melting points than those of the corresponding alcohols (compare Section **III,27,*1***) and do not differ widely from ethyl to *n*-heptyl. The best results are obtained with 2 : 4-dinitrochlorobenzene.

1. **Alkyl (or Aryl) 2 : 4-dinitrophenyl-sulphides (or thioethers) and the corresponding sulphones.** Mercaptans react with 2 : 4-dinitrochlorobenzene in alkaline solution to yield crystalline thioethers (2 : 4-dinitrophenyl-sulphides) (I) :



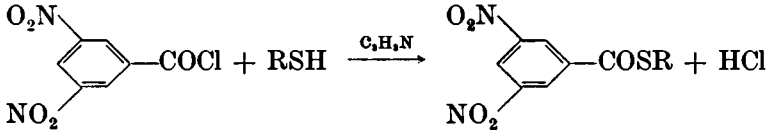
The sulphides (I) can be readily oxidised in glacial acetic acid solution by potassium permanganate to the corresponding sulphones (II); the latter exhibit a wide range of melting points and are therefore particularly valuable for the characterisation of mercaptans :



Preparation of 2 : 4-dinitrophenyl-sulphides. Dissolve about 0·5 g. (or 0·005 mol) of the mercaptan in 10–15 ml. of rectified spirit (or in the minimum volume necessary for solution ; warming is permissible) and add 2 ml. of 10 per cent. sodium hydroxide solution. Mix the resulting sodium mercaptide solution with a solution of 1 g. of 2 : 4-dinitrochlorobenzene in 5 ml. of rectified spirit. Reaction may occur immediately with precipitation of the thioether. In any case reflux the mixture for 10 minutes on a water bath in order to ensure the completeness of the reaction. Filter the hot solution rapidly ; allow the solution to cool when the sulphide will crystallise out. Recrystallise from alcohol.

Preparation of the sulphones. Dissolve the 2 : 4-dinitrophenyl-sulphide in the minimum volume of warm glacial acetic acid and add 3 per cent. potassium permanganate solution with shaking as fast as decolourisation occurs. Use a 50 per cent. excess of potassium permanganate : if the sulphide tends to precipitate, add more acetic acid. Just decolourise the solution with sulphur dioxide (or with sodium bisulphite or alcohol) and add 2–3 volumes of crushed ice. Filter off the sulphone, dry, and recrystallise from alcohol.

2. **3 : 5-Dinitrothiobenzoates.** Mercaptans react with 3 : 5-dinitrobenzoyl chloride in the presence of pyridine as a catalyst to yield 3 : 5-dinitrothiobenzoates :



Mix 0·2 g. of 3 : 5-dinitrobenzoyl chloride, 6 drops of the mercaptan and 1–3 drops of pyridine in a test-tube, and heat the mixture in a beaker of boiling water until fumes of hydrogen chloride cease to appear (15–30 minutes). Add a few drops of water, followed by a drop or two of pyridine to eliminate the excess of the reagent. The product solidifies upon stirring with a glass rod. Add water, filter, and recrystallise from dilute alcohol or dilute acetic acid.

The melting points of the derivatives of the more commonly occurring thiols are collected in Table **III,168.**

TABLE III,168. MERCAPTANS (THIOLS)

Mercaptan (Thiol)	B.P.	M.P.	2 : 4-Dinitrophenyl-thioether	2 : 4-Dinitrophenyl-sulphone	3 : 5-Dinitrothiobenzoate
Methyl	6°	—	128°	190°	—
Ethyl	36	—	115	160	62°
n-Propyl	67	—	81	128	52
iso-Propyl	58	—	95	141	84
n-Butyl	97	—	66	92	49
iso-Butyl	88	—	76	106	64
n-Amyl	126	—	80	83	40
iso-Amyl	117	—	59	95	43
n-Hexyl	151	—	74	97	—
n-Heptyl	176	—	82	101	53
n-Octyl	199	—	78	98	—
n-Nonyl	220	—	86	92	—
n-Decyl	114°/13	—	85	93	—
n-Dodecyl (lauryl)	154°/24	—	89	101	—
n-Hexadecyl (cetyl)	—	51°	91	105	—
Allyl	90	—	72	105	—
*cyclo*Hexyl	159	—	148	172	—
Furfuryl	84°/65	—	130	—	—
Dimethylene di- (1)	146	—	248	—	—
Trimethylene di-	169	—	194	—	—
Pentamethylene di-	123°/27	—	170	—	—
Hexamethylene di-	119°/15	—	218	—	—
Phenyl (thiophenol)	169	—	121	161	149
o-Thiocresol	194	15	101	155	—
m-Thiocresol	195	—	91	145	—
p-Thiocresol	195	44	103	190	—
Benzyl	194	—	130	183	120
α-Phenylethyl	105°/23	—	90	133	—
α-Thionaphthol	161°/20	—	176	—	—
β-Thionaphthol	162°/20	81	145	—	—
Diphenyl	—	111	146	170	—
Thienyl	166	—	119	143	—

(1) Ethylene dithioglycol.

RESOLUTION OF A RACEMIC COMPOUND

III,169. DETERMINATION OF THE ROTATORY POWER

When a beam of light is passed through a crystal of Iceland spar, two beams are transmitted, each vibrating in a plane which is perpendicular to the other. A Nicol prism is composed of two sections of Iceland spar so cut, and again scaled with Canada balsam, that one of the rays is refracted to the side and absorbed so that all the light which passes through is vibrating in one plane only. The light is said to be **plane polarized**. If this polarized light is examined by means of another Nicol prism, it will be found that on rotating the latter, the field of view appears alternately light and dark and the minimum of brightness follows the maximum as the prism is rotated through an angle of 90° : the field of view will appear dark when the axes of the two prisms are at right angles to one another. The prism by which the light is polarized is termed the **polarizer**, and the second prism, by which the light is examined, is called the **analyzer**.

If, when the field of view appears dark, a tube containing a solution of cane sugar (sucrose) is placed between the two prisms, the field lights up ; one of the prisms must be turned through a certain angle α before the original dark field is restored. The solution of cane sugar has therefore the power of turning or rotating the plane of polarized light through a certain angle, and is accordingly said to be **optically active**. Since the plane of vibration of polarized light may be rotated either clockwise or anti-clockwise, it is necessary to observe a convention regarding the sign of rotation. When, in order to obtain darkness, the analyzer has to be turned clockwise (*i.e.*, to the right), the optically active substance is said to be **dextro-rotatory** ; it is **laevo-rotatory** when the analyzer must be rotated anti-clockwise (*i.e.*, to the left).

The obvious disadvantage of the above simple instrument (**polarimeter**) is the difficulty of determining the precise "end point" or the point of maximum darkness. The human eye is a poor judge of absolute intensities, but is capable of matching the intensities of two simultaneously viewed fields with great accuracy. For this reason all precision polarimeters are equipped with an optical device that divides the field into two or three adjacent parts (half-shadow or triple-shadow polarimeter) such that when the "end point" is reached the sections of the field become of the same intensity. A very slight rotation of the analyzer will cause one part to become lighter and the other darker. The increase in sensitivity so attained is illustrated by the fact that an accuracy of at least $\pm 0{\cdot}01°$ is easily obtained with the use of an "end point" device, whereas with the unaided eye the settings are no more accurate than $\pm$ 4–5°.

A **half-shadow polarimeter** (Lippich type) * is illustrated diagrammatically in Fig. *III, 169*, 1. Here two polarized rays are produced by means of the main Nicol prism P and a small Nicol prism P' ; the latter

* For further details and a description of the triple-shadow polarimeter, see text books of practical physical chemistry, for example, Daniels, Mathews and Williams, *Experimental Physical Chemistry*, 4th Edition, 1949, p. 34 (McGraw-Hill) ; Findlay and Kitchener, *Practical Physical Chemistry*, 1954, p. 180 (Longmans, Green and Co. Ltd.).

covers half the field of the large polarizer P and its plane of polarization is slightly inclined to that of P. The angles between the planes of polarization may be altered by a slight rotation of the polarizer P. Upon rotating the analyzer A, a position will be found at which one beam will be completely, the other only partially, extinguished ; the one half of the

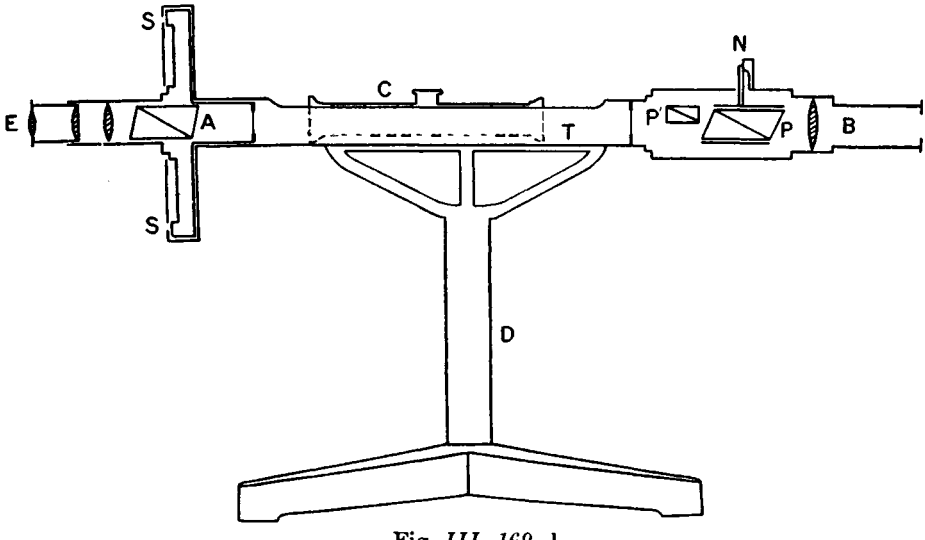


Fig. *III*, *169*, 1.

field of view will therefore appear dark, while the other will still remain light (as in Fig. *III*, *169*, 2, *a*). Upon rotating the analyzer A still further, a second position will be found at which only the second beam will be extinguished and the field will have the appearance shown in (*c*). When, however, the analyzer occupies an intermediate position, the field of view will appear of uniform brightness (as in *b*) and this is the position

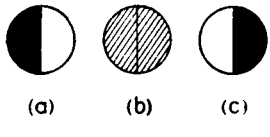


Fig. *III*, *169*, 2.

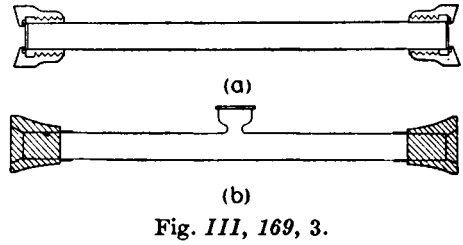


Fig. *III*, *169*, 3.

to which the analyzer must be set. In Fig. *III*, *169*, 1, B is a collimator tube, P the polarizer, P' the subsidiary Nicol prism, N is a device for moving P and thus altering the "half-shadow angle," T the trough (shown without cover) which houses the polarimeter tube C, A is the analyzer, E the eyepiece, S the circular scale fitted with vernier, and D the heavy support stand for the apparatus. Two forms of polarimeter tube are shown in Fig. *III*, *169*, 3. The common type (*a*) consists of a tube of thick glass with accurately ground ends : the tube is closed by

means of circular plates of glass with parallel sides, which are pressed together against the ends of the tube by means of screw caps. The caps must not be screwed so tightly as to cause strain as this would cause a rotation ; the glass plates at the end must be clear and the exposed surfaces must be dry. In a modification, the tube is surrounded by a jacket to permit the circulation of water at constant temperature by means of a pump. Tube (*b*) has the opening at the side. The unit of length in polarimetry is 1 dm., hence the tubes are generally made in lengths which are fractions or multiples of this quantity, *e.g.*, 0·5, 1, 2 or 4 dm.

The magnitude of the optical rotation depends upon (i) the nature of the substance, (ii) the length of the column of liquid through which the light passes, (iii) the wave length of the light employed, (iv) the temperature, and (v) the concentration of the optically active substance, if a solute. In order to obtain a measure of the rotatory power of a substance, these factors must be taken into account. As a rule the wave length employed is either that for the sodium D line, 5893 Å (obtained with a sodium vapour lamp) or the mercury green line, 5461 Å (produced with a mercury vapour lamp provided with a suitable filter). The temperature selected is 20° or that of the laboratory *t*° C. The **specific rotation** for a **homogeneous active liquid** at a temperature *t* for the *D* sodium line is given by :

$$[\alpha]_D^t = \frac{\alpha}{ld}$$

where α is the angular rotation, l is the length of the column of liquid in decimetres and d is the density at temperature t. The **specific rotation for a solution of an optically active substance** is likewise given by :

$$[\alpha]_D^t = \frac{100\alpha}{lc} = \frac{100\alpha}{lpd}$$

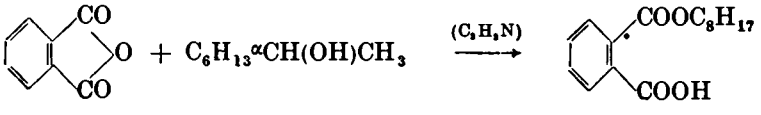
where l is the length of the column of liquid in decimetres, c is the number of grams of the substance dissolved in 100 ml. of the solution, p is the number of grams of the substance dissolved in 100 *g*. of the solution and d is the density of the solution at the temperature t. In expressing the specific rotation of a substance in solution, the concentration and the solvent (which has an influence on the rotation) must be clearly stated. The **molecular rotation** is :

$$[M]_D^t = \frac{[\alpha]_D^t \times M}{100};$$

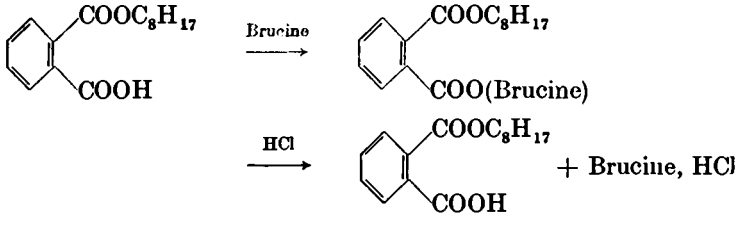
M is the molecular weight.

III,170. RESOLUTION OF *sec.*-OCTYL ALCOHOL (*dl*-2-OCTANOL) INTO ITS OPTICALLY ACTIVE COMPONENTS (*d*- AND *l*-2-OCTANOL)

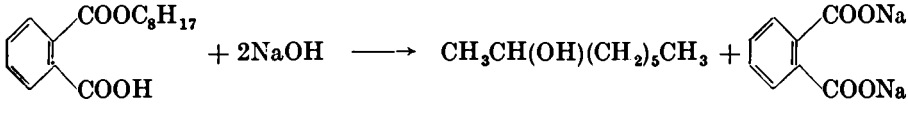
sec.-Octyl alcohol {methyl *n*-hexyl carbinol $CH_3CH(OH)(CH_2)_5CH_3 \equiv C_8H_{17}OH$} is converted by heating with phthalic anhydride into *sec.*-octyl hydrogen phthalate :



This substance (*dA*, *lA*) contains a free carboxyl group and is treated in warm acetone solution with an equimolecular quantity of the optically active base brucine (*lB*); upon cooling, the brucine salt (*dA*, *lB*) separates out first in a moderately pure condition, whilst the brucine salt (*lA*, *lB*) remains in solution:



The latter upon decomposition with dilute hydrochloric acid yields *laevo sec.*-octyl hydrogen phthalate: the crystalline brucine salt, when similarly treated, affords the *dextro sec.*-octyl hydrogen phthalate. These are recrystallised and separately hydrolysed with sodium hydroxide solution to yield pure *l*- and *d-sec.*-octyl alcohols:



* Heat a mixture of 65 g. of dry *sec.*-octyl alcohol (b.p. 178–180°), 74 g. of pure phthalic anhydride (1) and 40 g. of dry pyridine on a water bath for 1 hour, and allow to cool. Dissolve the resulting viscous mass in an equal volume of acetone. Add slowly, preferably with stirring, 55 ml. of concentrated hydrochloric acid diluted with an approximately equal volume of crushed ice: if an oil separates before all the hydrochloric acid has been added, introduce more acetone to render the mixture homogeneous. Add ice-water until the oil is completely precipitated; this usually sets to a hard mass within 1–2 hours. If the resulting mass is semi-solid or pasty (2), transfer it to a large flask and pass steam through it until the methyl *n*-hexyl ketone is removed, *i.e.*, until the steam distillate is clear; pour the contents of the flask whilst still warm into a beaker. The *dl-sec.*-octyl hydrogen phthalate solidifies completely on cooling. Filter the octyl hydrogen phthalate at the pump, wash it with water, grind it thoroughly in a mortar with water, filter again and dry in the air. The crude material is quite satisfactory for the subsequent resolution (3).

Introduce 197 g. of anhydrous brucine or 215 g. of the air-dried dihydrate (4) into a warm solution of 139 g. of *dl-sec.*-octyl hydrogen phthalate in 300 ml. of acetone and warm the mixture under reflux on a water bath until the solution is clear. Upon cooling, the brucine salt (*dA*, *lB*) separates as a crystalline solid. Filter this off on a sintered glass funnel, press it well to remove mother liquor, and wash it in the funnel with 125 ml. of acetone. Set the combined filtrate and washings (W) aside. Cover the crystals with acetone and add, slowly and with stirring, a slight excess (to Congo red) of dilute hydrochloric acid (1 : 1 by volume; about 60 ml.); if the solution becomes turbid before the introduction of

* The following experimental details were kindly supplied by Dr. J. Kenyon, F.R.S.

the acid is complete, add more acetone to produce a clear liquid. Add ice-water until the precipitation of the active *sec.*-octyl hydrogen phthalate (crude *dA*) is complete ; filter (5), wash with cold water and dry in the air. The yield is about half that of the *dl*-ester originally taken (6).

Concentrate the combined filtrate and washings (W) to about half the original volume, and pour it into slightly more than the calculated amount of dilute hydrochloric acid (use a mixture of 30 ml. of concentrated hydrochloric acid and 30 ml. of ice-water) ; then add about 300 ml. of water. Collect the active *sec.*-octyl hydrogen phthalate (crude *lA*) as above (5). The weight of the air-dried ester is about half that of the *dl*-ester originally used (7).

Crystallise the two lots of crude active *sec.*-octyl hydrogen phthalates separately twice from 90 per cent. acetic acid ; use 2 g. of acetic acid to each gram of solid. The recrystallised esters, if optically pure (8), will melt sharply at 75° ; if the melting points are below 75°, further recrystallisation is necessary. The yields of optically pure products, m.p. 75°, are 48 g. and 49 g. respectively.

To obtain optically pure *l*- and *d*-*sec.*-octyl alcohols, steam distil the respective esters with 30 per cent. sodium hydroxide solution ; use the proportions 1 mol of ester to 2 mols of sodium hydroxide. Separate the alcohols from the steam distillate, dry over anhydrous potassium carbonate, and distil under diminished pressure. Both samples boil at 86°/20 mm. (9) and have the following rotations :

$$[\alpha]_D^{17^\circ} + 9{\cdot}9^\circ,\ [\alpha]_{5461}^{17^\circ} + 11{\cdot}8^\circ\ ;\ [\alpha]_D^{17^\circ} - 9{\cdot}9^\circ,\ [\alpha]_{5461}^{17^\circ} - 11{\cdot}8^\circ.$$

The yields from the *sec.*-octyl hydrogen phthalates are almost quantitative.

Notes.

(1) If the presence of phthalic acid is suspected, it may be readily removed by mixing with cold chloroform ; phthalic anhydride dissolves readily, but the acid is insoluble.

(2) This is due to methyl *n*-hexyl ketone in the original *sec.*-octyl alcohol ; it is most easily separated by steam distillation as described.

(3) The inactive *sec.*-octyl hydrogen phthalate may be recrystallised from light petroleum, b.p. 60–80°, or from glacial acetic acid, and then melts at 55°.

If the *sec.*-octyl alcohol is pure, the yield of pure material is almost quantitative.

(4) Commercial brucine is usually the tetrahydrate $C_{23}H_{26}O_4N_2,4H_2O$; upon air drying, this loses two molecules of water of crystallisation and passes into the dihydrate.

(5) The filtrates from the decomposition of the brucine salts with dilute hydrochloride acid should be carefully preserved. The brucine is recovered by the addition of an excess of dilute ammonia solution (1 : 4) ; if the solution becomes turbid before all the ammonia solution is added, introduce a little alcohol until the solution becomes clear. After several hours in an open beaker, filter off the brucine, wash it well with cold water and dry it in the air.

(6) The rotation in absolute alcohol is about $[\alpha]_D + 44^\circ$, $[\alpha]_{5461} + 47^\circ$.

(7) The rotation in absolute alcohol is about $[\alpha]_D - 44^\circ$, $[\alpha]_{5461} - 47^\circ$.

(8) The optically pure salts have rotations in alcohol of $[\alpha]_D - 48{\cdot}4^\circ$ $[\alpha]_{5461} - 58{\cdot}5^\circ$, and $[\alpha]_D + 48{\cdot}4^\circ$, $[\alpha]_{5461} + 58{\cdot}5^\circ$ respectively. A preliminary check of the optical purity is, however, more simply made by a m.p. determination ; the rotation is determined, if desired, when the m.p. is 75°.

(9) The boiling point under atmospheric pressure in 179°.