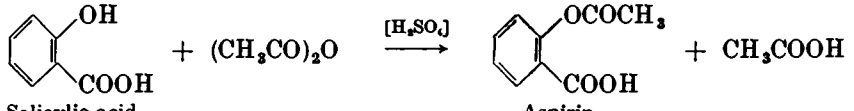
CHAPTER IX

SOME PHYSIOLOGICALLY ACTIVE COMPOUNDS

IX,1. ASPIRIN (ACETYLSALICYLIC ACID)

Phenols, unlike amines, cannot be acetylated satisfactorily in aqueous solution : acetylation proceeds readily with acetic anhydride in the presence of a little concentrated sulphuric acid as catalyst. Salicylic acid (o-hydroxybenzoic acid) upon acetylation yields acetylsalicylic acid or aspirin :



Salicylic acid — Aspirin

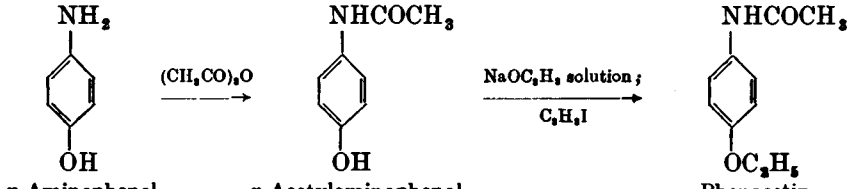
Place 10 g. of dry salicylic acid and 15 g. (14 ml.) of acetic anhydride in a small conical flask, add 5 drops of concentrated sulphuric acid, and rotate the flask in order to secure thorough mixing. Warm on a water bath to about 50–60°, stirring with the thermometer, for about 15 minutes. Allow the mixture to cool and stir occasionally. Add 150 ml. of water, stir well and filter at the pump. Recrystallise the crude acetylsalicylic acid from a mixture of equal volumes of acetic acid and water.

The following is an alternative method of purifying the crude aspirin. Dissolve the solid in about 30 ml. of hot alcohol and pour the solution into about 75 ml. of warm water : if a solid separates at this point, warm the mixture until solution is complete and then allow the clear solution to cool slowly. Beautiful needle-like crystals will separate. The yield is 13 g. The air-dried crude product may also be recrystallised from benzene or from ether - light petroleum (b.p. 40–60°).

Acetylsalicylic acid decomposes when heated and does not possess a true, clearly-defined m.p. Decomposition points ranging from 128° to 135° have been recorded ; a value of 129–133° is obtained on an electric hot plate (Fig. *II*, *11*, 1). Some decomposition may occur if the compound is recrystallised from a solvent of high boiling point or if the boiling period during recrystallisation is unduly prolonged.

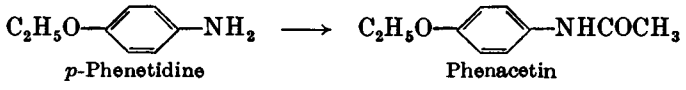
IX,2. PHENACETIN

Phenacetin may be conveniently prepared in the laboratory from *p*-aminophenol. The latter is readily acetylated with acetic anhydride to give *p*-acetylaminophenol ; this is ethylated in the form of the sodio derivative to yield acetyl *p*-phenetidine (phenacetin) :



p-Aminophenol — *p*-Acetylaminophenol — Phenacetin

Phenacetin may also be prepared by acetylation of the commercially available *p*-phenetidine : *



p-Phenetidine Phenacetin

Method A

Suspend 11 g. of *p*-aminophenol in 30 ml. of water contained in a 250 ml. beaker or conical flask and add 12 ml. of acetic anhydride. Stir (or shake) the mixture vigorously and warm on a water bath. The solid dissolves. After 10 minutes, cool, filter the solid acetyl derivative at the pump and wash with a little cold water. Recrystallise from hot water (about 75 ml.) and dry upon filter paper in the air. The yield of *p*-acetylaminophenol, m.p. 169° (1), is 14 g.

Place 1·55 g. of clean sodium in a 250 ml. round-bottomed flask equipped with a reflux condenser. Add 40 ml. of absolute alcohol (or rectified spirit). If all the sodium has not disappeared after the vigorous reaction has subsided, warm the flask on a water bath until solution is complete. Cool the mixture and add 10 g. of *p*-acetylaminophenol. Introduce 15 g. (8 ml.) of ethyl iodide slowly through the condenser and reflux the mixture for 45–60 minutes. Pour 100 ml. of water through the condenser at such a rate that the crystalline product does not separate ; if crystals do separate, reflux the mixture until they dissolve. Then cool the flask in an ice bath : collect the crude phenacetin with suction and wash with a little cold water. Dissolve the crude product in 80 ml. of rectified spirit ; if the solution is coloured, add 2 g. of decolourising carbon and filter. Treat the clear solution with 125 ml. of hot water and allow to cool. Collect the pure phenacetin at the pump and dry in the air. The yield is 9·5 g., m.p. 137°.

Method B

Dissolve 14 g. of *p*-phenetidine (2) in 240 ml. of water to which 20 ml. of 5*N* hydrochloric acid (or 9 ml. of the concentrated acid) have been added ; stir the solution with about 5 g. of decolourising carbon for 5 minutes, warm, and filter the solution with suction. Transfer the cold filtered solution of *p*-phenetidine hydrochloride to a 700 ml. conical flask, add 13 g. (12 ml.) of acetic anhydride and swirl the contents to dissolve the anhydride. Immediately add a solution of 16 g. of crystallised sodium acetate in 50 ml. of water and stir (or swirl) the contents of the flask vigorously. Cool the reaction mixture in an ice bath, filter with suction and wash with cold water. Recrystallise from hot water (with the addition of a little decolourising carbon, if necessary), filter and dry. The yield of pure phenacetin, m.p. 137°, is 12 g.

Notes.

(1) If the m.p. is unsatisfactory, dissolve the product in dilute alkali in the cold and then reprecipitate it by the addition of acid to the neutralisation point. This procedure will eliminate traces of the diacetate of *p*-aminophenol which may be

* Prepared *inter alia* thus :

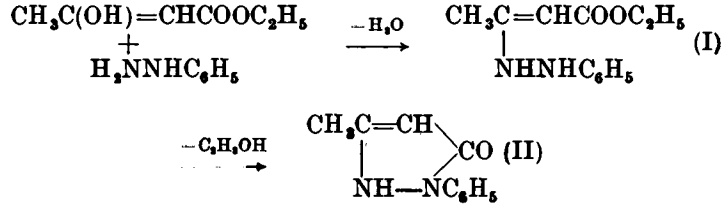
present ; the acetyl group attached to nitrogen is not affected by cold dilute alkali, but that attached to oxygen is readily hydrolysed by the reagent.

(2) The *p*-phenetidine is usually coloured and the procedure given permits a preliminary treatment with decolourising carbon, thus leading to an almost colourless phenacetin directly.

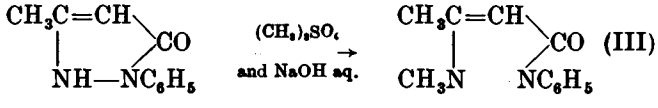
Acetylation of the amine may also be effected by boiling with 20 ml. of glacial acetic acid and 14 ml. of acetic anhydride for 15–20 minutes, followed by decomposition of the excess of anhydride with water and, after boiling for 5 minutes, pouring with stirring into about 75 ml. of water ; the product is appreciably coloured.

IX,3. ANTIPYRIN

When ethyl acetoacetate is warmed with an equivalent quantity of phenylhydrazine, the compound (I), which is not a true hydrazone, is first formed ; this undergoes ring formation (II) with loss of ethyl alcohol upon further heating. The product (II) is *N* or 1-phenyl-3-methyl-5-pyrazolone.



This substance may be conveniently methylated with dimethyl sulphate to yield 1-phenyl-2 : 3-dimethyl-5-pyrazolone or antipyrin (III) :



1-Phenyl-3-methyl-5-pyrazolone. Mix together 50 g. (49 ml.) of redistilled ethyl acetoacetate (Section **III,151**) and 40 g. (36·5 ml.) of phenylhydrazine (*CAUTION* in handling) (Section **IV,89**) in a large evaporating dish. Heat the mixture on a water bath in the fume cupboard for 1 hour and stir from time to time with a glass rod. Allow the heavy reddish syrup to cool somewhat, add about 100 ml. of ether and stir the mixture vigorously. The syrup, which is insoluble in ether, will solidify within 15 minutes. Filter the solid at the pump and wash it thoroughly with ether to remove coloured impurities. Recrystallise it from hot water or from a mixture of equal volumes of alcohol and water. The yield of phenylmethylpyrazolone (colourless crystals, m.p. 127°) is 52 g.

1-Phenyl-2 : 3-dimethyl-5-pyrazolone (antipyrin). In a 500 ml. three-necked flask, equipped with a dropping funnel, a mercury-sealed stirrer and a double surface condenser and set up in the fume cupboard, place a solution of 10 g. of sodium hydroxide in a small volume of water and also a solution of 43·5 g. of phenylmethylpyrazolone in 20 ml. of methyl alcohol. Warm the mixture on a water bath and add 36 g. (27 ml.) of dimethyl sulphate (*CAUTION :* toxic, see discussion prior to

Section IV,49). Reflux the mixture for 1 hour and allow to cool, with continuous stirring. Distil off the methyl alcohol. Add hot water to the residue, filter from impurities, extract the antipyrine with benzene, and evaporate the solvent. Recrystallise the crude product from benzene or benzene - light petroleum or from hot water with the addition of a little decolourising carbon. The yield of antipyrin (white crystalline solid, m.p. 113°) is 35 g.

IX,4. BROMURAL (α-BROMO-*ISO*-VALERYLUREA)

iso-Valeric acid is converted by phosphorus and bromine into α-bromo-*iso*-valeryl bromide ; the latter upon heating with urea gives bromural :

$$(CH_3)_2CHCH_2COOH \xrightarrow{P,\ Br_2} (CH_3)_2CHCHBrCOBr$$

iso-Valeric acid — α-Bromo-*iso*-valeryl bromide

$$(CH_3)_2CHCHBrCOBr \xrightarrow{CO(NH_2)_2} (CH_3)_2CHCBrCONHCONH_2$$

Bromural

Equip a 1 litre bolt-head flask with dropping funnel and a double surface reflux condenser * ; to the top of the latter attach a device (*e.g.*, Fig. *II*, *8*, 1, *c*) for the absorption of the hydrogen bromide evolved. Place 100 g. (108 ml.) of dry *iso*-valeric acid (Section **III,80**) and 12 g. of purified red phosphorus (Section **II,50**,*5*) in the flask. Add 255 g. (82 ml.) of dry bromine (Section **II,49**,*8*) slowly through the dropping funnel at such a rate that little or no bromine is lost with the hydrogen bromide evolved ; the addition occupies 2–3 hours. Warm the reaction mixture on a water bath until the evolution of hydrogen bromide is complete and the colour of the bromine has disappeared. Pour off the liquid reaction product into a Claisen flask and distil under the reduced pressure of a water pump. Collect the α-bromo-*iso*-valeryl bromide at 117–122°/25–30 mm. The yield is 150 g.

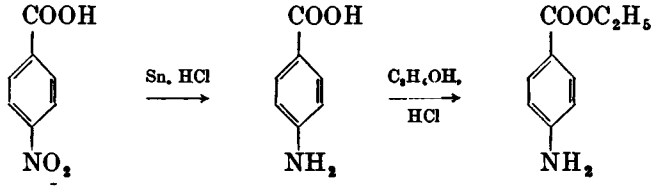
In a 500 ml. bolt-head flask provided with a thermometer (reaching almost to the bottom) and a calcium chloride (or cotton wool) guard tube, place 100 g. of α-bromo-*iso*-valeryl bromide and 50 g. of dry, finely-divided urea. Start the reaction by warming the flask on a water bath ; the temperature soon rises to about 80°. Maintain this temperature for about 3 hours ; the mass will liquefy and then resolidify. Transfer the sticky reaction product to a large beaker containing saturated sodium bicarbonate solution, stir mechanically and add more saturated sodium bicarbonate solution in small quantities until effervescence ceases. Filter at the pump, suck as dry as possible and dry the crude bromural upon filter paper in the air. Recrystallise the dry product from toluene. Alternatively, recrystallise the moist product from hot water (*ca.* 700 ml.). The yield of pure bromural, m.p. 154–155°, is 28 g.

* It is best to employ an apparatus with ground glass joints. Failing this, an old rubber stopper or a cork covered with paraffin wax may be used.

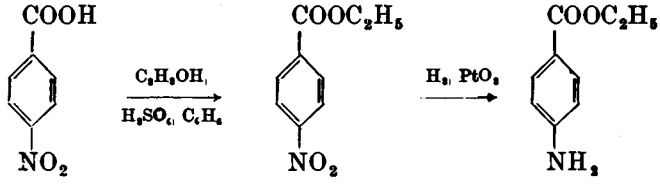
IX,5. BENZOCAINE (ETHYL *p*-AMINOBENZOATE)

Benzocaine (or anaesthesine) is conveniently prepared from *p*-nitrobenzoic acid by either of the following methods:

(i) *p*-Nitrobenzoic acid is first reduced with tin and hydrochloric acid to *p*-aminobenzoic acid, and the latter is esterified with ethyl alcohol in the presence of hydrogen chloride:



(ii) *p*-Nitrobenzoic acid is first converted into the ethyl ester and the latter is reduced with hydrogen in the presence of Adams' platinum oxide catalyst:



Method 1. **p-Aminobenzoic acid.** Place 15 g. of *p*-nitrobenzoic acid (Section IV,154) in a 1 litre round-bottomed flask fitted with a reflux condenser. Introduce 35 g. of powdered tin and 75 ml. of concentrated hydrochloric acid. Heat the mixture gently until the reaction commences, and remove the flame. Shake the flask frequently and take care that the insoluble acid adhering to the sides of the flask is transferred to the reaction mixture: occasional gentle warming may be necessary. After about 20 minutes, most of the tin will have reacted and a clear solution remains. Allow to cool somewhat and decant the liquid into a 1 litre beaker; wash the residual tin by decantation with 15 ml. of water, and add the washings to the contents of the beaker. Add concentrated ammonia solution (sp. gr. 0·88) until the solution is just alkaline to litmus; filter off the precipitate of hydrated tin oxide and wash well with water. If the total volume of the combined filtrate and washings exceeds 200 ml., evaporate in a large evaporating dish on a water bath until the volume has been reduced to 175–200 ml.: filter off any solid which separates. Acidify the liquid to litmus with glacial acetic acid and evaporate on a water bath until crystals commence to separate; cool in ice, filter the crystals at the pump and dry in the steam oven. The yield of *p*-aminobenzoic acid, m.p. 192°, is 13 g.

Ethyl *p*-aminobenzoate (*esterification of* p-*aminobenzoic acid*). Place 80 ml. of absolute ethyl alcohol in a 250 ml. conical flask equipped with a two-holed cork and wash-bottle tubes. Pass dry hydrogen chloride (Section II,48,*1*) through the alcohol until saturated—the increase in weight is about 20 g.—and transfer the solution to a 250 ml. round-bottomed flask. Introduce 12 g. of *p*-aminobenzoic acid, fit a double surface condenser to the flask, and reflux the mixture for 2 hours. Upon

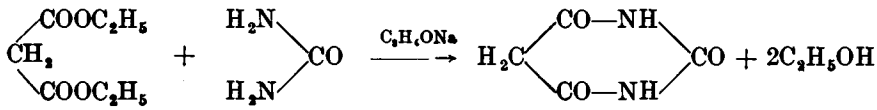
cooling, the reaction mixture sets to a solid mass of the hydrochloride of ethyl *p*-aminobenzoate. It is better, however, to pour the hot solution into excess of water (no hydrochloride separates) and add sodium carbonate to the clear solution until it is neutral to litmus. Filter off the precipitated ester at the pump and dry in the air. The yield of ethyl *p*-aminobenzoate, m.p. 91°, is 10 g. Recrystallisation from rectified (or methylated) spirit does not affect the m.p.

Method 2. **Ethyl *p*-nitrobenzoate.** Place 21 g. of *p*-nitrobenzoic acid (Section **IV,154**), 11·5 g. of absolute ethyl alcohol, 3·8 g. of concentrated sulphuric acid, and 30 ml. of sodium-dried A.R. benzene in a 250 ml. round-bottomed flask, fit a reflux condenser, and heat the mixture under reflux for 16 hours. Add 50 ml. of ether to the cold reaction mixture, wash the extract successively with sodium bicarbonate solution and water, dry with anhydrous magnesium sulphate or calcium chloride, and distil off the solvent on a water bath. Remove the last traces of benzene either by heating in an open evaporating dish on a water bath or in a bath at 100–110°. The residual ethyl *p*-nitrobenzoate (21 g.) solidifies completely on cooling and melts at 56°.

Ethyl *p*-aminobenzoate (*catalytic reduction of ethyl* p-*nitrobenzoate*). The general experimental details may be adapted from those described in Section **III,150.** Place a solution of 9·75 g. of ethyl *p*-nitrobenzoate in 100 ml. of rectified spirit together with 0·1 g. of Adams' platinum oxide catalyst in the hydrogenation bottle, and shake in hydrogen in the usual manner. The theoretical volume of hydrogen (*ca.* 3360 ml. at 24° and 760 mm.) is absorbed in 2·5 hours. Filter off the platinum through a " quantitative " filter paper with suction and rinse the reaction vessel with rectified spirit. Evaporate the alcohol from the combined filtrate and washings on a water bath; the residue solidifies on cooling and weighs 8·2 g. Dissolve the crude ethyl *p*-aminobenzoate in rectified spirit, add a little decolourising charcoal, boil and filter; heat the filtrate to the boiling point, add hot water to incipient crystallisation and allow to cool. The resulting pure benzocaine has m.p. 90°; the recovery is about 90 per cent.

IX,6. BARBITURIC ACID

Ethyl malonate condenses with urea in the presence of sodium ethoxide to yield barbituric acid (malonylurea):



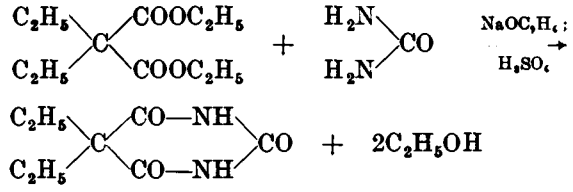
In a 2 litre round-bottomed flask, fitted with a double surface reflux condenser, place 11·5 g. of clean sodium. Add 250 ml. of absolute alcohol in one portion: if the reaction is unduly vigorous, immerse the flask momentarily in ice. When all the sodium has reacted, add 80 g. (76 ml.) of ethyl malonate (Section **III,153**), followed by a solution of 30 g. of dry urea in 250 ml. of hot (*ca.* 70°) absolute alcohol. Shake the mixture well, fit a calcium chloride (or cotton wool) guard tube to the top

of the condenser, and reflux the mixture for 7 hours on an oil bath heated to 110°. A white solid separates. Treat the reaction mixture with 450 ml. of hot (50°) water and then with concentrated hydrochloric acid, with stirring, until the solution is acid (about 45 ml.). Filter the resulting almost clear solution and leave it in the ice box overnight. Filter the solid at the pump, wash it with 25 ml. of cold water, drain well, and then dry at 100° for 4 hours. The yield of barbituric acid is 50 g. It melts with decomposition at 245°.

IX,7. DIETHYLBARBITURIC ACID (VERONAL)

The condensation of 1 mol of ethyl malonate with two mols of ethyl iodide in the presence of two mols of sodium ethoxide gives a good yield of ethyl diethylmalonate. Upon allowing the latter to react with the theoretical quantity of urea in the presence of an alcoholic solution of sodium ethoxide, veronal (diethylbarbituric acid or diethylmalonylurea) is produced.

$$CH_2(COOC_2H_5)_2 + 2NaOC_2H_5 + 2C_2H_5I \longrightarrow (C_2H_5)_2C(COOC_2H_5)_2 + 2NaI + 2C_2H_5OH$$

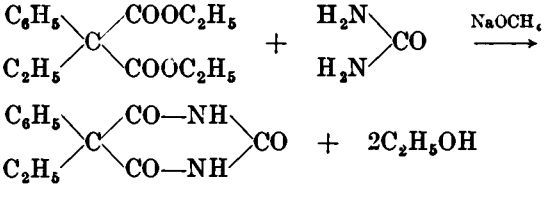


Ethyl diethylmalonate. Equip a 1 litre three-necked flask with a mercury-sealed mechanical stirrer, a dropping funnel (with calcium chloride or cotton wool guard tube) and a double surface reflux condenser; it is important that the apparatus be perfectly dry. Place 23 g. of clean sodium in the flask and add 300 ml. of "super-dry" ethyl alcohol (Section **II,47,5**). It may be necessary to warm the flask gently on a water bath towards the end of the reaction in order to complete the solution of the sodium. Insert a guard tube into the top of the condenser. Allow the sodium ethoxide solution to cool with stirring; when the sodium ethoxide commences to separate out, add 75 g. (71 ml.) of ethyl malonate (dried over anhydrous calcium sulphate) during 1 hour. Towards the end of the addition some solid may separate; it is then necessary to heat on a water bath to dissolve the solid. When all the ethyl malonate has been introduced, heat the mixture on a water bath for 15 minutes, and then allow to cool. When the ethyl sodiomalonate commences to crystallise out, add 156 g. (81 ml.) of dry ethyl iodide over a period of 1 hour. Heat on a water bath for 3 hours to complete the reaction. Rearrange the flask for distillation but keep the stirrer in position; distil off as much as possible of the alcohol on a water bath (it is advisable to wrap the flask in a cloth or towel). Dilute the residue in the flask with water and extract with three 75 ml. portions of ether. Wash the combined ethereal extracts with water, dry with anhydrous calcium chloride or magnesium sulphate, remove the ether on a water bath and distil the residue from a 200 ml. Claisen flask. Collect the ethyl diethylmalonate at 218–222° (mainly 221°); the yield is 84 g.

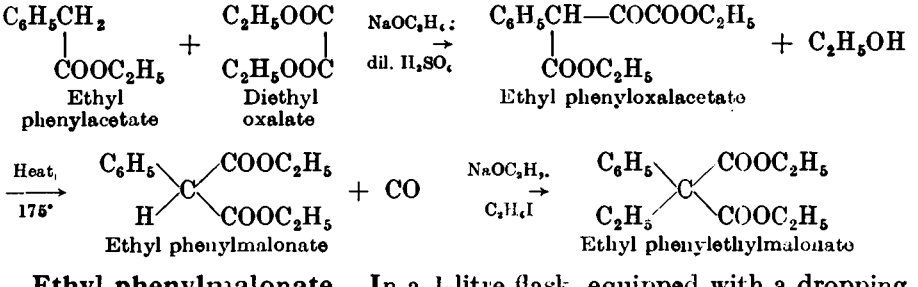
Diethylbarbituric acid. In a dry 250 ml. distilling flask, fitted with a thermometer reaching to within 3–4 cm. of the bottom and a condenser, place 5·1 g. of clean sodium and add 110 g. (140 ml.) of "super-dry" ethyl alcohol (Section **II,47,5**). When all the sodium has reacted, introduce 20 g. of ethyl diethylmalonate and 7·0 g. of dry urea (dried at 60° for 4 hours). Heat the flask in an oil bath and slowly distil off the ethyl alcohol. As soon as the temperature of the *liquid* reaches 110–115°, adjust the flame beneath the bath so that the contents of the flask are maintained at this temperature for at least 4 hours. Allow the flask to cool somewhat, add 100 ml. of water and warm until the solid (veronal-sodium) dissolves. Pour the solution into a beaker, and add a further 100 ml. of water but containing 7·0 ml. of concentrated sulphuric acid; this will liberate the veronal from the sodium derivative. The veronal usually crystallises out; if it does not, add a few more drops of dilute sulphuric acid until the solution is acid to Congo red. Heat the contents of the beaker, with stirring and the addition of more water if necessary, until all the veronal dissolves at the boiling point. Allow the hot solution to cool, filter off the crystals of veronal and dry in the air. The yield is 12 g., m.p. 190°.

IX,8. PHENYLETHYLBARBITURIC ACID (PHENOBARBITONE)

Phenylethylbarbituric acid (also termed luminal and phenobarbitone) may be prepared by condensing ethyl phenylethylmalonate with urea in the presence of sodium methoxide:



The ethyl phenylethylmalonate may be obtained from ethyl phenylacetate by the following series of reactions:



Ethyl phenylmalonate. In a 1-litre flask, equipped with a dropping funnel, mercury-sealed stirrer and reflux condenser,* place 11·5 g. of clean sodium pieces (see Section **III,7**, *Note* 1); add 250 ml. of "super-dry" ethyl alcohol (Section **II,47,5**) and allow the vigorous reaction to

* It is important that the apparatus be dry: calcium chloride or cotton wool guard tubes should be placed in the funnel and condenser respectively.

proceed, cooling only if the reaction appears to be beyond control. When all the sodium has reacted, cool the solution to 60°, and add 73 g. (67 ml.) of pure, freshly distilled, neutral diethyl oxalate (compare Section **III,100**) from the dropping funnel in a rapid stream with vigorous stirring. Wash this down with 5 ml. of absolute ethanol and add immediately 87·5 g. (85 ml.) of pure ethyl phenylacetate (Section **IV,179**). Discontinue stirring, lower the reaction flask from the stirrer and have a 1-litre beaker at hand. Within 4–7 minutes after the ethyl phenylacetate has been added, crystallisation commences; transfer the contents of the flask immediately to the beaker at the first sign of crystallisation. Allow the nearly solid paste of the sodio derivative to cool to room temperature and then stir thoroughly with 400 ml. of dry ether. Collect the solid by suction filtration and wash it repeatedly with dry ether. Transfer the solid to a beaker and liberate the ethyl phenyloxalacetate with ice-cold dilute sulphuric acid (14–15 ml. of concentrated sulphuric acid in 250 ml. of water). Separate the almost colourless oil and extract the aqueous layer with three 50 ml. portions of ether; dry the combined oil and ethereal extracts with anhydrous magnesium sulphate, remove the ether on a steam bath by "flash distillation" (compare Fig. *II, 13,* 4) from a modified Claisen flask with fractionating side arm. Heat the flask under a pressure of about 15 mm. of mercury (water pump) in an oil or Wood's metal bath. Raise the temperature of the bath gradually to 175° and maintain this temperature until the evolution of carbon monoxide is complete (*FUME CUPBOARD!*); if the pressure rises unduly during the heating (owing to a rather rapid evolution of gas), discontinue the heating momentarily. When the reaction is complete (5–6 hours), return the oil which has passed over to the flask, and distil under reduced pressure. Collect the ethyl phenylmalonate at 159–161°/10 mm. (or at 165–166°/15 mm.). The yield is 95 g.

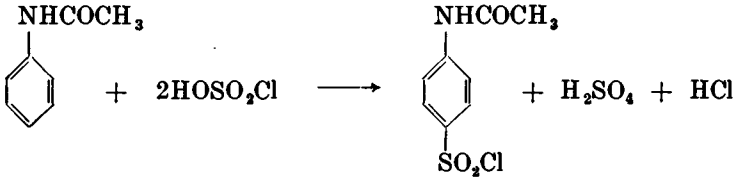
Ethyl phenylethylmalonate. In a dry 500 ml. round-bottomed flask, fitted with a reflux condenser and guard tube, prepare a solution of sodium ethoxide from 7·0 g. of clean sodium and 150 ml. of "super dry" ethyl alcohol in the usual manner; add 1·5 ml. of pure ethyl acetate (dried over anhydrous calcium sulphate) to the solution at 60° and maintain this temperature for 30 minutes. Meanwhile equip a 1 litre three-necked flask with a dropping funnel, a mercury-sealed mechanical stirrer and a double surface reflux condenser: *the apparatus must be perfectly dry* and guard tubes should be inserted in the funnel and condenser respectively. Place a mixture of 74 g. of ethyl phenylmalonate and 60 g. of ethyl iodide in the flask. Heat the apparatus in a bath at 80° and add the sodium ethoxide solution, with stirring, at such a rate that a drop of the reaction mixture when mixed with a drop of phenolphthalein indicator is never more than faintly pink. The addition occupies 2–2·5 hours; continue the stirring for a further 1 hour at 80°. Allow the flask to cool, equip it for distillation under reduced pressure (water pump) and distil off the alcohol. Add 100 ml. of water to the residue in the flask and extract the ester with three 100 ml. portions of benzene. Dry the combined extracts with anhydrous magnesium sulphate, distil off the benzene at atmospheric pressure and the residue under diminished pressure. Collect the ethyl phenylethylmalonate at 159–160°/8 mm. The yield is 72 g.

Phenylethylbarbituric acid. In a 250 ml. round-bottomed flask, fitted with an efficient reflux condenser and guard tube, prepare a solution of sodium methoxide from 4·6 g. of clean sodium and 50 ml. of "super dry" methyl alcohol (Section II,47,*6*). Add 15 g. of urea (previously dried at 60° for 4 hours), and insert a separatory funnel, charged with 26·4 g. of ethyl phenylethylmalonate, into the top of the condenser by means of a grooved cork. Add the ester dropwise, and then reflux the mixture for 6 hours. Remove the excess of methyl alcohol under reduced pressure (do not allow the temperature of the external water bath to rise above 60°), transfer the residue to a small beaker cooled in a freezing mixture and add 100 ml. of ice-water with mechanical stirring: the temperature of the reaction mixture must be kept below 5° since barbiturates are decomposed by concentrated alkali into the salt of the corresponding malonic acid, sodium carbonate and ammonia. Filter and extract the filtrate with two 50 ml. portions of benzene in order to remove esters; acidify the aqueous solution cautiously to Congo red, allow to stand for a few hours, and filter off the crude phenobarbitone at the pump. The yield after drying at 90–100° is 13 g. Recrystallisation from hot water yields reasonably pure phenylethylbarbituric acid, m.p. 171°. A somewhat higher m.p. (175–176°) is obtained if rectified spirit is employed for recrystallisation, but the recovery is considerably less.

IX,9. *p*-AMINOBENZENESULPHONAMIDE (SULPHANILAMIDE)

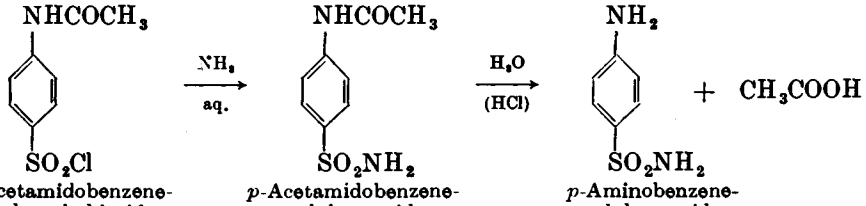
The synthesis of this important compound may be accomplished by the following series of reactions:

(i) Treatment of acetanilide with excess of chlorosulphonic acid affords *p*-acetamidobenzenesulphonyl chloride—a solid, m.p. 149°:



(ii) This is converted by aqueous ammonia into *p*-acetamidobenzenesulphonamide—the pure compound has m.p. 218°.

(iii) By boiling with dilute hydrochloric acid the protecting acetyl group is removed without hydrolysing the sulphonamido group. The liberated sulphonamide passes into solution as the hydrochloride, and the free base (*p*-aminobenzenesulphonamide) is obtained by neutralisation with sodium bicarbonate or aqueous ammonia.



p-Acetamidobenzenesulphonyl chloride — *p*-Acetamidobenzenesulphonamide — *p*-Aminobenzenesulphonamide

p-Acetamidobenzenesulphonyl chloride. Equip a 500 ml. bolt-head flask with a two-holed cork carrying a dropping funnel and a reflux condenser : attach the top of the latter to a device for the absorption of hydrogen chloride (*e.g.*, Fig. *II*, *8*, 1, *c*). Place 20 g. of dry acetanilide in the flask and 50 ml. (90 g.) of a good grade of chlorosulphonic acid {*CAUTION ;* (1)} in the dropping funnel and insert a calcium chloride guard tube into the latter. Add the chlorosulphonic acid in small portions and shake the flask from time to time to ensure thorough mixing (2). When the addition has been made, heat the reaction mixture on a water bath for 1 hour in order to complete the reaction. Allow to cool and pour the oily mixture in a thin stream with stirring into 300 g. of crushed ice (or ice water) contained in a 1 litre beaker. Carry out this operation carefully in the fume cupboard since the excess of chlorosulphonic acid reacts vigorously with the water. Rinse the flask with a little ice water and add the rinsings to the contents of the beaker. Break up any lumps of solid material and stir the mixture for several minutes in order to obtain an even suspension of the granular white solid. Filter off the *p*-acetamidobenzenesulphonyl chloride at the pump and wash it with a little cold water ; press and drain well. *Use the crude product* (3) *immediately in the next stage.*

p-Acetamidobenzenesulphonamide. Transfer the crude *p*-acetamidobenzenesulphonyl chloride to the rinsed reaction flask, and add a mixture of 70 ml. of concentrated ammonia solution (sp. gr. 0·88) and 70 ml. of water. Mix the contents of the flask thoroughly, and heat the mixture with occasional swirling (*FUME CUPBOARD*) to just below the boiling point for about 15 minutes. The sulphonyl chloride will be converted into a pasty suspension of the corresponding sulphonamide. Cool the suspension in ice, and then add dilute sulphuric acid until the mixture is just acid to Congo red paper. Collect the product on a Buchner funnel, wash with a little cold water, and drain as completely as possible. It is desirable, but not essential, to dry the crude *p*-acetamidobenzenesulphonamide at 100° : the yield is about 18 g. The material is sufficiently pure (4) for the next stage.

p-Aminobenzenesulphonamide. Transfer the crude *p*-acetamidobenzenesulphonamide to a 500 ml. flask, add 10 ml. of concentrated hydrochloric acid and 30 ml. of water. Boil the mixture gently under reflux for 30–45 minutes. The solution, when cooled to room temperature should deposit no solid amide ; if a solid separates, heat for a further short period. Treat the cooled solution with 2 g. of decolourising carbon, heat the mixture to boiling, and filter with suction through a hardened filter paper. Place the filtrate (a solution of sulphanilamide hydrochloride) in a litre beaker and cautiously add 16 g. of solid sodium bicarbonate in portions with stirring. After the evolution of gas has subsided, test the suspension with litmus paper and if it is still acid, add more sodium bicarbonate until neutral. Cool in ice, filter off the sulphanilamide with suction, and dry. The yield is 15 g., m.p. 161–163°. A pure product, m.p. 163–164°, may be obtained by recrystallisation from water or from alcohol.

Notes.

(1) *Chlorosulphonic acid* must be handled with great care : it is very corrosive to the skin and to clothing, and reacts with water with great violence. If the

specimen is impure or discoloured, it should be redistilled in an all-glass apparatus and the fraction, b.p. 148–150°, collected : due precautions should be taken to protect the distillate from moisture.

(2) The reaction may be more easily controlled and the chlorosulphonic acid added all at once if the acetanilide is employed in the form of a hard cake. The latter is prepared by melting the acetanilide in the flask over a free flame and causing the compound to solidify over the lower part of the flask by swirling the liquid. If the reaction becomes too vigorous under these conditions, cool the flask momentarily by immersion in an ice bath.

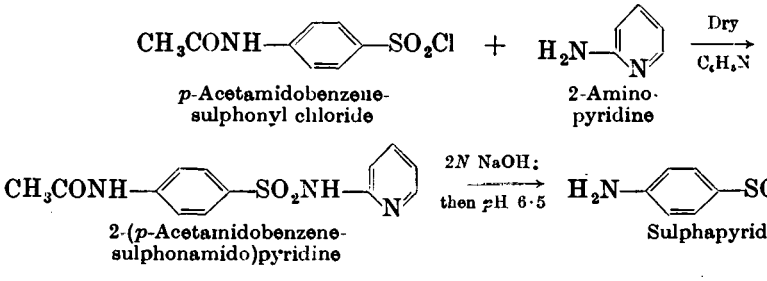
(3) The crude sulphonyl chloride, even if dry, cannot be kept without considerable decomposition. It may be purified by dissolving it in a mixture of equal volumes of benzene and acetone, separating the water, and allowing the solvent to evaporate until crystallisation occurs : the recrystallised substance may be preserved for long periods.

An alternative method of purification consists in dissolving the crude sulphonyl chloride in the minimum volume of boiling chloroform, transferring rapidly to a warm separatory funnel, and separating the lower chloroform layer ; upon cooling the chloroform solution, the crystalline sulphonyl chloride separates, and is collected by filtration with suction. A further quantity is obtained by concentrating the mother liquor.

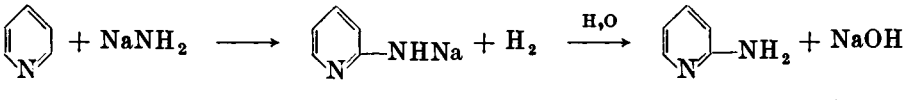
(4) A small portion may be recrystallised from water, with the addition of a little decolourising carbon if necessary. The pure compound has m.p. 218°.

IX,10. 2-(*p*-AMINOBENZENESULPHONAMIDO)PYRIDINE (SULPHAPYRIDINE)

The important drug sulphapyridine (or M. & B. 693 or 2-sulphanilylaminopyridine) may be readily synthesised from 2-aminopyridine and *p*-acetamidobenzenesulphonyl chloride (Section **IX,9**) as follows :



The 2-aminopyridine is prepared by adding pure, dry pyridine to sodamide in dry toluene at 110° :



It has been stated (Tschitschibabin, 1914) that the addition of a little dry ethyl acetate helps the reaction.

2-Aminopyridine. In a 1 litre three-necked flask, equipped with a sealed mechanical stirrer, reflux condenser, thermometer and inlet tube for nitrogen, place 300 ml. of dry toluene (1) and 75 g. of fine granular sodamide (2) ; bubble a steady stream of nitrogen through the toluene. Stir the mixture vigorously and heat the flask in an oil bath until the internal temperature is 110° (the bath temperature required is approximately 130°). Add 100 g. of pure dry pyridine (compare Section **II,47,22**)

dropwise through the condenser over a period of 4 hours : maintain the very efficient stirring and the stream of nitrogen. After 1 hour the reaction mixture becomes black in colour, and after 3 hours becomes viscous, and bubbling and slight frothing occur, due to liberation of hydrogen. When all the pyridine has been introduced, continue the heating for a further 5 hours whilst maintaining the internal temperature at 110°. Towards the end of the reaction, stirring may become difficult owing to the separation of a solid or viscous cake. Allow the reaction mixture to cool (without the stream of nitrogen and without stirring); then introduce 175 ml. of water very slowly through the condenser over a period of 2 hours whilst continuing the passage of the stream of nitrogen. During the addition the temperature rises to about 50° ; resume the stirring as soon as possible. Transfer the contents of the flask to a separatory funnel, separate the lower aqueous solution and extract it with two 150 ml. portions of toluene. Dry the combined main toluene layer and toluene extracts over anhydrous potassium carbonate for 2 hours ; filter and remove the toluene by distillation. Distil the syrupy residue from an oil bath under diminished pressure through an air condenser : adjust the bath temperature to 120–130°. Collect the 2-aminopyridine at 95°/10 mm. ; this solidifies on cooling to a colourless solid, m.p. 55° (3). The yield is about 80 g.

Sulphapyridine. Dissolve 18·8 g. of 2-aminopyridine in 40 ml. of dry pyridine (Section **II,47,*22***) in a 250 ml. flask and add 48·0 g. of *p*-acetamidobenzenesulphonyl chloride (4) ; the temperature rises to about 70°. Cool, add excess of water, filter the precipitated 2-(*p*-acetamidobenzenesulphonamido)pyridine (≡ acetyl-sulphapyridine) at the pump and recrystallise it from 50 per cent. acetic acid. The yield of pure product, m.p. 224°, is 46·5 g.

Hydrolyse the acetyl-sulphapyridine by boiling it with 10 parts of 2*N* sodium hydroxide for 1 hour, and allow to cool. Precipitate the base by the addition of 50 per cent. acetic acid until the mixture is just acid to litmus (*p*H about 6·5) ; avoid a large excess of acid. Filter off the crude sulphapyridine, wash well with water, and dry at 90° to constant weight (about 12 hours ; any acetate formed will be decomposed). The yield is 35 g. Recrystallise from 90 per cent. acetone (5) ; the recovery of the pure compound, m.p. 190–191°, is about 80 per cent.

Notes.

(1) Technically pure toluene can be conveniently dried by distilling 350 ml. from a litre flask and rejecting the first 50 ml.

(2) It is important to use recently-prepared pure sodamide, which must be of fine granular form. Old material of irregular lumpy form, even if ground gives poor results, and should not be employed. The sodamide may be prepared as detailed in Section II,50,*δ*. A satisfactory grade is marketed by May and Baker Ltd.

(3) The residue in the flask is said to contain 4-amino- and 2 : 6-diamino-pyridine, γγ-dipyridyl and αα′-dipyridylamine in varying amounts.

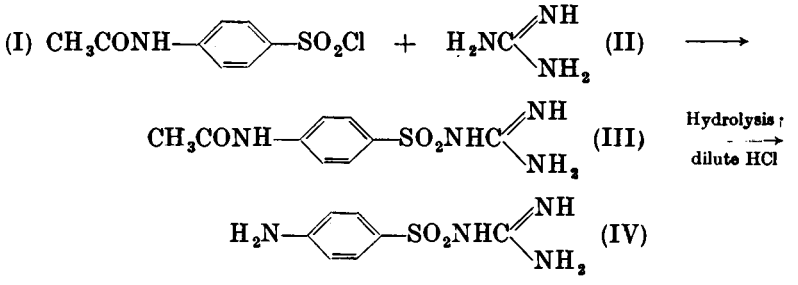
(4) The *p*-acetamidobenzenesulphonyl chloride (Section IX,9) must be pure : under no circumstances should it contain more than 1–2 per cent. of the corresponding sulphonic acid. This may be ensured by lixiviating the sulphonyl chloride with pure anhydrous acetone and filtering the solution from the acid.

(5) An alternative method of purification, well adapted for large scale practice, is as follows. Dissolve the crude sulphapyridine in 1·05 mols of 30 per cent. *w*/*v* sodium hydroxide, salt out the sodium derivative with excess of sodium chloride,

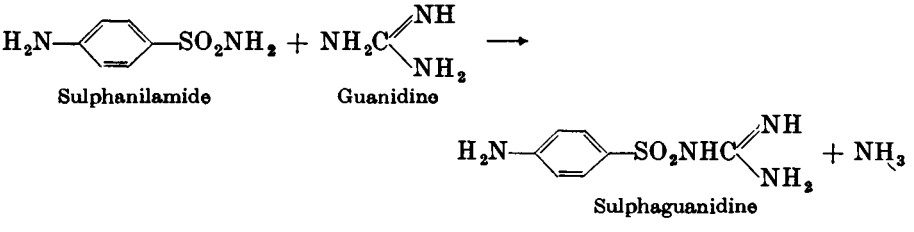
cool and filter. Dissolve in the minimum volume of hot water, treat with about 0·5 per cent. by weight of decolourising carbon, filter, precipitate the base with 50 per cent. acetic acid until just acid to litmus (avoid an excess of acid), filter off the sulphapyridine at the pump, wash thoroughly with hot water, and dry to constant weight at 90° (about 12 hours). Alternatively, the cold solution of the sodium salt may be just acidified with dilute hydrochloric acid with very vigorous stirring : the presence of a local excess of acid must be avoided since sulphapyridine is hydrolysed by mineral acids to sulphanilic acid and 2-aminopyridine.

IX,11. SULPHAGUANIDINE

p-Aminobenzenesulphonylguanidine (sulphanilylguanidine or sulphaguanidine) is an important chemotherapeutic reagent and its structure (IV) follows from its preparation by the condensation of *p*-acetamidobenzenesulphonyl chloride (I) with guanidine (II), followed by the hydrolysis of the *p*-acetamidobenzenesulphonylguanidine (III) at the acetamido group :



It is conveniently prepared in the laboratory by the interaction of sulphanilamide and guanidine (from guanidine nitrate and sodium methoxide solution) ; the resulting guanidine salt of sulphanilamide decomposes upon heating at 150–160° into sulphaguanidine and ammonia :

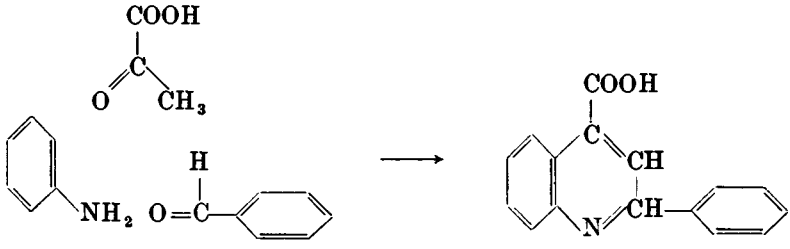


In a 500 ml. three-necked flask, equipped with a thermometer, mechanical stirrer and efficient reflux condenser, dissolve 16 g. of sodium hydroxide pellets in 95 ml. of hot methyl alcohol. Add 49 g. of guanidine nitrate, stir the mixture at 50–65° for 15 minutes, and then cool to about 20°. Filter off the separated sodium nitrate and wash with two 12 ml. portions of methyl alcohol. Return the combined filtrates to the clean reaction flask, add 69 g. of sulphanilamide (Section IX,9) and stir at 50–55° for 15 minutes. Detach the reflux condenser and, with the aid of a still-head (" knee-tube "), arrange the apparatus for distillation from an oil bath with stirring ; about 100 ml. of methyl alcohol are recovered. Add 12 g. of pure *cyclo*hexanol. Raise the temperature of the oil bath to 180–190° and continue the distillation. Reaction commences with the evolution of ammonia when the internal temperature reaches 145°. Maintain the

internal temperature at 150–160° for 2 hours. Pour the warm reaction mixture into 450 ml. of 1·5*N* hydrochloric acid and stir until all the solid passes into solution ; precipitate the sulphanilylguanidine by the gradual addition, with stirring, of sodium hydroxide solution until alkaline. After cooling, filter the crude sulphaguanidine at the pump, recrystallise it from 400 ml. of hot water, and dry. The yield of sulphanilylguanidine, m.p. 189–190°, is 54 g.

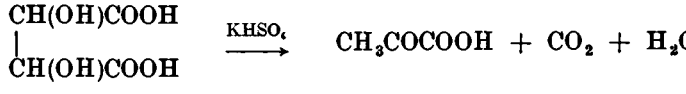
IX,12. 2-PHENYLQUINOLINE-4-CARBOXYLIC ACID (ATOPHAN)

Atophan (or cinchophen) may be prepared by condensing equimolecular proportions of benzaldehyde, aniline and pyruvic acid in alcoholic solution :

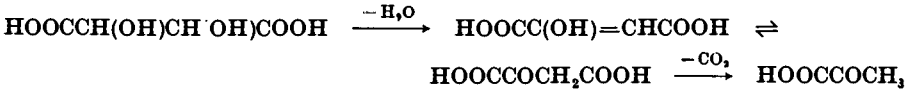


This is an example of the **Doebner synthesis of quinoline-4-carboxylic acids** (cinchoninic acids) ; the reaction consists in the condensation of an aromatic amine with pyruvic acid and an aldehyde. The *mechanism* is probably similar to that given for the Doebner-Miller synthesis of quinaldine (Section V,2), involving the intermediate formation of a dihydroquinoline derivative, which is subsequently dehydrogenated by the Schiff's base derived from the aromatic amine and aldehyde.

Pyruvic acid is conveniently prepared by the distillation of tartaric acid with a dehydrating agent, such as potassium bisulphate :



The reaction probably proceeds through oxalacetic acid as an intermediate :



Pyruvic acid. Grind together in a glass mortar 200 g. of powdered tartaric acid and 300 g. of freshly *fused* potassium bisulphate to form an intimate mixture. Place the mixture in a 1500 ml. round-bottomed flask ; connect the latter with a Liebig's condenser which is filled with water, but does not have any water flowing through it. Heat the flask in an oil bath maintained at 210–220° until liquid no longer distils over. If the foaming is considerable and there is danger of the mixture frothing over, heat the upper part of the flask with a free flame. Fractionate the distillate under reduced pressure and collect the pyruvic acid at 75–80°/25 mm. The yield is 60 g.

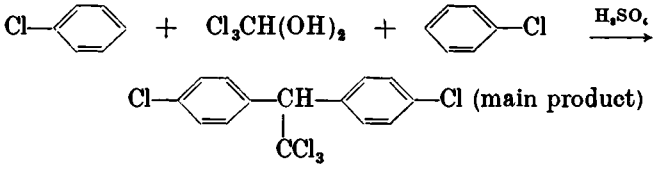
Atophan. In a 1 litre round-bottomed flask, equipped with a reflux condenser, place 25 g. (24 ml.) of purified benzaldehyde (Section IV,115), 22 g. of freshly-distilled pyruvic acid and 200 ml. of absolute ethyl alcohol. Heat the mixture to the boiling point on a water bath and add slowly, with frequent shaking, a solution of 23 g. (22·5 ml.) of pure aniline in 100 ml. of absolute ethyl alcohol. The addition usually occupies about 1 hour. Reflux the mixture on a water bath for 3 hours, and allow to stand overnight. Filter off the crude atophan (1) at the pump and wash the crystals with a little ether. Recrystallise from ethyl alcohol (about 20 ml. per gram). The yield of pure 2-phenylquinoline-4-carboxylic acid, m.p. 210°, is 30 g.

Note.

(1) If the atophan does not crystallise—this is rarely the case unless pyruvic acid which has been standing for some time is employed—pour the reaction mixture into a solution of 25 g. of potassium hydroxide in 1 litre of water, and extract the resulting solution two or three times with ether. Place the ether extracts in the *ETHER RESIDUES* bottle. Treat the aqueous layer with 70 ml. of glacial acetic acid with vigorous stirring. Allow to stand for several hours and collect the crude atophan by filtration with suction.

IX,13. 2 : 2-*bis*(p-CHLOROPHENYL)-1 : 1 : 1-TRICHLOROETHANE (D.D.T.)

The name D.D.T. is derived from *di*chloro*di*phenyl*tri*chloroethane : this is a misnomer since the name represents 27 different compounds. As commonly employed it refers to 2 : 2-*bis*(*p*-chlorophenyl)-1 : 1 : 1-trichloroethane. It is conveniently prepared by the condensation of chlorobenzene and chloral hydrate in the presence of concentrated sulphuric acid :



Method 1

In a 1 litre three-necked flask, equipped with a thermometer, glycerine-sealed mechanical stirrer (compare Fig. *II*, 7, 10) and calcium chloride (or cotton wool) guard tube, introduce successively 700 g. (380 ml.) of concentrated sulphuric acid, 100 g. (53 ml.) of oleum (20 per cent. SO_3), 90 g. (81·5 ml.) of chlorobenzene and 68 g. of chloral hydrate. Stir the mixture rapidly enough to keep the materials well mixed for 1 hour : during this period the temperature rises to about 50° and some granular D.D.T. separates. Stir the mixture for a further 1 hour in order to complete the reaction. Pour the reaction mixture with stirring into 3 litres of a 2 : 1 mixture of ice and water. Filter the precipitated somewhat sticky solid at the pump and wash it well with cold water. Remove the occluded acid by transferring the crude product to a beaker containing 1 litre of boiling water and stirring well : this causes the D.D.T. to melt. Decant the aqueous layer, and repeat the washing with two further

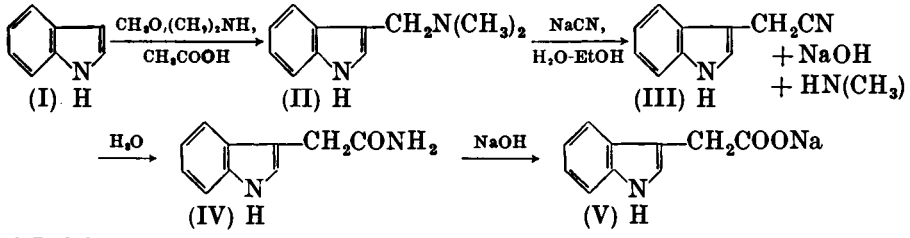
1-litre portions of water. To the third washing add a little sodium bicarbonate and stir until the mixture is neutral to litmus. Filter at the pump, and dry upon filter paper in the air or in an air oven at 50–60°. The yield of crude product, m.p. *ca.* 90°, is 90 g.; the low m.p. is due to the presence of isomers of the *para* compound. The pure substance, m.p. 108°, may be obtained with 50–60 per cent. recovery by recrystallisation from *n*-propyl alcohol (5 ml. per gram).

Method 2

Place 17 g. of chloral hydrate crystals and 25·5 g. (23 ml.) of chlorobenzene in a 500 ml. Pyrex glass-stoppered reagent bottle and warm on a water bath, with occasional shaking, until all the crystals have dissolved. Cool to room temperature and slowly add 180 ml. of concentrated sulphuric acid. Secure the glass stopper (rubber tubing over stopper held tightly by copper wire round neck of bottle) and shake mechanically for 1 to 1·5 hours, and then allow to stand for 15 minutes. Pour the contents of the reagent bottle slowly and with constant stirring into 700 ml. of water contained in a litre beaker. When cold, filter the crude D.D.T. through a sintered glass funnel and wash several times with water. (A further 1·5 g. of impure D.D.T. may be obtained by diluting the filtrate considerably.) Transfer the solid to a beaker and stir it for 5–10 minutes with 50 ml. of 2 per cent. sodium carbonate solution or 4 per cent. sodium bicarbonate solution. Filter and wash with distilled water until the filtrate is neutral to litmus; suck the solid as dry as possible. Transfer the residue to a small mortar, add 100 ml. of ethyl alcohol and triturate with a pestle for 5–10 minutes. Filter through a dry Buchner funnel, wash twice with 25 ml. portions of ethanol, and continue the suction until most of the solvent has been removed. Dry the residue at 70° in a steam oven (or on a water bath). The yield of D.D.T., m.p. 107°, is 15 g. The perfectly pure compound, m.p. 108°, may be obtained by recrystallisation from *n*-propyl alcohol (5 ml. per gram).

IX,14 3-INDOLEACETIC ACID

Indole (I) condenses with formaldehyde and dimethylamine in the presence of acetic acid (Mannich reaction; see Section VI,20) largely in the 3-position to give 3-dimethylaminomethylindole or **gramine** (II). The latter reacts in hot aqueous ethanol with sodium cyanide to give the nitrile (III); upon boiling the reaction mixture, the nitrile undergoes hydrolysis to yield 3-indoleacetamide (IV), part of which is further hydrolysed to 3-indoleacetic acid (V, as sodium salt). The product is a readily separable mixture of 20 per cent. of (IV) and 80 per cent. of (V).



3-Indoleacetic acid is a plant growth hormone.

Dimethylaminomethylindole (gramine). Cool 42·5 ml. of aqueous methylamine solution (5·2*N* ; *ca.* 25 per cent. w/v) contained in an 100 ml. flask in an ice bath, add 30 g. of cold acetic acid, followed by 17·2 g. of cold, 37 per cent. aqueous formaldehyde solution. Pour the solution on to 23·4 g. of indole ; use 10 ml. of water to rinse out the flask. Allow the mixture to warm up to room temperature, with occasional shaking as the indole dissolves. Keep the solution at 30–40° overnight and then pour it, with vigorous stirring, into a solution of 40 g. of potassium hydroxide in 300 ml. of water ; crystals separate. Cool in an ice bath for 2 hours, collect the crystalline solid by suction filtration, wash with three 50 ml. portions of cold water, and dry to constant weight at 50°. The yield of gramine is 34 g. ; this is quite suitable for conversion into 3-indoleacetic acid. The pure compound may be obtained by recrystallisation from acetone-hexane ; m.p. 133–134°.

3-Indoleacetic acid In a 1-litre flask, fitted with a reflux condenser, place a solution of 35·2 g. of sodium cyanide in 70 ml. of water, then add 25 g. of gramine and 280 ml. of 95 per cent. ethanol. Reflux the mixture (steam bath) for 80 hours. Dilute the cooled reaction mixture with 35 ml. of water, shake with a little activated charcoal (*e.g.*, Norit), filter and concentrate to about 350 ml. under reduced pressure (water pump) in order to remove most of the alcohol. Cool to about 5°, filter off the solid and wash it with a little cold water ; keep the filtrate (*A*). Recrystallise the solid from alcohol-ether to give 5·0 g. of 3-indoleacetamide, m.p. 150–151°.

Cool the filtrate (*A*) to 5–10° and add concentrated hydrochloric acid dropwise and with vigorous stirring (*FUME CUPBOARD :* hydrogen cyanide is evolved) to a *p*H of 1–2 (about 50 ml.) ; a crude, slightly pink 3-indoleacetic acid is precipitated. The yield of crude acid, m.p. 159–161°, is 20 g. Recrystallise from ethylene dichloride containing a small amount of ethanol ; 17·5 g. of pure 3-indoleacetic acid, m.p. 167–168°, are obtained.

Hydrolyse the 5 g. of 3-indoleacetamide by heating it under reflux for 4 hours with a solution of 6 g. of sodium hydroxide in 40 ml. of water. Cool to 5°, treat with decolourising carbon (if necessary), filter, render strongly acid with concentrated hydrochloric acid (*p*H about 1·5). Collect the acid which precipitates and dry it at 70° ; the crude acid weighs 4·5 g. Purify as above.