Some Chlorinated Hydroxyphenoxyacetic Acids.

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The synthesis of 4-chloro-2-hydroxyphenoxyacetic acid, a bacterial metabolite of 4-chlorophenoxyacetic acid, is described; the isomeric 5-chloro-2-hydroxyphenoxyacetic acid has been made from 4-chlorocatechol and by unambiguous synthesis. 3 : 5-Dichloro-2- and 2 : 4-dichloro-6-hydroxyphenoxyacetic acid have been prepared by unambiguous routes. The latter is identical with the product prepared by Cavill and Ford (*J.*, 1954, 565) from 3 : 5-dichlorocatechol. A bacterial metabolite of 2 : 4-dichlorophenoxyacetic acid is not identical with any of the above acids or with 2-chloro-4-hydroxyphenoxyacetic acid, the synthesis of which is also described.

When this study was commenced, current theories on the fate of 2 : 4-dichlorophenoxyacetic acid in the plant and in soil substrates favoured *ortho*-hydroxylation to 2 : 4-dichloro-6-hydroxyphenoxyacetic acid as the initial step. Simultaneously we learned (personal communication) that Professor W. C. Evans had isolated from cultures of bacteria grown on a medium containing 4-chlorophenoxyacetic acid a hydroxy-acid which he believed to be 4-chloro-2-hydroxyphenoxyacetic acid. The preparation of these two possible metabolites for phytotoxicity studies seemed of interest.

2-Amino-4-chlorophenoxyacetic acid which cyclised to the lactam at low pH values was readily obtained by nitration of 4-chlorophenoxyacetic acid and reduction of the product. Attempts to replace the amino-group by hydroxyl in the amino-acid and its derived dimethylamide failed. An unsuccessful attempt was also made to oxidise 2-acetyl-4-chlorophenoxyacetic acid to the required 4-chloro-2-hydroxyphenoxyacetic acid.

Reaction of the monosodium salt of 4-chlorocatechol with ethyl chloroacetate, and subsequent hydrolysis of the product, gave a mixture of acids, which on repeated crystallisation gave 5-chloro-2-hydroxyphenoxyacetic acid. The identity of this acid was established by comparison of its methyl ether with the phenoxyacetic acid from 4-chloroguaiacol (Jona and Pozzi, *Gazzetta*, 1911, **41**, I, 730; cf. Ballio and Almirante, *Ann. Chim. appl.*, 1951, **41**, 421). 5-Chloro-2-hydroxy- and 5-chloro-2-methoxy-phenoxyacetic acid were also prepared from the corresponding 5-nitro-compounds by conventional methods, 4-nitroguaiacol and chloroacetic acid giving either 2-hydroxy- or 2-methoxy-5-nitrophenoxyacetic acid depending on the concentration of alkali employed in the condensation. The required 4-chloro-2-hydroxyphenoxyacetic acid was finally obtained by demethylation of the methoxyacetic acid derived from 5-chloroguaiacol (*idem, loc. cit.*). Comparison of this product with the metabolite isolated from cultures of bacteria grown on a medium containing 4-chlorophenoxyacetic acid as the sole source of carbon, showed that the two were identical (Evans and Smith, *Biochem. J.*, 1954, **57**, xxx).

In the preparation of 2 : 4-dichloro-6-hydroxyphenoxyacetic acid we were anticipated by Cavill and Ford (*J.*, 1954, 565) who simply condensed 3 : 5-dichlorocatechol with butyl chloroacetate and hydrolysed the product. In view of our own results with 4-chlorocatechol and ethyl chloroacetate, the success of this method was surprising and, since the diagnostic evidence on which the constitution of the product was based appeared inconclusive, it was decided to prepare samples of 2 : 4-dichloro-6- and 3 : 5-dichloro-2-hydroxyphenoxyacetic acid by unambiguous routes.

Methylation of the *N*-acetyl derivative of the amine obtained by reduction of 2 : 4-dichloro-6-nitrophenol readily gave 2-acetamido-4 : 6-dichloroanisole, which was converted into 4 : 6-dichloroguaiacol and thence into 3 : 5-dichloro-2-hydroxyphenoxyacetic acid by methods similar to those already described. The acid and its methyl ether differed in physical properties from those reported for 2 : 4-dichloro-6-hydroxyphenoxyacetic by Cavill and Ford (*loc. cit.*) and from those of an acid, apparently identical with that prepared by these authors, obtained by condensation of 3 : 5-dichlorocatechol with ethyl chloroacetate.

Oxidation of 2 : 4-dichloroaniline (cf. Boyland, Manson, and Sims, *J.*, 1953, 3623) by potassium persulphate, followed by selective acetylation of the product, gave some of the expected 2-acetamido-3 : 5-dichlorophenol but the yield was so poor that this route was abandoned as a source of 2-amino-3 : 5-dichloroanisole, a precursor of 3 : 5-dichloroguaiacol. It is of interest that methylation of the acetamidophenol led to attack at both the amido- and the hydroxyl group, giving 2-*N*-methylacetamido-3 : 5-dichloroanisole. Decarboxylation of 5-chlorovanillic acid gave 3-chloroguaiacol in low yield but attempts to monochlorinate this material to the required 3 : 5-dichloroguaiacol failed. An alternative approach from 5-chlorovanillic acid was successful. The carboxyl group was replaced by an amino-group by use of the Schmidt reaction, and replacement of the amino-group by chlorine in the normal way gave the required product. 3 : 5-Dichloroguaiacol was also prepared from 2 : 4 : 6-trichloronitrobenzene by way of 3 : 5-dichloro-2-nitroanisole and 2-amino-3 : 5-dichloroanisole. When the *N*-acetyl derivative of this amine was treated with methyl iodide in the presence of potassium carbonate, 2-*N*-methylacetamido-3 : 5-dichloroanisole identical with that obtained previously was formed.

3 : 5-Dichloroguaiacol was converted into 2 : 4-dichloro-6-hydroxyphenoxyacetic acid by the usual sequence of reactions, and the identity of the acid and its methyl ether with the condensation product of 3 : 5-dichlorocatechol and chloroacetic acid and the derived methyl ether confirmed the structures assigned to these products by Cavill and Ford. We have been informed (Professor W. C. Evans, personal communication) that neither 2 : 4-dichloro-6- nor 4-chloro-2-hydroxyphenoxyacetic acid is identical with a compound, believed to be a hydroxy-acid, produced by bacteria growing on a medium containing 2 : 4-dichlorophenoxyacetic acid.

2-Chloro-4-hydroxyphenoxyacetic acid has also been synthesised for comparison with this unknown hydroxy-acid. In a direct approach, 2-chlorophenoxyacetic acid was converted by nitration, esterification, and reduction into methyl 4-amino-2-chlorophenoxyacetate (the orientation of which was checked by replacement of the amino-group with chlorine, followed by hydrolysis). Replacement of the amino- by a hydroxyl group and

subsequent hydrolysis gave 2-chloro-4-hydroxyphenoxyacetic acid identical with the product formed by demethylation of the phenoxyacetic acid from 2-chloro-4-methoxyphenol. This acid also differed in chromatographic behaviour from the 2 : 4-dichlorophenoxyacetic acid metabolite (Professor W. C. Evans, personal communication).

Experimental

4-Chloro-2-nitrophenoxyacetic Acid.—4-Chlorophenoxyacetic acid (10 g.) was heated at 90° for 2 hr. with concentrated nitric acid (100 ml.). The *nitro-acid* separated on cooling in pale yellow needles (7·0 g.), m. p. 170—175°, and recrystallised from aqueous methanol as needles, m. p. 173—175° (Found : C, 42·2; H, 2·4. $C_8H_6O_5NCl$ requires C, 41·6; H, 2·6%).

Reduction of 4-Chloro-2-nitrophenoxyacetic Acid.—The nitro-acid (1·0 g.) was dissolved in 2N-sodium carbonate (10 ml.) and water (10 ml.), and treated at 90° with sodium hyposulphite (dithionite) (2·5 g.) during 10 min. The solution was cooled to 0° and neutralised. No product separated during 1 hr. but on acidification to pH 4 white needles, m. p. 215—218° (0·15 g.), slowly separated. The filtrate was boiled with 32% hydrochloric acid (10 ml.), and more of the same substance (0·52 g.) rapidly separated. This *6-chloro-3 : 4-dihydro-3-oxobenzoxazine* crystallised from ethanol as white needles, m. p. 217—218° (Found : C, 52·9; H, 3·5. $C_8H_6O_2NCl$ requires C, 52·3; H, 3·3%). The lactam (0·6 g.) dissolved in boiling 2N-sodium hydroxide (2 ml.) but was reprecipitated by water (24 ml.).

2-Amino-4-chlorophenoxy-NN-dimethylacetamide.—4-Chloro-2-nitrophenoxyacetic acid (5·0 g.) was boiled with benzene (50 ml.) and thionyl chloride (8·0 ml.) for 8 hr. Benzene and excess of thionyl chloride were evaporated under reduced pressure, and a 20% solution of dimethylamine (4·0 g.) in benzene was added to a solution of the residue in benzene (20 ml.). A yellow precipitate began to separate after 1 hr. After being kept overnight, the mixture was concentrated to 15 ml., cooled, and filtered, and the filtrate was further concentrated to 5 ml. The crude *nitro-amide* (4·7 g.), m. p. 84°, was twice recrystallised from methanol, separating as pale yellow needles, m. p. 100—101° (Found : C, 47·0; H, 4·1. $C_{10}H_{11}O_4N_2Cl$ requires C, 46·4; H, 4·3%). The nitro-amide (3·9 g.) was added in portions during 10 min. to a stirred suspension of iron (9·4 g.) in ethanol (27 ml.), water (47 ml.), and acetic acid (1·9 ml.) at 80°. After 1 hour's heating at 90° the mixture was diluted with hot ethanol (200 ml.) and filtered. The filtrate was concentrated to 30 ml., again filtered at 70° to remove traces of tar, and allowed to cool. The *amino-amide* separated as off-white needles (2·0 g.). Recrystallisation from benzene (5·0 ml.) gave pale buff prisms (1·3 g.), m. p. 117—121°. Concentration of the alcohol and benzene liquors gave less pure product (0·8 g.), m. p. 116—117°. An analytical specimen separated from ethanol as pale cream needles, m. p. 121° (Found : C, 52·4; H, 5·7. $C_{10}H_{13}O_2N_2Cl$ requires C, 52·5; H, 5·7%).

2-Acetyl-4-chlorophenoxyacetic Acid.—5-Chloro-2-hydroxyacetophenone (Auwers and Wittig, *Ber.*, 1924, **57**, 1270) (2·8 g.) was boiled with sodium hydroxide (3·2 g.) and monochloracetic acid (4·7 g.) in water (30 ml.) for 4 hr., with addition of fresh sodium hydroxide (0·3 g.) whenever oil separated. On cooling and acidification, *2-acetyl-4-chlorophenoxyacetic acid* (2·4 g.) was obtained. Recrystallisation from toluene (100 ml.) gave greyish plates (1·8 g.), m. p. 175—178°. An analytical sample was recrystallised from aqueous methanol as greyish-white needles, m. p. 177—178° (Found : C, 52·5; H, 3·9. $C_{10}H_9O_4Cl$ requires C, 52·5; H, 3·9%).

Reaction of 4-Chlorocatechol and Ethyl Chloroacetate.—4-Chlorocatechol (Frejka, Šefránek, and Zika, *Coll. Czech. Chem. Comm.*, 1937, **9**, 238) (14·8 g.) was added to a solution of sodium (2·8 g.) in dry ethanol (60 ml.). To the stirred boiling mixture, ethyl chloroacetate (3·7 g.) in ethanol (40 ml.) was added during 15 min. After boiling for a further 15 min., the solution was kept overnight at room temperature, then poured into water (600 ml.). The oil was extracted with benzene and washed repeatedly with water. The benzene was removed and the product redissolved in ether and shaken with 2N-sodium hydroxide (60 ml.). The mixture became warm and, on acidification of the alkaline layer, impure *5-chloro-2-hydroxyphenoxyacetic acid* (6·4 g.) separated. The crude acid was dissolved in boiling water (75 ml.), then cooled to 40°, and the purified acid (3·0 g.) recovered by filtration. An analytical sample was twice recrystallised from water, forming long, shining colourless needles, m. p. 157°. These were evidently hydrated, losing crystal form on drying at 100° (Found : C, 47·7; H, 3·4; Cl, 17·2. $C_8H_7O_4Cl$ requires C, 47·4; H, 3·5; Cl, 17·5%). The compound gave a blue colour with either aqueous or alcoholic ferric chloride. The acid (0·4 g.) formed a *methyl ether* (0·3 g.), m. p. 137—138°, on treatment

with methyl sulphate and hot 20% aqueous sodium hydroxide. Recrystallisation from aqueous methanol gave pale cream needles, m. p. 143—145° (Found: C, 50·5; H, 4·2. $C_9H_9O_4Cl$ requires C, 49·9; H, 4·2%).

4-Chloroguaiacol.—4-Nitroguaiacol (Paul, *Ber.*, 1906, **39**, 2773) (3·0 g.) in methanol was reduced with hydrogen at room temperature and atmospheric pressure over palladium–charcoal. The reduced compound was filtered into a flask containing excess of methanolic hydrogen chloride. Evaporation of solvent gave 4-aminoguaiacol hydrochloride, which was dissolved in warm 32% hydrochloric acid (30 ml.) and water (10 ml.). The solution was rapidly cooled to 0°, and the resultant slurry diazotised with a solution of sodium nitrite (1·4 g.) in water (5·0 ml.). After destruction of the excess of nitrous acid with urea, a solution of cuprous chloride (from cupric sulphate pentahydrate, 16·6 g.) in 32% hydrochloric acid (30 ml.) was added. After 2 hr. at room temperature and 1 hr. at 90°, the mixture was steam-distilled and 4-chloroguaiacol extracted from the distillate into ether. Evaporation of the dried extract gave a brown oil (1·6 g.) from which the crystalline compound (1·0 g.), m. p. 36—37°, separated at 20°.

5-Chloro-2-methoxyphenoxyacetic Acid.—4-Chloroguaiacol (0·2 g.), chloroacetic acid (0·7 g.), sodium hydroxide (0·5 g.), and water (3·0 ml.) were mixed and heated at 95° for 2 hr. The hot solution was poured into 32% hydrochloric acid (2·0 ml.). An oil (0·2 g.) separated which slowly solidified, and recrystallised from benzene in needles, m. p. 141—143°, undepressed on admixture with the product from 4-chlorocatechol.

Condensation of 4-Nitroguaiacol with Chloroacetic Acid.—(*a*) 4-Nitroguaiacol (1·7 g.), chloroacetic acid (2·9 g.), and sodium hydroxide (2·0 g.) in water (25 ml.) were mixed and the solution boiled for 18 hr. When cloudiness was noticed, sodium hydroxide was added in 0·5-g. amounts. On cooling and acidification, a gelatinous precipitate was obtained which on crystallisation from aqueous methanol (8·0 ml.) formed long, pale cream prisms (0·6 g.), m. p. 191°, of *2-hydroxy-5-nitrophenoxyacetic acid* (Found: C, 44·8; H, 3·3. $C_8H_7O_6N$ requires C, 45·1; H, 3·3%).

(*b*) 4-Nitroguaiacol (8·45 g.), chloroacetic acid (14·2 g.), sodium hydroxide (8 g.), and water (100 ml.) were mixed and the solution boiled for 8 hr. Whenever the solution became cloudy, a drop of 2N-sodium hydroxide was added. After acidification and cooling *2-methoxy-5-nitrophenoxyacetic acid* (9·4 g.), m. p. 180—182°, was obtained. Recrystallisation from aqueous methanol yielded shining, pale yellow prisms, m. p. 182—185° (Found: C, 47·1; H, 4·0. $C_9H_9O_6N$ requires C, 47·6; H, 4·0%).

Conversion of 2-Hydroxy- and 2-Methoxy-5-nitrophenoxyacetic Acids into the 5-Chlorophenoxyacetic Acids.—2-Hydroxy-5-nitrophenoxyacetic acid (0·5 g.) in methanol (50 ml.) was reduced with hydrogen at atmospheric pressure and room temperature with a catalyst from palladium chloride. The amino-acid was rather insoluble in methanol and was removed from the catalyst with alkali. Diazotised and treated with cuprous chloride in the usual way, it furnished crude 5-chloro-2-hydroxyphenoxyacetic acid (0·11 g.), which after recrystallisation from water and from aqueous methanol formed off-white needles, m. p. and mixed m. p. 157° (Found: C, 47·2; H, 3·6. Calc. for $C_8H_7O_4Cl$: C, 47·4; H, 3·5%). Similar treatment of 2-methoxy-5-nitrophenoxyacetic acid gave *5-amino-2-methoxyphenoxyacetic acid* which formed shining buff prisms, m. p. 232°, from water (Found: C, 54·3; H, 5·7. $C_9H_{11}O_4N$ requires C, 54·8; H, 5·6%), and 5-chloro-2-methoxyphenoxyacetic acid (0·39 g. from 0·55 g. of amino-acid) which separated from aqueous methanol in off-white needles, m. p. 140—142°, mixed m. p. 141—143°.

5-Chloroguaiacol.—From 5-nitroguaiacol (Pollecoff and Robinson, *J.*, 1918, **113**, 1647) (4·0 g.), 5-chloroguaiacol (1·2 g.) was obtained by the method described above for 4-chloroguaiacol. This compound has not previously been obtained crystalline but on storage at 0° our sample deposited flaky prisms, m. p. 16—17°.

4-Chloro-2-methoxyphenoxyacetic Acid.—The crude 5-chloroguaiacol (1·5 g.) was treated with chloroacetic acid in the usual way, and the gummy *methoxy-acid* crystallised from benzene, forming needles (0·7 g.), m. p. 135—136°, mixed m. p. with the 5-chloro-2-methoxyphenoxyacetic acid from 4-chlorocatechol, 125—137°. An analytical sample was recrystallised from aqueous methanol (Found: C, 50·1; H, 3·9. $C_9H_9O_4Cl$ requires C, 49·9; H, 4·2%).

4-Chloro-2-hydroxyphenoxyacetic Acid.—4-Chloro-2-methoxyphenoxyacetic acid (0·2 g.) was boiled for 1 hr. with 48% aqueous hydrobromic acid (2·0 ml.). On cooling, the *hydroxy-acid* (0·15 g.) separated. Recrystallisation from water (2 ml.) gave off-white needles (0·1 g.) which lost their sheen at 90° and slowly melted at 110°. The m. p. on rapid heating varied from 124° to 130° (Found: C, 47·0; H, 3·5. $C_8H_7O_4Cl$ requires C, 47·4; H, 3·5%). The substance gave a blue colour with aqueous or alcoholic ferric chloride.

Ethyl 2-Methoxy-4-nitrophenoxyacetate.—5-Nitroguaiacol (2·0 g.) was added to sodium (0·25 g.), dissolved in methanol (20 ml.). Ethyl chloroacetate (1·5 g.) was added and the

mixture boiled for 32 hr. Evaporation of the methanol and boiling of the residue with water (100 ml.) left undissolved oil (0·5 g.) which solidified on cooling, and recrystallised from methanol in pale yellow needles, m. p. 88—91° (Found : C, 51·3; H, 4·9. $C_{11}H_{13}O_6N$ requires C, 51·8; H, 5·1%).

Reaction of 3 : 5-*Dichlorocatechol and Ethyl Chloroacetate.*—3 : 5-Dichlorocatechol (3·75 g.), treated with ethyl chloroacetate in the manner described for 4-chlorocatechol, yielded as the least soluble component of the resultant mixture 2 : 4-dichloro-6-hydroxyphenoxyacetic acid (0·55 g.). An analytical sample was recrystallised from water, forming shining needles which did not lose sheen at 100°. The m. p. varied with the rate of heating between 130° and 155° (Found : C, 41·1; H, 2·8. Calc. for $C_8H_6O_4Cl_2$: C, 40·5; H, 2·6%). The substance gave a cloudy violet solution with aqueous or alcoholic ferric chloride. With methyl sulphate and alkali as described by Cavill and Ford (*loc. cit.*) it formed a methyl ether, m. p. 174—176°.

2-*Acetamido*-4 : 6-*dichlorophenol.*—2 : 4-Dichlorophenol (29 g.) was added in small portions to concentrated nitric acid (58 ml.), at 30—40°. On cooling and addition of water (100 ml.), 2 : 4-dichloro-6-nitrophenol (32·6 g.), m. p. 122—124°, was obtained. The crude nitrophenol (13·7 g.) was dissolved in a solution of sodium carbonate (50 g.) in water (780 ml.) at 90°. Sodium hyposulphite (dithionite) (44 g.) was added during 20 min. The clear, pale yellow solution was neutralised with acetic acid, and the amino-phenol which separated was acetylated by shaking with acetic anhydride (25 ml.) until all solid had liquefied. When kept, the oil solidified and 2-*acetamido*-4 : 6-*dichlorophenol* (8·0 g.) was recovered by filtration. An analytical sample formed colourless needles, m. p. 138—140°, from aqueous ethanol (Found : C, 43·2; H, 3·2. $C_8H_7O_2NCl_2$ requires C, 43·7; H, 3·2%).

2-*Acetamido*-4 : 6-*dichloroanisole.*—The crude 2-acetamido-4 : 6-dichlorophenol (8·3 g.) was boiled in acetone (50 ml.) with methyl iodide (15 ml.) and potassium carbonate (20 g.) for 6 hr. After evaporation of solvent, water (50 ml.) was added and the oily product extracted into ether. The *anisole* separated from the evaporated solution in large plates (4·0 g.) and recrystallised from light petroleum (b. p. 60—80°) in squat white prisms, m. p. 112—114° (Found : C, 45·8; H, 3·5. $C_9H_9O_2NCl_2$ requires C, 46·1; H, 3·8%).

2-*Amino*-4 : 6-*dichloroanisole.*—2-Acetamido-4 : 6-dichloroanisole (3·8 g.) was boiled with 20% hydrochloric acid (150 ml.) for 1 hr. On cooling, 2-*amino*-4 : 6-*dichloroanisole hydrochloride* separated in white needles, m. p. 196° (previous softening) (from dilute hydrochloridc acid) (Found : C, 36·7; H, 3·6. $C_9H_{10}O_2NCl_3$ requires C, 36·7; H, 3·5%). The remainder of the hydrochloride was converted into the amine by addition of sodium hydroxide. The amine was isolated as a brown oil (2·8 g.), f. p. 16°, by extraction into ether.

4 : 6-*Dichloroguaiacol.*—2-Amino-4 : 6-dichloroanisole (6·1 g.) in concentrated sulphuric acid (38 ml.) was diazotised by addition of sodium nitrite (2·8 g.) at 5°. After 3 hr. the dark solution was poured on ice (100 g.), and the clear diazonium solution was then slowly added to cupric sulphate pentahydrate (100 g.) in water (100 ml.), with simultaneous passage of steam. From the steam-distillate the products were extracted into ether, and purified by dissolution in, and precipitation from, 2N-sodium hydroxide. The light-brown oil (3·3 g.) deposited colourless crystals of 4 : 6-*dichloroguaiacol* (1·7 g.), needles, m. p. 63—64° [from light petroleum (b. p. 60—80°)] (Found : C, 43·6; H, 3·2. $C_7H_6O_2Cl_2$ requires C, 43·5; H, 3·1%). This compound gave with aqueous ferric chloride a violet colour which was destroyed by addition of alcohol.

3 : 5-*Dichloro*-2-*hydroxyphenoxyacetic Acid.*—4 : 6-Dichloroguaiacol (0·5 g.) was converted in the usual way into 3 : 5-*dichloro*-2-*methoxyphenoxyacetic acid* (0·5 g.), white needles, m. p. 106—107° (from toluene) (Found : C, 43·7; H, 3·3. $C_9H_8O_4Cl_2$ requires C, 43·0; H, 3·2%). This methoxy-acid (0·2 g.) was boiled with 48% hydrobromic acid (2·0 ml.) for 1 hr. On cooling, the *hydroxy-acid* (0·12 g.) separated. It formed colourless needles, m. p. 154° (from water), which lost their sheen at 100° (Found : C, 40·4; H, 2·6. $C_8H_6O_4Cl_2$ requires C, 40·5; H, 2·6%). The substance gives a royal-blue colour with aqueous or alcoholic ferric chloride.

2-*Acetamido*-3 : 5-*dichlorophenol.*—2 : 4-Dichloroaniline (12 g.), dissolved in a mixture of acetone (450 ml.) and water (700 ml.), containing potassium hydroxide (11 g.), was treated during 5 hr. at 25° with a solution of potassium persulphate (20 g.) in water (450 ml.). Next morning potassium hydroxide (1·0 g.) was added, and the liquors concentrated to 250 ml. under reduced pressure. The solution was neutralised, extracted with ether to remove neutral impurities, and then evaporated to dryness (steam-bath). Boiling alcohol (3 × 100 ml.) extracted crystals (1·5 g.) from the residue. These were boiled with 20% hydrochloric acid (3·0 ml.) for 1 hr. The resultant solution was basified with sodium hydrogen carbonate, and acetic anhydride (0·5 ml.) was added to the resultant suspension of 2-amino-3 : 5-dichlorophenol.

The *acetamidophenol* (0·4 g.) crystallised from aqueous methanol in cream-coloured plates, m. p. 190—193° (Found: C, 43·5; H, 3·2. $C_8H_7O_2NCl_2$ requires C, 43·7; H, 3·2%).

2-N-*Methylacetamido*-3 : 5-*dichloroanisole*.—The foregoing acetamidophenol (0·3 g.), methyl iodide (0·7 g.), potassium carbonate (1·4 g.), and acetone (1·5 ml.) were heated under reflux for 6 hr. The solvent was removed, water (3 ml.) added, and the *methylamide* crystallised from light petroleum (b. p. 60—80°) or aqueous methanol in squat prisms, m. p. 107—109° (Found: C, 48·7; H, 4·7. $C_{10}H_{11}ONCl_2$ requires C, 48·4; H, 4·4%).

3-*Chloroguaiacol*.—5-Chlorovanillic acid (Raiford and Potter, *J. Amer. Chem. Soc.*, 1933, **55**, 1683) (9·0 g.) in glycerol (90 ml.) containing copper bronze (0·2 g.) was heated at 250—260° for 10 min. Steam was passed through the mixture, and 3-*chloroguaiacol* (1·7 g.) was recovered from the distillate by filtration and by ether-extraction. It formed colourless needles, m. p. 54°, from light petroleum (b. p. 60—80°) (Found: C, 52·9; H, 4·2. $C_7H_7O_2Cl$ requires C, 53·0; H, 4·4%). The aqueous solution of the compound gave with ferric chloride a red colour and then a reddish-brown precipitate. A benzene solution of the compound did not react with sulphuryl chloride at room temperature. Boiling it with a large excess of sulphuryl chloride gave a mixed product from which a *trichloroguaiacol*, colourless needles, m. p. 102—104° [from light petroleum (b. p. 60—80°)], was isolated in 5% yield (Found: C, 39·5; H, 2·5. $C_7H_5O_2Cl_3$ requires C, 39·7; H, 2·5%). This substance gave no colour with aqueous or alcoholic ferric chloride. 3-Chloroguaiacol formed a *phenoxyacetic acid* in the usual way in 82% yield (off-white needles, m. p. 130°, from toluene) (Found: C, 50·3; H, 4·3. $C_9H_9O_4Cl$ requires C, 49·9; H, 4·2%).

3 : 5-*Dichloroguaiacol*.—(*a*) 5-Chlorovanillic acid (5·0 g.) was dissolved in warm concentrated sulphuric acid (30 ml.), chloroform (50 ml.) was added, and the mixture stirred at 45° while sodium azide (2·5 g.) was added during 30 min. After 30 min. at 45° the mixture was poured on ice (100 g.), and a trace of unchanged acid removed by filtration. If the mixture is basified with sodium carbonate at this stage, a rapidly discolouring precipitate of 5-amino-3-chloroguaiacol is obtained which can be converted by addition of acetic anhydride into crude 5-*acetamido*-3-*chloroguaiacol* (3·0 g.). A sample of the latter formed pink leaflets, m. p. 165°, from water (Found: C, 49·6; H, 4·9. $C_9H_{10}O_3NCl$ requires C, 50·1; H, 4·7%). To obtain 3 : 5-dichloroguaiacol, the mixture was treated with barium chloride dihydrate (135 g.) in hot water (400 ml.), and the barium sulphate filtered from the amine hydrochloride solution. The latter was diazotised at 5° with sodium nitrite (2·0 g.), kept for 15 min., and treated with urea (1·0 g.) and a solution of cupric chloride from cupric sulphate pentahydrate (83 g.) in hydrochloric acid. This mixture was kept overnight at 20°, heated at 95° for 30 min., and finally steam-distilled. From the distillate (250 ml.) a brown oil (0·5 g.) was extracted with ether, and distilled at 15 mm. (bath-temp. 170°). The pale orange distillate (0·3 g.) partially solidified and was recrystallised three times from light petroleum (b. p. 60—80°), to give 3 : 5-*dichloroguaiacol* as pale yellow needles, m. p. 64—65° (Found: C, 43·7; H, 3·2. $C_7H_6O_2Cl_2$ requires C, 43·5; H, 3·1%). The compound gave no colour with aqueous or alcoholic ferric chloride.

(*b*) 2 : 4 : 6-Trichloronitrobenzene (Loudon, *J.*, 1940, 1527) was condensed with sodium methoxide in boiling methanol as described by Holleman and van Haeften (*loc. cit.*). The crude product, m. p. 41—63°, gave pale yellow cubes of 3 : 5-dichloro-6-nitroanisole, m. p. 70—72° (Found: C, 37·8; H, 2·1; N, 6·2. Calc. for $C_7H_5O_3NCl_2$: C, 37·9; H, 2·3; N, 6·3%), in 40% yield on three recrystallisations from ethanol. Rapid cooling of the hot ethanol solutions gave needles which reverted to the cubic form during several hours. The dichloronitroanisole (3·7 g.) in ethanol (75 ml.) was shaken with hydrogen at atmospheric temperature and pressure in the presence of Raney nickel (1·5 g.) for 24 hr. Evaporation of the filtered solution, finally *in vacuo*, gave 2-amino-3 : 5-dichloroanisole (3·2 g.) as a dark oil. With acetic anhydride it gave 2-*acetamido*-3 : 5-*dichloroanisole*, colourless needles, m. p. 169·5—171·5° (from toluene) (Found: C, 46·2; H, 4·2; N, 5·5; Cl, 30·0. $C_9H_9O_2NCl_2$ requires C, 46·2; H, 3·9; N, 6·0; Cl, 30·3%), and reaction of the amide in acetone with methyl iodide and potassium carbonate gave 2-*N*-methylacetamido-3 : 5-dichloroanisole, m. p. and mixed m. p. 107—109°. 2-Amino-3 : 5-dichloroanisole (3·7 g.) in concentrated sulphuric acid (20 ml.) was converted into 3 : 5-dichloroguaiacol as described in the diazotisation of 2-amino-4 : 6-dichloroanisole. The crude product (0·4 g.), a pale yellow oil, crystallised from light petroleum (b. p. 60—80°) in clusters of pale yellow needles, m. p. and mixed m. p. with sample from (*a*) 60—62·5°.

2 : 4-*Dichloro*-6-*hydroxyphenoxyacetic Acid*.—3 : 5-Dichloroguaiacol (0·6 g.) yielded 2 : 4-dichloro-6-methoxyphenoxyacetic acid (0·7 g.) in the usual way. After two recrystallisations from toluene it formed pale cream-coloured needles, m. p. 174—175°, not depressed on admixture with the methoxy-acid from 3 : 5-dichlorocatechol (Found: C, 42·9; H, 3·7. Calc. for $C_9H_8O_4Cl_2$:

C, 43·0; H, 3·2%). This methoxy-acid (0·2 g.) was boiled under reflux with 48% hydrobromic acid (6 ml.) for 3 hr. Some 3 : 5-dichloroguaiacol was formed and solidified in the condenser. After cooling, the solid (0·15 g.) was filtered off and boiled with water (3 ml.). The insoluble unchanged methoxy-acid was removed by filtration and 2 : 4-dichloro-6-hydroxyphenoxyacetic acid (0·05 g.) separated from the cool filtrate. It recrystallised from water in needles, the m. p. varying between 135° and 155° according to the rate of heating (Found : C, 41·0; H, 2·8. Calc. for $C_8H_6O_4Cl_2$: C, 40·5; H, 2·6%). The substance gave a cloudy violet colour with aqueous or alcholic ferric chloride.

2-Chloro-4-hydroxyphenoxyacetic Acid (with ANN M. SALAMAN and J. R. SURTEES).—(*a*) 2-Chlorophenoxyacetic acid (12·5 g.) was boiled with concentrated nitric acid (60 ml.) for 5 min., water (50 ml.) was added, and the mixture cooled. *2-Chloro-4-nitrophenoxyacetic acid* (10 g.) separated as plates, m. p. 178—181°. A specimen recrystallised from aqueous ethanol in pale yellow prisms, m. p. 179—181° (Found : C, 42·2; H, 2·8. $C_8H_6O_5NCl$ requires C, 41·6; H, 2·6%). Esterification of the acid (12·5 g.) with methanol and concentrated sulphuric acid gave the methyl ester (10·5 g.) as pale yellow prisms, m. p. 124°. Hydrogenation of the ester in methanol over a palladium catalyst at room temperature and ordinary pressure produced *methyl 4-amino-2-chlorophenoxyacetate*, white needles, m. p. 69° [from a large volume of petroleum ether (b. p. 60—80°)] (Found : C, 50·0; H, 4·5. $C_9H_{10}O_3NCl$ requires C, 50·1; H, 4·6%). The amino-ester (1·0 g.), in water (20 ml.) and concentrated sulphuric acid (2·0 ml.), was diazotised in the usual manner and added dropwise to a boiling solution of cupric sulphate pentahydrate (20 g.) in water (20 ml.). The product was isolated in ether, dissolved in boiling aqueous sodium hydroxide, reprecipitated with acid, dried, and treated with boiling benzene (5·0 ml.). The fraction (0·5 g.) insoluble in benzene was recrystallised twice from water, to give sand-coloured prisms of *2-chloro-4-hydroxyphenoxyacetic acid* (0·1 g.), m. p. 146—147° (Found : C, 46·9; H, 3·1. $C_8H_7O_4Cl$ requires C, 47·4; H, 3·5%). The *methyl ether* formed off-white prisms, 136—138°, from toluene (Found : C, 50·4; H, 4·6. Calc. for $C_9H_9O_4Cl$: C, 49·9; H, 4·2%).

2 : 4-Dichlorophenoxyacetic acid (0·12 g.), m. p. 138—139°, identical with an authentic specimen, was obtained by treatment of the diazonium solution from the above amino-ester (0·6 g.) with cuprous chloride in the usual way.

(*b*) To a stirred solution of *p*-methoxyphenol (30 g.), in chloroform (75 ml.), was added dropwise, during 3 hr., sulphuryl chloride (20 ml.) in chloroform (25 ml.). After 20 hr., solvent was removed and the product distilled. The colourless distillate, b. p. 108°/15 mm., soon solidified. It recrystallised from light petroleum (b. p. 60—80°) in colourless prisms, m. p. 46—47° (Found : C, 52·5; H, 4·5; Cl, 22·5. $C_7H_7O_2Cl$ requires C, 53·0; H, 4·4; Cl, 22·3%) (cf. Nametkin, Bokarev, and Melnikov, *Doklady Akad. Nauk S.S.S.R.*, 1951, **77**, 293, who obtained a liquid, b. p. 97—103°/40 mm., when chlorine was used in this chlorination). This phenol (2·0 g.) formed a phenoyxacetic acid (2·4 g.) in the usual way. A sample, recrystallised from toluene, formed white prisms, m. p. 139°, undepressed on admixture with the above 2-chloro-4-methoxyphenoxyacetic acid. The methyl ether (0·3 g.) was boiled with 48% hydrobromic acid (2·5 ml.) for 1 hr. On cooling, the hydroxy-acid (0·13 g.) separated and formed off-white prisms, m. p. and mixed m. p. 146—147°, from water (Found : C, 47·0; H, 3·6. Calc. for $C_8H_7O_4Cl$: C, 47·4; H, 3·5%).

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