89. *Antituberculous Compounds. Part IV. Compounds related to Diethyl-ω-aryloxyalkylamines.*

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A series of compounds related to the active diethyl-ω-aryloxyalkylamines (I; X = O) (Part I; *J.*, 1949, 2680) has been prepared in which X = S, SO, SO_2, NH, NAlkyl, CO, CH_2, CO·O, or O·CO, n = 1 or 2, and Ar = trihalogenophenyl, phenyl, or naphthyl. In addition, the effect of interpolating a phenylene- or a phenyleneoxy-group [cf. V; X = C_6H_4(-*p*) or O·C_6H_4(-*p*)] next to the terminal amino-group was tried in a few cases. Although high *in vitro* activities were obtained in certain cases, no *in vivo* activity could be demonstrated.

Part I of this series (*loc. cit.*) dealt with the effect on the activity against *Mycobacterium tuberculosis* of such structural features of diethyl-ω-aryloxyalkylamines (I; X = O) as the number and position of halogen substituents in the aryl nucleus, the chain length n, and the replacement of the terminal diethylamino-group by other basic groups. As no evidence was available about the contribution of the ether linkage to the activity of these compounds, it was

(I.) $Ar{\cdot}X{\cdot}[CH_2]_n{\cdot}NEt_2$ $\qquad$ $C_6H_5{\cdot}CO{\cdot}CH(CH_2{\cdot}NEt_2,HCl){\cdot}CH_2{\cdot}CO{\cdot}C_6H_5$ (II.)

though of interest to investigate compounds in which the oxygen atom was replaced by other atoms or groups. This paper describes the preparation of a number of such compounds. Wherever practicable, compounds halogenated in the aryl nucleus were prepared since, although such substitution in the aryloxy-series generally resulted in an increased activity only in the absence of serum, two cases had been observed where this increased activity had been maintained in the presence of serum (Part I, *loc. cit.*). The compounds prepared are listed in the accompanying table, together with the results of biological tests, further details of which will be published elsewhere. In the following discussion the numbers in parentheses following the names of compounds refer to the numbers of the compounds in the table. For convenience, compounds are referred to as the free bases although in most cases they were isolated as their water-soluble hydrochlorides or as Reineckates which were converted into aqueous solutions of the hydrochlorides for test.

As a first step, the effect of replacing the oxygen atom by a sulphur atom, or a sulphinyl or sulphonyl group was investigated. 2 : 4 : 6-Trichlorophenyl 2-diethylaminoethyl sulphide (1), sulphoxide (2), and sulphone (3) were prepared by conventional methods from the *sodium* salt 2 : 4 : 6-trichlorothiophenol. The sulphone could not be prepared from 2 : 4 : 6-*trichlorobenzenesulphinic acid*, the sodium salt of which failed to condense with diethylaminoethyl chloride. It will be seen that, while the sulphide corresponds very closely in activity to its oxygen analogue (Part I), the activity is reduced in the case of the sulphoxide and is of a very low order in the case of the sulphone.

Nitrogen analogues were prepared by the direct chlorination of *N*-2-diethylaminoethylanilines (I; n = 2, X = NR where R = H or alkyl) in acetic acid solution. This led to the formation of trichloro-derivatives (5, 7, 10) when the group attached to the nitrogen atom was small (R = H, Me, and $CH_2{\cdot}CH_2{\cdot}NEt_2$). With a larger alkyl group attached to the nitrogen, as in the case of the *N*-octyl and N-*cetyl* (12) compounds, dichloro-derivatives (11, 13) were produced, accompanied by considerable quantities of non-basic tars, presumably formed by fission of the side-chain. Three of these compounds (5, 7, 11) showed high activity in the absence of serum. In the only case (compound 5) where the activity was maintained sufficiently in the presence of serum to justify an *in vivo* test, no effect could be observed on the course of experimental tuberculosis in guinea pigs. Direct iodination and thiocyanation of *N*-methyl-*N*-2-diethylaminoethylaniline afforded *p*-iodo-*N*-methyl-*N*-2-diethylaminoethylaniline (8) and the *p*-thiocyanato-analogue (9) respectively, neither of which showed increased activity in comparison with the parent compound. *N*-2′-Diethylaminoethyl-1- and -2-naphthylamines (14, 15) showed low activity. In these cases direct chlorination led to extensive decomposition, and chloro-derivatives could not be prepared by this method. The orientation of the halogen atoms and the thiocyanato-group in all the foregoing compounds was not proved but the assigned positions were inferred by analogy with the behaviour of simple derivatives of aniline.

Diethyl-2-benzoylethylamine (16) showed a reduced activity in comparison with the oxygen analogue, diethyl-2-phenoxyethylamine (Part I). This compound (16) was prepared by the Mannich condensation of acetophenone with paraformaldehyde and diethylammonium chloride according to the method of Blicke and Burckhalter (*J. Amer. Chem. Soc.*, 1942, **64**, 451). The

low yield in this reaction is ascribable, at least in part, to the simultaneous formation of major quantities of a *substance*, probably diethyl-2 : 4-dibenzoylbutylammonium chloride (II), resulting from the condensation of two molecules each of acetophenone and formaldehyde with one of

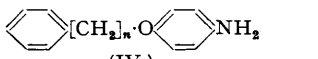
Compound.	Structure. (R = ·$[CH_2]_2$·NEt_2.)	Activity.* In absence of serum.	In presence of 10% serum.
(1) 2 : 4 : 6-Trichlorophenyl 2′-diethylaminoethyl sulphide	2 : 4 : 6-$C_6H_2Cl_3$·S·R	100 (500)	10
(2) 2 : 4 : 6-Trichlorophenyl 2′-diethylaminoethyl sulphoxide	2 : 4 : 6-$C_6H_2Cl_3$·SO·R	50	—
(3) 2 : 4 : 6-Trichlorophenyl 2′-diethylaminoethyl sulphone	2 : 4 : 6-$C_6H_2Cl_3$·SO_2·R	5 (10)	—
(4) *N*-2-Diethylaminoethylaniline	C_6H_5·NHR	—	1
(5) 2 : 4 : 6-*Trichloro*-N-2′-*diethylaminoethylaniline*	2 : 4 : 6-$C_6H_2Cl_3$·NHR	100—500	50
(6) *N*-Methyl-*N*-2-diethylaminoethylaniline	C_6H_5·NMeR	10	1—5
(7) 2 : 4 : 6-*Trichloro*-N-*methyl*-N-2′-*diethylaminoethylaniline*	2 : 4 : 6-$C_6H_2Cl_3$·NMeR	500—1000 (5000)	10—50
(8) *p*-Iodo-*N*-methyl-*N*-2-diethylaminoethylaniline	*p*-I·C_6H_4·NMeR	10	—
(9) *p*-Thiocyanato-*N*-methyl-*N*-2-diethylaminoethylaniline	*p*-NCS·C_6H_4·NMeR	10	—
(10) 2 : 4 : 6-*Trichloro*-NN-*bis*-2′-*diethylaminoethylaniline*	2 : 4 : 6-$C_6H_2Cl_3$·NR_2	10	10
(11) 2 : 4-Dichloro-*N*-2′-diethylaminoethyl-*N*-octylaniline	2 : 4-$C_6H_3Cl_2$·$N(C_8H_{17})$·R	1000	10
(12) N-2-*Diethylaminoethyl*-N-*hexadecylaniline*	C_6H_5·$N(C_{16}H_{33})$·R	1—5	—
(13) 2 : 4-Dichloro-*N*-2′-diethylaminoethyl-*N*-hexadecylaniline	2 : 4-$C_6H_3Cl_2$·$N(C_{16}H_{33})$·R	5 (50)	—
(14) *N*-2′-Diethylaminoethyl-1-naphthylamine	α-$C_{10}H_7$·NHR	—	1 (10)
(15) *N*-2′-Diethylaminoethyl-2-naphthylamine	β-$C_{10}H_7$·NHR	—	10 (50)
(16) Diethyl-2-benzoylethylamine	C_6H_5·CO·R	5	—
(17) Diethyl-2-*m*-aminobenzoylethylamine	*m*-NH_2·C_6H_4·CO·R	1	<1
(18) Diethyl-3-phenylpropylamine	C_6H_5·CH_2R	50—100	10—50
(19) 2′-Diethylaminoethyl 2 : 4 : 6-trichlorobenzoate	2 : 4 : 6-$C_6H_2Cl_3$·CO·OR	1—5	—
(20) 2′-Diethylaminoethyl 2 : 3 : 5-tri-iodobenzoate	2 : 3 : 5-$C_6H_2I_3$·CO·OR	10	1
(21) 2 : 4 : 6-Trichlorophenyl diethylaminoacetate	2 : 4 : 6-$C_6H_2Cl_3$·O·CO·CH_2·NEt_2	10	5—10
(22) *Phenyl* p-*aminobenzyl ether*	C_6H_5·O·CH_2·C_6H_4·NH_2-*p*	—	1—5
(23) 1-*Phenoxy*-2-p-*aminophenoxyethane*	C_6H_5·O·CH_2·CH_2·O·C_6H_4·NH_2-*p*	50—500	10
(24) 1-*Phenoxy*-2-(p-*diethylaminophenoxy*)*ethane*	C_6H_5·O·CH_2·CH_2·O·C_6H_4·NEt_2-*p*	500	50—100
(25) 1-(2 : 4 : 6-*Trichlorophenoxy*)-2-p-*aminophenoxyethane*	2 : 4 : 6-$C_6H_2Cl_3$·O·CH_2·CH_2·O·C_6H_4·NH_2-*p*	—	—

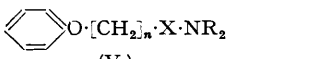
* Dilution (in thousands) at which complete inhibition of the growth of *M. tuberculosis* (human virulent strain) was maintained for 4 weeks in modified Long's medium (by the floating-pellicle method). Figures in parentheses represent dilutions at which partial inhibition occurred. Under the same conditions of test 4-aminosalicylic acid gave a value of 10 in the absence of serum.

diethylammonium chloride. Attempts to prepare the 2 : 4 : 6-trichloro-derivative of compound (16) by several methods failed. Thus, 1 : 3 : 5-trichloro-2-iodobenzene formed a normal Grignard compound but this failed to react with 2-diethylaminoethyl cyanide. 2 : 4 : 6-Trichlorophenyl cyanide did not react with methylmagnesium iodide, but 2 : 4 : 6-*trichloroacetophenone* was readily prepared from 2 : 4 : 6-trichlorobenzoyl chloride and dimethylcadmium. This acetophenone was devoid of ketonic properties and could not be induced to undergo the Mannich reaction with formaldehyde and diethylammonium chloride, presumably owing to the reduction of the cationoid properties of the carbonyl group by the chlorine atoms. Steric factors probably played little part in this inactivation, since 2 : 3 : 5-*trichloroacetophenone* displayed a similar inertness. Finally, diethyl-2-*m*-aminobenzoylethylamine (17) was prepared by a Mannich condensation of *m*-benzamidoacetophenone with paraformaldehyde and diethylammonium chloride and hydrolysis of the resulting diethyl-2-*m*-benzamidobenzoylethylamine. It was hoped that this compound would yield by chlorination diethyl-2-(2 : 4 : 6-trichloro-3-aminobenzoyl)ethylamine and thence by deamination the required diethyl-2-(2 : 4 : 6-trichlorobenzoyl)ethylamine. Chlorination, however, led to non-basic gums, indicating degradation of the side-chain.

Catalytic reduction of diethyl-2-benzoylethylamine furnished the methylene analogue, diethyl-3-phenylpropylamine (18). This showed increased activity in comparison with diethyl-2-phenoxyethylamine in the absence of serum, but reduced activity in the presence of serum together with high toxicity precluded *in vivo* activity.

$CH_2{:}CH{\cdot}NEt_2,HCl$ (III.)


(IV.)


(V.)

Compounds were also prepared in which the oxygen atom of (I; X = O) was replaced by ester groups of the type (–CO·O–) and (–O·CO–). 2′-Diethylaminoethyl 2 : 4 : 6-trichlorobenzoate (19) and 2 : 3 : 5-tri-iodobenzoate (20) were prepared from 2-diethylaminoethanol and the corresponding acid chlorides. In the former case considerable quantities of a by-product were obtained, apparently identical with diethylvinylammonium chloride (III), obtained by Ladenburg (*Ber.*, 1882, **15**, 1148) by the action of hydrogen iodide on diethylaminoethanol and conversion of the product into the chloride. It is presumably formed here by the elimination of the elements of 2 : 4 : 6-trichlorobenzoic acid from the ester. 2 : 4 : 6-Trichlorophenyl diethylaminoacetate (21) was prepared by the condensation of 2 : 4 : 6-trichlorophenol and diethylaminoacetyl chloride hydrochloride. It could not be prepared from 2 : 4 : 6-*trichlorophenyl chloroacetate* which with diethylamine underwent rapid fission to give *diethylammonium* 2 : 4 : 6-*trichlorophenoxide*. None of the compounds (19, 20, 21) showed high activity.

Finally, in view of the activity of compounds of type (IV) (Barry, O'Rourke, and Twomey, *Nature*, 1947, **160**, 800), it was thought of interest to prepare a few compounds of the type [V; n = 1 or 2, R = H or Et, X = C_6H_4(-*p*) or O·C_6H_4(-*p*)]. *Phenyl* p-*aminobenzyl ether* (22), prepared from the corresponding nitro-compound by reduction with aluminium amalgam, was an unstable compound as shown by its ready hydrogenolysis by other reducing agents and the formation of phenol in cold solutions of its *hydrochloride*. Chloro-derivatives were therefore not prepared. 1-*Phenoxy*-2-p-*aminophenoxyethane* (23), prepared by the reduction of 1-phenoxy-2-*p*-nitrophenoxyethane (Ryan and Kenny, *Sci. Proc. Roy. Dublin Soc.*, 1924, **17**, 305), had high activity only in the absence of serum. Ethylation gave 1-*phenoxy*-2-(p-*diethylaminophenoxy*)-*ethane* (24), the high activity of which was less affected by serum. No *in vivo* activity could, however, be demonstrated. Although 1-phenoxy-2-*p*-aminophenoxyethane was of normal basic strength, 1-(2 : 4 : 6-*trichlorophenoxy*)-2-p-*aminophenoxyethane* (24), prepared by similar methods, was, unexpectedly, a very weak base, the *hydrochloride* and *lactate* of which were extensively hydrolysed by water and activity determinations were not carried out.

Experimental.

2 : 4 : 6-*Trichlorobenzenesulphinic Acid.*—2 : 4 : 6-Trichloroaniline (5 g.) was added at 30° to a solution of sodium nitrite (1·8 g.) in concentrated sulphuric acid (100 c.c.). The solution was then cooled and crushed ice (150 g.) added in portions at 5—8°. A small quantity of tar was removed from the surface, and the clear red solution was saturated at 3—5° with sulphur dioxide. A paste of copper powder (45 g.) and water was then added and the mixture stirred for 3 hours, the temperature being raised to 40° towards the end. The product was isolated as the ferric salt by the method of Thomas (*J.*, 1909, **95**, 342) except that, to avoid separation of the insoluble sulphinic acid, the ferric chloride was added to the filtrate before the addition of the ammoniacal extract of the copper powder. The orange precipitate was filtered off, washed with ethanol to remove coloured impurities, and decomposed with dilute ammonia. Filtration, acidification, and extraction with ether gave 2 : 4 : 6-*trichlorobenzenesulphinic acid* as a colourless solid, m. p. 115° (Found : S, 13·6. $C_6H_3O_2Cl_3S$ requires S, 13·0%). Attempts to condense the sodium salt with diethylaminoethyl chloride in ethanol, methanol, or benzene failed, the sulphinic acid being recovered unchanged.

Sodium Salt of 2 : 4 : 6-*Trichlorothiophenol.*—2 : 4 : 6-Trichloroaniline (5 g.) was diazotised by the method of Hodgson and Mahadevan (*J.*, 1947, 173), the dry diazonium sulphate (8·5 g.) dissolved in ice-water (100 c.c.), and a solution of potassium xanthate (4·5 g.) in ice-water (100 c.c.) added. The yellow, turbid solution was allowed to attain room temperature slowly overnight. (It was found that, if the mixture was allowed to reach room temperature immediately, the temperature rose and a violent reaction occurred.) The heavy brown oil (4·9 g.) was isolated with ether and refluxed for 45 minutes under nitrogen with a solution of potassium hydroxide (0·8 g.) in ethanol (50 c.c.). The solution was then evaporated *in vacuo* and the brown residue dissolved in water and shaken with ether to remove disulphide. The aqueous layer was acidified with acetic acid and extracted with ether, and the ethereal extract washed with water and dried. Titration of the solution with concentrated ethanolic sodium ethoxide until alkaline to phenolphthalein afforded a precipitate of the *sodium* salt of 2 : 4 : 6-trichlorothiophenol, obtained as a colourless solid (1·9 g.) after filtration and washing with ether (Found : S, 13·55; Na, 9·8. $C_6H_2Cl_3SNa$ requires S, 13·5; Na, 9·7%).

2 : 4 : 6-*Trichlorophenyl* 2′-*Diethylaminoethyl Sulphide Hydrochloride.*—The above sodium salt (3·7 g.) was refluxed with diethylaminoethyl chloride (2·1 g.) in absolute ethanol (60 c.c.) under nitrogen for 30 minutes. The mixture was evaporated to dryness *in vacuo* and the residue extracted with ether.

The ethereal solution was extracted with dilute hydrochloric acid, and the crude base liberated with alkali and extracted into ether. Addition of ethereal hydrogen chloride to the dried solution afforded 2 : 4 : 6-*trichlorophenyl* 2′-*diethylaminoethyl sulphide hydrochloride* (2·2 g.), long prisms (from ethanol–ether), m. p. 183° (Found : N, 4·0. $C_{12}H_{17}NCl_4S$ requires N, 4·0%).

2 : 4 : 6-*Trichlorophenyl* 2′-*Diethylaminoethyl Sulphoxide.*—The free base from the foregoing hydrochloride (1·78 g.) was dissolved in glacial acetic acid (10 c.c.), and hydrogen peroxide (100 vol.; 0·8 c.c.; 1·3 mols.) added gradually at 10—15°. The mixture was kept overnight at room temperature and then evaporated *in vacuo*. The crude sulphoxide, liberated with dilute aqueous ammonia, was extracted into ether. Addition of ethereal picric acid afforded the *picrate* (1·81 g.), flat yellow needles (from absolute ethanol), m. p. 140° (Found : C, 39·0; H, 3·4; N, 10·2. $C_{18}H_{19}O_9N_4Cl_3S$ requires C, 38·75; H, 3·4; N, 10·0%). For test the picrate was converted into the free base with lithium hydroxide and dissolved in an equivalent of dilute hydrochloric acid.

2 : 4 : 6-*Trichlorophenyl* 2′-*Diethylaminoethyl Sulphone Hydrochloride.*—The free base from the sulphide hydrochloride (2·0 g.) was dissolved in 50% acetic acid (10 c.c.), and a solution of potassium permanganate (2·2 g.) in 50% acetic acid (74 c.c.) added at 0—3° during 1 hour. After a further 30 minutes at 5°, the mixture was decolourised with sulphur dioxide and evaporated to dryness *in vacuo*. The crude sulphone, liberated with aqueous ammonia, was extracted with ether. Addition of ethereal picric acid afforded the *picrate* (2·1 g.), flat needles (from ethanol), m. p. 145° (Found : C, 38·1; H, 3·0; N, 10·0. $C_{18}H_{19}O_9N_4Cl_3S$ requires C, 37·6; H, 3·3; N, 9·8%). The free base, obtained from the picrate with lithium hydroxide, was neutralised with ethanolic hydrogen chloride. Evaporation afforded the *hydrochloride*, colourless needles (from ethanol–ether), m. p. 170° (Found : N, 3·8. $C_{12}H_{17}O_2NCl_4S$ requires N, 3·7%).

N-2-*Diethylaminoethylaniline and* NN-*Bis*-(2-*diethylaminoethyl*)*aniline.*—Aniline (93 g.), diethylaminoethyl chloride hydrochloride (172 g.), and powdered anhydrous sodium carbonate (106 g.) were mixed and heated on the steam-bath for 8 hours by which time evolution of carbon dioxide had ceased. The mixture was diluted with water and made slightly alkaline to Titan-yellow with aqueous sodium hydroxide, and the oil separated, dried, and fractionated. After a forerun of aniline (18 g.), *N*-2-diethylaminoethylaniline (108 g.; b. p. 110—114°/1·8 mm.) was collected (Dewar, *J.*, 1944, 622, gives b. p. 162—164°/25 mm.) and finally a third fraction, b. p. 115—155°/1·8 mm. (32 g.). Repeated fractionation of the last fraction through an 8″ Vigreux column gave pure *N*-bis-(2-diethylaminoethyl)aniline (8·6 g.), b. p. 146—148°/1·2 mm. (Found : N, 14·3. Calc. for $C_{18}H_{33}N_3$: N, 14·4%) (Stahmann and Cope, *J. Amer. Chem. Soc.*, 1946, **68**, 2494, give b. p. 174—177°/6 mm.). The *dipicrate* crystallised from ethoxyethanol in yellow plates, m. p. 170—170·5° (Found : C, 48·3; H, 5·1; N, 16·9. $C_{30}H_{39}O_{14}N_9$ requires C, 48·1; H, 5·2; N, 16·8%).

2 : 4 : 6-*Trichloro*-N-2′-*diethylaminoethylaniline.*—Chlorine was passed into a mixture of *N*-2-diethylaminoethylaniline (10 g.) and glacial acetic acid (100 c.c.) at 20° until the gain in weight was 11·1 g. (= 3 mols. of chlorine). Water (200 c.c.) was added, and the solution neutralised with solid sodium carbonate and finally made alkaline to Titan-yellow with sodium hydroxide. The liberated oil was isolated with ether and distilled, the fraction of b. p. 145—150°/1·5 mm. (7·2 g.) being collected. The redistilled product (6·2 g.; b. p. 157—158°/2·5 mm.) was converted into the *picrate*, which after repeated crystallisation from methanol (yellow rhomboidal plates) had m. p. 150—151° (6·4 g.) (Found : N, 13·6. $C_{18}H_{20}O_7N_5Cl_3$ requires N, 13·3%). Reconversion of the picrate into the free base gave 2 : 4 : 6-*trichloro*-N-2′-*diethylaminoethylaniline* as a colourless liquid (2·72 g.), b. p. 150—152°/2 mm. (Found : N, 9·9. $C_{12}H_{17}N_2Cl_3$ requires N, 9·5%).

2 : 4 : 6-*Trichloro*-NN-*bis*-(2′-*diethylaminoethyl*)*aniline.*—*NN*-Bis-(2-diethylaminoethyl)aniline (8·0 g.), chlorinated similarly, gave much tar and a fraction (2·8 g.), b. p. 168—178°/2 mm. Purified through the *dipicrate*, yellow prisms (from ethoxyethanol), m. p. 206—207° after sintering at 204° (Found : N, 15·0. $C_{30}H_{36}O_{14}N_9Cl_3$ requires N, 14·8%), this afforded 2 : 4 : 6-*trichloro*-NN-*bis*-(2′-*diethylaminoethyl*)-*aniline* as a colourless liquid (1·04 g.), b. p. 170°/1·8 mm. (Found : N, 11·0. $C_{18}H_{30}N_3Cl_3$ requires N, 10·65%).

2 : 4 : 6-*Trichloro*-N-*methyl*-N-2′-*diethylaminoethylaniline.*—*N*-Methyl-*N*-2-diethylaminoethylaniline, prepared by the method used for *N*-2-diethylaminoethylaniline, had b. p. 124—125°/3 mm. (Dewar, *loc. cit.*, gives b. p. 165—170°/20 mm.). This material (10 g.), chlorinated in acetic acid, afforded a fraction, b. p. 148—152°/2·5 mm. (11·6 g.). Purified through the *picrate* (4·7 g.), m. p. 149—150° after repeated crystallisation from methanol (rhomboidal plates) (Found : N, 13·4. $C_{19}H_{22}O_7N_5Cl_3$ requires N, 13·0%), this gave 2 : 4 : 6-*trichloro*-N-*methyl*-N-2′-*diethylaminoethylaniline* as a colourless liquid (1·7 g.), b. p. 142°/1 mm. (Found : N, 9·3. $C_{13}H_{19}N_2Cl_3$ requires N, 9·05%).

p-*Iodo*-N-*methyl*-N-2′-*diethylaminoethylaniline Hydrochloride.*—*N*-Methyl-*N*-2′-diethylaminoethylaniline (32·2 g.) was dissolved in concentrated hydrochloric acid (1 l.), and an excess (115 g., 4·5 mols.) of iodine monochloride in concentrated hydrochloric acid (300 c.c.) added. An oil separated which gradually formed greenish-yellow crystals when kept. The product (76 g.) was a complex of the desired compound with iodine monochloride. It dissolved readily in acetone (500 c.c.), the solution rapidly depositing a greyish-white solid (42 g.). The mother-liquor became dark and lachrymatory, probably owing to the formation of iodoacetone. Crystallisation from methanol–acetone afforded needles of p-*iodo*-N-*methyl*-N-2′-*diethylaminoethylaniline hydrochloride* (24 g.) in a solvated form, m. p. 135—140° (decomp.). When heated at 100° for some hours this lost 15% by weight and then crystallised from acetone in prisms, m. p. 168—169° (Found : C, 42·9; H, 6·0; N, 8·0. $C_{13}H_{22}N_2ClI$ requires C, 42·3; H, 6·0; N, 7·6%). Neither form could be converted into the other by seeding. They both afforded the same picrate, red needles m. p. 141—142°. Reconversion of the picrate into the hydrochloride *via* the free base afforded the solvated form irrespective of the origin of the picrate.

p-*Thiocyanato*-N-*methyl*-N-2′-*diethylaminoethylaniline Hydrochloride.*—To *N*-methyl-*N*-2′-diethylaminoethylaniline (5·1 g.) in carbon tetrachloride (10 c.c.) was added a solution of thiocyanogen in carbon tetrachloride (1·1 mols.; Wood and Fieser, *J. Amer. Chem. Soc.*, 1941, **63**, 2327). The solution became warm and the red oil which separated soon solidified. Recrystallisation from ethanol and aqueous methanol afforded the water-insoluble p-*thiocyanato*-N-2′-*diethylaminoethylaniline monothiocyanate* as

almost colourless needles, m. p. 95—96° (Found: N, 17·4. $C_{15}H_{22}N_4S_2$ requires N, 17·4%). The *picrate* separated from methanol in red needles, m. p. 125° (Found: N, 17·2. $C_{20}H_{24}O_7N_6S$ requires N, 17·2%). The free base was obtained by dissolving the crude thiocyanate (4·7 g.) in warm ethanol, adding an excess of 5N-hydrochloric acid, followed by an excess of dilute aqueous sodium carbonate, and isolating the resulting oil (2·8 g.) with ether. The *hydrochloride* separated from ethanol–ether in compact prisms (1·7 g.), m. p. 147—147·5° (Found: N, 14·1. $C_{14}H_{22}N_3ClS$ requires N, 14·0%).

2 : 4-*Dichloro*-N-2′-*diethylaminoethyl*-N-*octylaniline*.—*N*-2-Diethylaminoethylaniline (20 g.), octyl bromide (20 g.), and anhydrous potassium carbonate (20 g.) were heated at 150—160° for 7 hours. Water was then added, and the mixture made strongly alkaline to Titan-yellow and extracted with ether. The aqueous layer and a dark interface layer of quaternary hydroxide were discarded and the ether layer was concentrated. The residue afforded on distillation *N*-2′-diethylaminoethyl-*N*-octylaniline as a colourless oil (16·25 g.), b. p. 175—180°/2 mm. It was characterised as its *dipicrate*, yellow prisms (from methanol or ether), m. p. 82—83° (Found: N, 14·9. $C_{32}H_{42}O_{14}N_8$ requires N, 14·7%). Chlorination in acetic acid gave much tar and a fraction (8·1 g.), b. p. 188—195°/1·8 mm. Conversion into the Reineckate and repeated crystallisation from methanol afforded 2 : 4-*dichloro*-N-2′-*diethylaminoethyl*-N-*octylaniline Reineckate* as red plates, m. p. 140—142° (Found: C, 42·1; H, 5·85; N, 15·8; Cl, 11·1. $C_{24}H_{41}N_8Cl_2S_4Cr$ requires C, 41·5; H, 5·9; N, 16·2; Cl, 10·3%). The substance therefore probably contained some trichlorinated material. For test the Reineckate was converted into the hydrochloride with silver chloride in methanol, the methanol removed *in vacuo*, and the residue dissolved in water.

2 : 4-*Dichloro*-N-2′-*diethylaminoethyl*-N-*hexadecylaniline*.—In the same way N-2-*diethylaminoethyl*-N-*hexadecylaniline* was obtained in 50·5% yield as a colourless liquid, b. p. 238—244°/1·8 mm. and b. p. 239—242°/1·8 mm. on redistillation (Found: N, 6·9. $C_{28}H_{52}N_2$ requires N, 6·7%). Its *Reineckate* crystallised from methanol in red prisms, m. p. 135—136° (Found: N, 15·2. $C_{32}H_{59}N_8S_4Cr$ requires N, 15·2%). Chlorination of this material (20·8 g.) and fractionation of the product gave the dichloro-derivative as a colourless oil (9·6 g.), b. p. 246—250°/0·8 mm. It was purified as the *Reineckate*, red plates (from methanol), m. p. 131—132° (Found: C, 48·0; H, 7·2; N, 13·6; Cl, 8·4. $C_{32}H_{57}N_8Cl_2S_4Cr$ requires C, 47·8; H, 7·1; N, 13·9; Cl, 8·8%), and converted as above into the hydrochloride for testing.

N-2′-*Diethylaminoethyl*-1- and -2-*naphthylamines*.—Condensation of 1-naphthylamine (72 g.) and diethylaminoethyl chloride hydrochloride (86 g.) in the usual way afforded *N*-2′-diethylaminoethyl-1-naphthylamine as a colourless liquid (60·7 g.), b. p. 160—162°/0·8 mm. (Stahmann and Cope, *loc. cit.*, record b. p. 156—157°/1 mm.). Its *dipicrate* crystallised from ethanol in red prisms, m. p. 154—155° (Found: N, 16·3. $C_{28}H_{28}O_{14}N_8$ requires N, 16·0%). Its *dihydrochloride* separated from chloroform in tacky crystals, m. p. <100°, probably containing chloroform of crystallisation. Trituration with hot acetone yielded colourless crystals, m. p. 158—160° (Found: N, 9·2. $C_{16}H_{24}N_2Cl_2$ requires N, 8·9%). It gave a solution of low pH which could be adjusted to pH 5 without precipitation of the base. *N*-2′-Diethylaminoethyl-2-naphthylamine was prepared in similar yield as a colourless liquid with a strong blue fluorescence, b. p. 195°/3·5 mm. Its *monopicrate* separated from ethanol or acetic acid in yellow prisms, m. p. 152—153° (Found: N, 14·7. $C_{22}H_{25}O_7N_5$ requires N, 14·8%). For test the picrate was reconverted into the free base and dissolved in one equivalent of N-sulphuric acid. Attempted chlorination of both of these bases led to extensive decomposition and tar formation.

Diethyl-2-*benzoylethylammonium Chloride*.—Following the directions of Blicke and Burckhalter (*loc. cit.*), acetophenone (12 g.), diethylammonium chloride (11 g.), and paraformaldehyde (3·6 g.) were heated under reflux in absolute ethanol (20 c.c.) for 3 hours. The solution was filtered, the ethanol removed *in vacuo*, and the residue dissolved in water (50 c.c.). The free base was isolated by basification and extraction with ether. The ethereal solution was evaporated *in vacuo* and the residual oil kept over sulphuric acid *in vacuo* for 2 days to remove traces of diethylamine. (Failure to do this gave a low-melting final product very difficult to purify.) The oil was redissolved in ether, and the solution saturated with dry hydrogen chloride. The precipitated hydrochloride crystallised from acetone in needles (8·25 g.), m. p. 112—113° (Found: N, 5·85. Calc. for $C_{13}H_{20}ONCl$: N, 5·8%) (Blicke and Burckhalter, *loc. cit.*, give m. p. 108—110°).

In one experiment in which the aqueous solution was made just alkaline to Brilliant-yellow with aqueous sodium carbonate before extraction with ether, the aqueous layer subsequently deposited needles (7·6 g.), m. p. *ca.* 150°. Repeated crystallisation from methanol–ether and from water afforded a *substance*, probably diethyl-(2 : 4-dibenzoylbutyl)ammonium chloride, m. p. 193—194° after drying at 100° (Found: C, 70·5; H, 7·5; N, 3·8. $C_{22}H_{28}O_2NCl$ requires C, 70·6; H, 7·5; N, 3·75%).

Diethyl-3-*phenylpropylammonium Chloride*.—Diethyl-2-benzoylethylammonium chloride (9·6 g.) was hydrogenated with palladised charcoal (10%; 4 g.). Hydrogenation was rapid at 50°/atmospheric pressure, nearly the theoretical for 2 moles of hydrogen being absorbed. The catalyst was filtered off and the ethanol removed *in vacuo*. The residue, which partly crystallised, was triturated with acetone, and the crystals were separated. Crystallisation from acetone afforded diethyl-3-phenylpropyl-ammonium chloride as non-hygroscopic colourless plates (3·2 g.), m. p. 117—118° (Found: N, 6·3. Calc. for $C_{13}H_{22}NCl$: N, 6·15%) (Mannich and Chang, *Ber.*, 1933, **66**, *B*, 418, describe it as a hygroscopic substance, m. p. 119—120°). The free base had b. p. 118°/13 mm. (Found: N, 7·55. Calc. for $C_{13}H_{21}N$: N, 7·3%) (von Braun, *Ber.*, 1910, **43**, 3217, records b. p. 137—139°/22 mm.).

Attempted Reaction between 2 : 4 : 6-*Trichlorophenylmagnesium Bromide and* 2-*Diethylaminoethyl Cyanide*.—A Grignard solution was prepared from 1 : 3 : 5-trichloro-2-iodobenzene (3·95 g., 1 mol.; prepared by the method of Hodgson and Mahadevan, *loc. cit.*) and magnesium (0·42 g., 1¼ mols.) in ether (50 c.c.), with ethyl bromide (0·5 g., ⅛ mol.) as entrainer. A solution of 2-diethylaminoethyl cyanide (2·1 g., 1⅛ mols.) was then added and the mixture refluxed for 30 minutes. After decomposition with ice and hydrochloric acid, the ethereal layer afforded 1 : 3 : 5-trichlorobenzene (2·2 g., 91%), m. p. 60° undepressed by admixture with authentic 1 : 3 : 5-trichlorobenzene, indicating at least 91% formation of trichlorophenylmagnesium iodide and practically no reaction of the latter with the diethylaminoethyl cyanide. The acid layer yielded only small quantities of basic ketonic material. Similar results were obtained when refluxing was continued for 24 hours or when the reaction was carried out in boiling

toluene or anisole. In the latter solvent some 2 : 2′ : 4 : 4′ : 6 : 6′-hexachlorodiphenyl, plates (from acetic acid), m. p. 112·5°, was isolated.

2 : 4 : 6- *and* 2 : 3 : 5-*Trichloroacetophenone.*—2 : 4 : 6-Trichlorophenyl cyanide (Meyer and Sudborough, *Ber.*, 1894, **27**, 3152) failed to react with methylmagnesium iodide in ether or anisole. Accordingly 2 : 4 : 6-trichlorobenzoyl chloride (11·5 g., 1 mol.) in benzene (50 c.c.) was added to a solution of dimethylcadmium (4 mols.) in benzene (prepared in the usual manner from methylmagnesium bromide and cadmium chloride). The mixture was heated under reflux for 3 hours and then decomposed with ice and hydrochloric acid, and the benzene layer washed with water, dried (Na_2SO_4), and concentrated. Fractionation of the residue afforded 2 : 4 : 6-*trichloroacetophenone* as a colourless liquid (6·8 g., 65%), b. p. 138—142°/7 mm., which quickly solidified and then had m. p. 60° (Found: C, 42·6; H, 2·6. $C_8H_5OCl_3$ requires C, 43·0; H, 2·2%). The substance did not form a 2 : 4-dinitrophenylhydrazone. Attempted condensation with dimethylammonium chloride and paraformaldehyde in acetic acid (Mannich and Dannehl, *Arch. Pharm.*, 1938, **276**, 206), *iso*amyl alcohol (Kamp and Mossettig, *J. Amer. Chem. Soc.*, 1936, **58**, 1568), or nitrobenzene (Fry, *J. Org. Chem.*, 1945, **10**, 259) failed to yield any Mannich base, and 2 : 4 : 6-trichloroacetophenone was recovered unchanged. 2 : 3 : 5-Trichloroacetophenone, b. p. 120°/1 mm. (Found: C, 44·0; H, 2·8. $C_8H_5OCl_3$ requires C, 43·0; H, 2·3%), was prepared similarly in poor yield (20%), the major product being a *substance*, needles (from chloroform), m. p. 230° (Found: C, 41·6; H, 1·8%).

Diethyl-2-(m-aminobenzoyl)ethylammonium Chloride.—*m*-Aminoacetophenone (95·5 g.) and benzoic anhydride (160 g.) were heated at 100° for 20 minutes. The crude product was boiled with successive quantities of 3% aqueous sodium carbonate until the supernatant solution no longer gave a precipitate of benzoic acid on acidification. The residue was washed with water, dried, and crystallised from light petroleum (b. p. 80—100°), affording *m*-benzamidoacetophenone as needles, m. p. 108° (170 g.). This was stirred with diethylammonium chloride (85·7 g., 1·1 mols.), paraformaldehyde (32 g., 1·5 mols.), and concentrated hydrochloric acid (2 c.c.) in a mixture of benzene (300 c.c.) and nitrobenzene (300 c.c.) (cf. Fry, *loc. cit.*) and heated for 2 hours (oil-bath, 110—115°). A water-entrainer was now incorporated in the apparatus, the oil-bath heated to 145—150°, and water (29 c.c.) collected during 1 hour. The mixture on cooling deposited a thick crop of needles. Recrystallisation from absolute ethanol afforded *diethyl-2-(m-benzamidobenzoyl)ethylammonium chloride* (154·5 g.) as needles, m. p. 142° (Found: N, 7·6. $C_{20}H_{25}O_2N_2Cl$ requires N, 7·8%). Evaporation of the benzene–nitrobenzene mother-liquor and crystallisation of the residue from ethanol–ether gave a further crop (14·5 g.), m. p. 137—138°. The combined crops (169 g.) were heated under reflux for 6 hours with concentrated hydrochloric acid (1400 c.c.). The solution was cooled and the benzoic acid filtered off. The filtrate was extracted with ether and concentrated *in vacuo* to 150 c.c. On cooling, *diethyl-2-(m-aminobenzoyl)ethylammonium chloride* separated in needles (100·5 g.), m. p. 185° unaltered by further crystallisation (Found: N, 9·5. $C_{13}H_{22}ON_2Cl_2$ requires N, 9·5%). A further crop (19 g., m. p. 183—184°) was obtained by evaporation of the mother-liquor *in vacuo* to dryness and crystallisation of the residue from ethanol. Attempted chlorination of this product led in all cases to non-basic gums.

2-*Diethylaminoethyl* 2 : 4 : 6-*Trichlorobenzoate Hydrochloride.*—2 : 4 : 6-Trichlorobenzoyl chloride (3 g.) (Sudborough, *J.*, 1894, **65**, 1030; 1895, **67**, 602) was added to diethylaminoethanol (1·6 g.) in pure chloroform (8 c.c.) and, after 3 hours at room temperature, the mixture was warmed to 40° for 7 hours. Precipitation with ether and fractional crystallisation of the crystalline product from benzene–ethanol afforded two compounds. The first, m. p. 133—134·5° (Found: N, 10·3. Calc. for $C_6H_{14}NCl$: N, 10·3%), afforded an aurichloride, plates (from hot water), m. p. 138°. Ladenburg (*loc. cit.*) records no properties for diethylvinylammonium chloride but states that the aurichloride has m. p. 138—140°. The compound is therefore distinct from the normal polymerisation product of diethylaminoethyl chloride, tetraethylpiperazinium dichloride, which has the same empirical formula but does not melt below 300° and gives a diaurichloride of m. p. 236—237° (Slotta and Behnisch, *Annalen*, 1932, **497**, 170). The second compound was dissolved in water and then basified with aqueous sodium hydroxide, and the resultant oil isolated with ether. Reconversion into the hydrochloride gave 2-*diethylaminoethyl* 2 : 4 : 6-*trichlorobenzoate hydrochloride* (0·3 g.), needles (from ethanol–ether), m. p. 193° (Found: N, 4·15. $C_{13}H_{17}O_2NCl_4$ requires N, 3·9%).

2-*Diethylaminoethyl* 2 : 3 : 5-*Tri-iodobenzoate Hydrochloride.*—2 : 3 : 5-Tri-iodobenzoic acid (5·0 g.) (Wheeler and Johns, *Amer. Chem. J.*, 1910, **43**, 407) was refluxed with thionyl chloride (3 c.c.) and benzene (15 c.c.) until a clear solution was obtained. The benzene and excess of thionyl chloride were evaporated *in vacuo*, the yellow crystalline residue was dissolved in pure chloroform (15 c.c.), and 2-diethylaminoethanol (1·3 g., 10% excess) added. Cooling overnight in the ice-chest gave 2-*diethylaminoethyl* 2 : 3 : 5-*tri-iodobenzoate hydrochloride* as a pale yellow solid (4·2 g.), m. p. *ca.* 180° after softening at 165°. Recrystallisation from chloroform–acetone and finally from ethanol gave the substance as colourless prisms (2·35 g.), m. p. 184—185° (Found: N, 2·4. $C_{13}H_{17}O_2NCII_3$ requires N, 2·2%).

2 : 4 : 6-*Trichlorophenyl Diethylaminoacetate Hydrochloride.*—(a) *Attempted preparation from* 2 : 4 : 6-*trichlorophenyl chloroacetate.* 2 : 4 : 6-Trichlorophenol (9·9 g.) was heated at 100° with excess of chloroacetyl chloride for 48 hours. Evolution of hydrogen chloride was slow and evidently incomplete. The mixture was poured into water and made faintly alkaline to Brilliant-yellow, and the solid filtered off. Recrystallisation from methanol gave 2 : 4 : 6-*trichlorophenyl chloroacetate* (3·8 g.), m. p. 69—70° unchanged by further crystallisation (Found: C, 34·6; H, 1·6. $C_8H_4O_2Cl_4$ requires C, 35·0; H, 1·5%). This substance (1·28 g.) was dissolved in dry ether (15 c.c.), and diethylamine (1·0 c.c.) added. Large prisms soon separated. The product (0·80 g.) recrystallised from ethanol in prisms, m. p. 157—159° (Found: N, 5·2. $C_{10}H_{14}ONCl_3$ requires N, 5·2%). It dissolved in dilute alkali to give free diethylamine and, on acidification, trichlorophenol. It was therefore *diethylammonium* 2 : 4 : 6-*trichlorophenoxide.*

(b) *From diethylaminoacetyl chloride and* 2 : 4 : 6-*trichlorophenol.* Chloroacetic acid (94·5 g., 1 mol.) was mixed with crushed ice, and diethylamine (219 g., 3 mols.) added portion-wise. The mixture was set aside at room temperature for 60 hours. It was then evaporated on the steam-bath after the addition of 5N-sodium hydroxide (400 c.c., 2 mol.-equivs.) until the smell of diethylamine had disappeared. The solution was then made strongly acid to Congo-red and evaporated to a thick syrup. The syrup was

taken up in ethanol, filtered from sodium chloride, and again evaporated. The residue partly crystallised on storage in a desiccator over sulphuric acid. Oil was removed by trituration with methanol–acetone (1 : 4). The residue (61 g.) was extracted with methanol (50 c.c.) and filtered. Dilution of the filtrate with acetone (200 c.c.) gave *diethylaminoacetic acid hydrochloride* (32 g.) as large prisms, m. p. 125—126°. A further crop (7·0 g.; m. p. 125—126°) was obtained by re-extraction of the insoluble residue with methanol (15 c.c.) and precipitation with acetone (60 c.c.). The material so obtained was slightly hygroscopic. Recrystallisation from methanol–acetone gave non-hygroscopic material, m. p. 125—126° (Found : N, 8·35. $C_6H_{14}O_2NCl$ requires N, 8·35%).

The foregoing salt (3·0 g.) was finely ground, dried at 100°, and refluxed with thionyl chloride (2 c.c.) in dry chloroform (15 c.c.) until the solid just dissolved (20 minutes). Chloroform and excess of thionyl chloride were removed *in vacuo*, the residual light-brown solid redissolved in chloroform, and 2 : 4 : 6-trichlorophenol (2·5 g.) added. The solution was cooled in ice-water, and pyridine (2 c.c.) added dropwise. After 4 hours, the chloroform was removed *in vacuo*, and the residue dissolved in water (10 c.c.) and acidified to pH 2 with concentrated hydrochloric acid. Unchanged trichlorophenol was extracted with ether, the aqueous layer basified with solid sodium hydrogen carbonate to pH 8—9, and the resulting oil isolated with ether. After removal of the last traces of pyridine *in vacuo* over sulphuric acid, the residual dark-red mobile liquid was dissolved in ether, and a slight excess of ethanolic hydrogen chloride added. The resulting 2 : 4 : 6-*trichlorophenyl diethylaminoacetate hydrochloride* (3·3 g.) crystallised from acetone in colourless prisms, m. p. 148° (decomp.) (Found : N, 4·2. $C_{12}H_{15}O_2NCl_4$ requires N, 4·0%).

Phenyl p-*Aminobenzyl Ether Hydrochloride*.—Phenyl *p*-nitrobenzyl ether (4 g.; m. p. 94—95°) (Kumpf, *Annalen*, 1884, **224**, 104, gives m. p. 91°), dissolved in wet ether (80 c.c.), was reduced with amalgamated aluminium (4 g.), water (12 c.c.) being added portion-wise at such a rate as to maintain vigorous reaction. After 24 hours, the ether was filtered from the sludge of alumina, and the product precipitated as the hydrochloride by the addition of ethanolic hydrogen chloride (5 c.c. of 4·5N.). The crude product (4 g.) decomposed on attempted crystallisation from methanol, phenol being liberated. It was therefore shaken with ether and excess of dilute aqueous sodium hydroxide, the ether evaporated, and the residue (2·4 g.) crystallised from benzene–light petroleum. *Phenyl* p-*aminobenzyl ether* separated in needles (1·62 g.), m. p. 78—78·5° (Found : N, 7·2. $C_{13}H_{13}ON$ requires N, 7·0%). Precipitation of its ethereal solution with ethanolic hydrogen chloride gave the *hydrochloride* as a white powder, m. p. 140—145° (decomp.) (Found : N, 5·85. $C_{13}H_{14}ONCl$ requires N, 5·9%). It dissolved in water to give a slightly turbid solution which developed the smell of phenol when kept. Other methods of reduction of the nitro-compound, *e.g.*, neutral iron, stannous chloride, or ammoniacal ferrous sulphate, caused fission of the molecule.

1-*Phenoxy*-2-p-*aminophenoxyethane*.—1-Phenoxy-2-*p*-nitrophenoxyethane was prepared by the condensation of potassium *p*-nitrophenoxide (45 g.) and 2-phenoxyethyl bromide (50·8 g.) in boiling butanol (228 c.c.) for 40 hours. The reaction mixture was filtered hot. The product (53 g.) separated, on cooling, in needles, m. p. 87—88°. A sample recrystallised from ethanol to constant m. p. had m. p. 90° (Found : N, 5·4. Calc. for $C_{14}H_{13}O_4N$: N, 5·4%). Ryan and Kenny (*loc. cit.*) give m. p. 86°. The nitro-compound (53 g.) was heated under reflux for 24 hours with a solution of hydrated sodium sulphide (98·5 g.) and sulphur (13·1 g.) in 50% ethanol (103 c.c.). The solid which separated on cooling was filtered off, washed, and dissolved in warm benzene (400 c.c.). The benzene solution was washed first with water and then shaken with 5N-hydrochloric acid (100 c.c.), and the insoluble 1-*phenoxy*-2-p-*aminophenoxyethane hydrochloride* (46 g.; m. p. 206—208°) filtered off and washed with benzene. Recrystallisation from dilute hydrochloric acid gave the pure substance as needles, m. p. 210° (Found : N, 5·6. $C_{14}H_{16}O_2NCl$ requires N, 5·3%). The free *base* (39 g.) was obtained by warming the crude hydrochloride with a mixture of benzene (500 c.c.) and N-sodium carbonate solution (550 c.c.) until all went into solution, separating the benzene layer, and evaporating it *in vacuo*. A portion, crystallised twice from ethanol, had m. p. 109—110° (Found : N, 6·55. $C_{14}H_{15}O_2N$ requires N, 6·1%). The *hemipicrate* crystallised from benzene in yellow plates, m. p. 158° (Found : N, 10·2. $C_{34}H_{33}O_{11}N_5$ requires N, 10·2%).

1-*Phenoxy*-2-p-*diethylaminophenoxyethane*.—The foregoing base (5·25 g.) was heated and stirred under reflux with acetone (100 c.c.), ethyl iodide (4·1 c.c., 2·1 mols.), and potassium carbonate (6·4 g.) for 20 hours. The acetone was evaporated, water added to the residue, and the oil extraced with ether. The ethereal extract was filtered from flocculent, insoluble material, dried (Na_2SO_4), and evaporated. The residual oil (5·7 g.), which partly solidified when kept, was dissolved in a hot solution of picric acid (5·7 g.) in ethanol (100 c.c.). On cooling, 1-*phenoxy*-2-(p-*diethylaminophenoxy*)*ethane picrate* (8·25 g.) separated in yellow plates, m. p. 135—137° raised to 137—138° by recrystallisation (Found : C, 55·5; H, 5·5; N, 11·1. $C_{24}H_{26}O_9N_4$ requires C, 56·1; H, 5·1; N, 10·9%). This was shaken with aqueous lithium hydroxide and ether, and the ethereal solution separated and evaporated. The residual oil (4·3 g.), crystallised from methanol (10 c.c.) at 0°, furnished the free *base*, m. p. 40—41° (Found : N, 5·05. $C_{18}H_{23}O_2N$ requires N, 4·9%). For test the substance was dissolved in an equivalent of dilute hydrochloric acid to give a solution of pH 5.

1-(2 : 4 : 6-*Trichlorophenoxy*)-2-p-*aminophenoxyethane*.—2 : 4 : 6-Trichlorophenol (15 g.) was dissolved in ethanol (100 c.c.), and a solution of sodium hydroxide (3·1 g.) in water (10 c.c.) added. The solution was then heated under reflux with ethylene dibromide (30 g.) for 30 hours. The ethanol was evaporated *in vacuo*, and the crystalline residue isolated with ether and distilled. 2-(2 : 4 : 6-*Trichlorophenoxy*)*ethyl bromide* was obtained as a colourless liquid (15·4 g.), b. p. 184—185°/3 mm., which soon solidified. Crystallisation of a small portion from ethanol afforded long needles, m. p. 49—50° (Found : C, 31·6; H, 2·2. $C_8H_6OCl_3Br$ requires C, 31·5; H, 2·0%).

The foregoing compound (14·8 g.) was added to a suspension of sodium *p*-nitrophenoxide formed by adding sodium hydroxide (2·0 g.) in water (5 c.c.) to a solution of *p*-nitrophenol (6·8 g.) in ethanol (100 c.c.). The mixture was heated under reflux for 20 hours, only a part of the solid having by then dissolved. The ethanol was evaporated *in vacuo* and the residue extracted with benzene. The benzene extract was shaken with dilute sodium hydroxide and evaporated, the residue solidifying on cooling. Crystallisation from ethanol (50 c.c.) afforded crude 1-(2 : 4 : 6-*trichlorophenoxy*)-2-p-*nitrophenoxyethane* (10·4 g.), m. p.

80—100°, contaminated with unchanged trichlorophenoxyethyl bromide. Recrystallisation of a small portion from methanol gave needles, m. p. 116—116·5° (Found: N, 4·4. $C_{14}H_{10}O_4NCl_3$ requires N, 3·9%). The crude product (8·5 g.) was reduced as previously with amalgamated aluminium (8·5 g.) in ether (340 c.c.), and ethanolic hydrogen chloride added to the ethereal filtrate. The precipitated crude hydrochloride was reconverted into the free base. Crystallisation from light petroleum–benzene gave 1-(2 : 4 : 6-*trichlorophenoxy*)-2-p-*aminophenoxyethane* (2·6 g.) as needles, m. p. 77—78° (Found: N, 4·3. $C_{14}H_{12}O_2NCl_3$ requires N, 4·2%). The *hydrochloride* crystallised from 2N-hydrochloric acid or methanol in rosettes of needles, m. p. 237—239° (Found: N, 3·7. $C_{14}H_{13}O_2NCl_4$ requires N, 3·8%). The *lactate* similarly crystallised from aqueous lactic acid in needles, m. p. 143—144° (Found: N, 3·5. $C_{17}H_{18}O_5NCl_3$ requires N, 3·3%).

Both salts were largely hydrolysed in solution, giving turbid solutions of pH 2 which deposited free base on cooling.

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