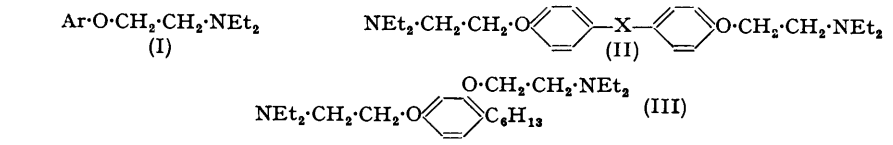
726. *Antituberculous Compounds. Part VIII.* Phenolic 2-Diethylaminoethyl Ethers and Analogues.*

By J. L. Lowe, D. A. Peak, and T. I. Watkins.

The observation by Chapman, Hager, and Shay (*J. Amer. Pharm. Assoc.*, 1947, **36**, 78) of the high activity, *in vitro*, of the bisdiethylaminoethyl ethers of stilbœstrol and hexylresorcinol has been extended by the preparation of a number of analogous bis- and mono-diethylaminoethyl ethers. Considerable simplification of the molecule is possible without loss of activity *in vitro*. As with the compounds examined by Chapman *et al.*, no activity *in vivo* could be observed.

Quinol monodiethylaminoethyl ether undergoes a novel type of disproportionation to quinol and the bis-ether.

In Part I of this series (*J.*, 1949, 2680) it was noted that several 2-aryloxyethyldiethylamines (I) possessed appreciable activity *in vitro* against *Mycobacterium tuberculosis*. This activity was in most cases augmented by substitution of chlorine in the aryl group but this increase was seldom maintained in the presence of serum. The observation by Chapman *et al.* (*loc. cit.*) of



(I) (II) (III)

the high activity, *in vitro*, of 3 : 4-bis-*p*-2′-diethylaminoethoxyphenylhex-3-ene (bisdiethylaminoethyl ether of stilbœstrol) (II; X = CEt:CEt) and 1 : 3-bis-2′-diethylaminoethoxy-4-hexylbenzene (bisdiethylaminoethyl ether of hexylresorcinol) (III) suggested that two diethylaminoethoxy-groups might be necessary for the development of maximum activity in this type of compound. These two compounds were therefore prepared for examination, as well as the analogous hexœstrol ether (II; X = CHEt·CHEt). The high activities of these compounds *in vitro* were confirmed (see table) but, as already reported (Croshaw and Dickinson, *Brit. J. Pharm.*, 1950, **5**, 178), no activity could be detected *in vivo* for either the hexylresorcinol or the hexœstrol ether, the latter being chosen in preference to the stilbœstrol ether because of its slightly lower toxicity. This accords with the results in a later publication by Shay *et al.* (*J. Amer. Pharm. Assoc.*, 1948, **37**, 486). The present communication describes a number of related compounds, prepared for the purpose of elucidating the structural features governing activity and in the hope of obtaining a chemotherapeutically effective compound. Data concerning the compounds prepared are summarised in the accompanying table, together with their activities *in vitro*. Compounds were tested in all cases as their soluble hydrochlorides, directly prepared where necessary in solution from the free bases or from their derivatives.

Introduction of iodine into the hexœstrol ether (II; X = CHEt·CHEt) gave a tetraiodo-derivative of reduced activity, even with due allowance for the increased molecular weight. The occasional dyschemotherapeutic effect of halogen has already been noted in Part I (*loc. cit.*).

(IV) (V)

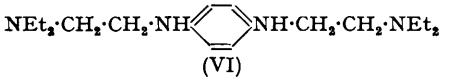
The simpler compounds, 4 : 4′-bis-2″-diethylaminoethoxydiphenyl and *p*-bis-2-diethylaminoethoxybenzene (quinol bisdiethylaminoethyl ether) (IV; R = H), showed the same high order of activity, particularly the latter, although again no activity could be detected *in vivo* (Croshaw and Dickinson, *loc. cit.*). That activity did not depend solely on the spatial separation of the two basic centres was shown by the inactivity of bis-*p*-2-diethylaminoethoxyphenyl sulphone (II; X = SO_2), a result in agreement with that of Shay *et al.* (*loc. cit.*). Further, the open-chain analogues, 1 : 8-bis-2′-diethylaminoethoxyoctane and bis-2-diethylaminoethyl ether were also inactive. The latter compound was first obtained as a by-product from the preparation

* Part VII, *J.*, 1951, 485.

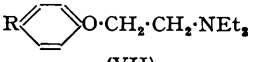
of 1-2′-diethylaminoethoxy-4-ethoxybenzene (V; R = Et) but was obtained in better yield by the reaction of sodium diethylaminoethoxide with diethylaminoethyl chloride.

In contrast to *p*-bis-2-diethylaminoethoxybenzene, the corresponding resorcinol and catechol derivatives were virtually inactive. Since the introduction of a hexyl group into the resorcinol derivative converts it into the highly active 1 : 3-bis-2′-diethylaminoethoxy-4-hexylbenzene (4-hexylresorcinol bis-2-diethylaminoethyl ether) (III), it was thought that similar introduction of a hexyl group into the already active quinol compound (IV; R = H) might lead to a compound of exceptional activity. 2-Hexanoyl-1 : 4-dimethoxybenzene (hexanoylquinol dimethyl ether) was prepared by a modification of the method described by Cruickshank and Robinson (*J.*, 1938, 2066) for the preparation of 2-hydroxy-5-methoxyvalerophenone. It is noteworthy that in this case no demethylation of the quinol dimethyl ether occurred. This is probably due to the temperature of reaction, which in our case did not exceed room temperature, whereas Cruickshank and Robinson do not specify their final reaction temperature. Clemmensen reduction of the hexanoyl compound caused extensive resinification but there was successful reduction to 2-hexyl-1 : 4-dimethoxybenzene (hexylquinol dimethyl ether) by the Kishner method (cf. Nagami, *Ber.*, 1935, **68**, 1500). Demethylation and alkylation with diethylaminoethyl chloride gave the required 1 : 4-bis-2′-diethylaminoethoxy-2-hexylbenzene (2-hexylquinol bis-2-diethylaminoethyl ether) (IV; R = C_6H_{13}) which, however, proved to be less active than the unsubstituted compound (IV; R = H).

p-Bis-2-diethylaminoethylaminobenzene (VI), the nitrogen analogue of compound (IV; R = H), was prepared by alkylation of *NN*′-diformyl-*p*-phenylenediamine with diethylaminoethyl chloride and hydrolysis of the product. It proved to be of low activity.



(VI)



(VII)

A series of 4-alkoxy-1-2′-diethylaminoethoxybenzenes (V; R = alkyl) was next examined. The first method of preparation attempted was the alkylation of *p*-2-diethylaminoethoxyphenol (quinol mono-2-diethylaminoethyl ether) (V; R = H) in ethanolic sodium ethoxide with an excess of the alkyl halide. The main non-acidic products were *p*-dimethoxybenzene (quinol dimethyl ether) with methyl iodide, *p*-diethoxybenzene (quinol diethyl ether) with ethyl iodide, and *p*-bis-2-diethylaminoethoxybenzene (IV; R = H) with hexyl bromide. The formation of these products can be explained only by the assumption that the *p*-2-diethylaminoethoxyphenol undergoes disproportionation into the bis-ether and quinol. In the first two cases, the quinol has been dialkylated while the bis-ether has been lost as a water-soluble quaternary salt formed with the excess of alkyl iodide. In the third case, the much slower rate of quaternisation and alkylation by hexyl bromide (Menschutkin, *Z. physikal. Chem.*, 1890, **5**, 589) has permitted the isolation of the bis-ether as the sole basic product. The yield of bis-ether in this case corresponded to a 90% disproportionation. In the other two cases the yields of quinol dialkyl ethers correspond to a 75% and 96% disproportionation respectively. Under the same conditions, in the absence of an alkylating agent, an amount of the bis-ether corresponding to a 45% disproportionation was isolated. The disproportionation is not reversible since, when an equimolecular mixture of the bis-ether and quinol was treated under the same conditions, a careful examination of the product failed to reveal any of the mono-ether.

The mechanism of the disproportionation has not been investigated, but it clearly involves the diethylamino-group since no such disproportionation could be detected with simple monoalkyl ethers of quinol. No close analogies of this facile trans-etherification appear to exist. Ipatieff and Burwell (*J. Amer. Chem. Soc.*, 1941, **63**, 969) have observed the interconversion of simple and mixed ethers but only under conditions of high-temperature catalysis. Other examples of trans-etherification, *e.g.*, of ethyl ββ-diethoxypropionate and ethyl αα-diethoxysuccinate with alcohols (Croxall *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 2736, 2741; 1950, **72**, 4274) and of alkyl β-alkoxypropionates with higher alcohols in the presence of sodium methoxide (Seeger, U.S.P. 2,293,000), are not analogous because of the special molecular environment of the ether groups in these cases.

The alternative route from the quinol monoalkyl ether and diethylaminoethyl chloride proved more successful. The usual conditions of condensation in boiling ethanol gave poor results, but condensation at room temperature in aqueous sodium hydroxide solution afforded satisfactory yields. The methoxy- and ethoxy-compounds (V; R = Me and Et, respectively) were of low activity but in the case of the butoxy- and the octyloxy-compound (V; R = C_4H_9 and C_8H_{17}, respectively) activity was restored to a level comparable with that of

p-bis-2-diethylaminoethoxybenzene. The second diethylaminoethyl group seems therefore to be exerting only a mass effect equally well provided by a simple alkyl group. Both diethylaminoethyl groups cannot be replaced, since *p*-dihexyloxybenzene (quinol dihexyl ether) is of very low activity.

Confirmation of this effect was found in a series of 4-alkyl-1-2′-diethylaminoethoxybenzenes (VII; R = Me, Pr, and C_6H_{13}, respectively), where the hexyl compound was highly active. 3 : 5-Dichloro-4-2′-diethylaminoethoxytoluene, 3 : 5-dichloro-2-2′-diethylaminoethoxytoluene, and 2 : 6-dichloro-1-2′-diethylaminoethoxy-4-hexylbenzene were also prepared. The last compound provided a further example of the occasional dyschemotherapeutic effect of chlorine.

Finally, a branched-chain analogue of compound (VII; R = C_6H_{13}) was prepared by reaction of *p*-2-diethylaminoethoxypropiophenone (VII; R = EtCO) with propylmagnesium bromide to give 1-2′-diethylaminoethoxy-4-(1-ethyl-1-hydroxy-*n*-butyl)benzene [VII; R = EtPrC(OH)] and dehydrating this to the unsaturated compound in which the position of the ethylenic linkage was not determined. Catalytic reduction afforded 1-2′-diethylaminoethoxy-4-(1-ethyl-*n*-butyl)benzene (VII; R = CHEtPr). This compound, which contains the partial skeleton of the hexœstrol ether (II; X = CHEt·CHEt), although highly active in the absence of serum, was almost inactivated by its presence; comparison with the isomeric compound (VII; R = C_6H_{13}) provides a further example of the unpredictability of the serum effect. The intermediate compound [VII; R = EtPrC(OH)] was less affected but no activity could be observed *in vivo* (Croshaw and Dickinson, *loc. cit.*).

Experimental.

Preparation of Phenolic Intermediates.

Known phenolic intermediates were prepared by the following methods: 4 : 4′-dihydroxydiphenyl (Hirsch, *Ber.*, 1889, **22**, 335); *p*-methoxyphenol (Robinson and Smith, *J.*, 1926, 393); *p*-ethoxy-, *p*-butoxy-, and *p*-octyloxy-phenol (Klarmann, Gatyas, and Schternov, *J. Amer. Chem. Soc.*, 1932, **54**, 298); 3 : 5-dichloro-4-hydroxytoluene (Zincke, *Annalen*, 1903, **328**, 278); 3 : 5-dichloro-2-hydroxytoluene (Claus and Riemann, *Ber.*, 1883, **16**, 1601); *p*-propylphenol (Clemmensen, *Ber.*, 1914, **47**, 53); *p*-hexylphenol (Coulthard, Marshall, and Pyman, *J.*, 1930, 280); and 2 : 6-dichloro-4-hexylphenol (U.S.P. 2,176,010), b. p. 121—125°/0·75 mm. (Found: C, 57·6; H, 6·8. Calc. for $C_{12}H_{16}OCl_2$: C, 58·3; H, 6·5%).

3 : 4-*Bis*-(4-*hydroxy*-3 : 5-*di*-*iodophenyl*)*hexane* (3 : 3′ : 5 : 5′-*Tetraiodohexœstrol*).—A solution of iodine (20·3 g., 8 atoms) in aqueous potassium iodide solution was added during 1 hour to a solution of hexœstrol (5·4 g., 1 mol.) in 0·5N-potassium hydroxide (320 c.c.). Stirring was continued for a further hour, and a little sodium hydrosulphite (dithionite) added to discharge the purplish colour of the solution. The product was isolated by salting out the potassium salt with 10N-potassium hydroxide (50 c.c.). This was filtered off, washed with 2N-potassium hydroxide, and dissolved in water, and the free *phenol* precipitated with sulphur dioxide. Crystallisation from ethyl acetate afforded the product as flat needles (10·5 g.), m. p. 239·5—240° (decomp.) (Found: C, 28·4; H, 2·3. $C_{18}H_{18}O_2I_4$ requires C, 27·9; H, 2·3%). (Prepared by Mr. P. Oxley.)

Hexylquinol.—Hexanoyl chloride (49 g.) was added to a suspension of powdered aluminium chloride (53 g., 1·1 mols.) in pure carbon disulphide (100 c.c.). The mixture was warmed on the steam-bath until all the solid had dissolved, two layers being formed. It was then cooled in a freezing-mixture, and a solution of quinol dimethyl ether (50 g., 1 mol.) in carbon disulphide (200 c.c.) was added during 1 hour with shaking. The mixture was then allowed to attain room temperature during which time hydrogen chloride was steadily evolved. After 21 hours, the dark oily complex which had separated was decomposed by pouring the mixture on dilute hydrochloric acid and ice. The solvent layer was separated, dried ($MgSO_4$), and concentrated. Distillation gave unchanged quinol dimethyl ether (25 g.; b. p. 70—72°/1 mm.) and then 2-*hexanoyl*-1 : 4-*dimethoxybenzene* (*hexanoylquinol dimethyl ether*) (38 g.; b. p. 132—134°/0·5 mm.) (Found: C, 71·4; H, 8·7. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5%). It slowly solidified to rod-like crystals, m. p. *ca.* 15°. It gave a transient blue followed by a permanent green colour with alcoholic ferric chloride. It was insoluble in sodium hydroxide solution.

A mixture of the above material (28 g.) with absolute ethanol (28 c.c.) and 82% hydrazine hydrate (14 g.) was heated under reflux for 2½ hours, and the ethanol removed *in vacuo*. The residue was heated to 150° in an oil-bath and finely powdered potassium hydroxide (56 g.) was added in one portion. Vigorous evolution of nitrogen ensued and continued for ½ hour. The temperature was then raised for a short time to 170° The cooled melt was diluted with water (75 c.c.), and the resultant oil isolated with ether. Distillation afforded 2-*hexyl*-1 : 4-*dimethoxybenzene* (2-*hexylquinol dimethyl ether*) (16·5 g.), b. p. 87—96°/0·1 mm. (mainly at 90—94°) (Found: C, 75·3; H, 9·6. $C_{14}H_{22}O_2$ requires C, 75·7; H, 9·9%).

The foregoing compound (5·25 g.) was heated under reflux for 2 hours with 48% hydrobromic acid (50 c.c.), and the resultant oil isolated with ether. Distillation of the product gave *hexylquinol* (3·18 g.), b. p. 152°/1 mm., small needles (from light petroleum–benzene), m. p. 88° (Found: C, 74·1; H, 9·9. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·3%).

p-2-*Diethylaminoethoxyphenol.*—This is a known compound (Bovet, *Arch. intern. Pharmacodyn.*, 1937, **56**, 33; Vallery-Radot, *Compt. rend. Soc. biol.*, 1943, **137**, 296) but its preparation and properties do not appear to have been described. Quinol (44 g.) was dissolved in an ice-cold solution of sodium

hydroxide (40 g.) in water (280 c.c.) under nitrogen. Diethylaminoethyl chloride (54·2 g., 1 mol.) was added, and the mixture shaken vigorously for 16 hours, and finally heated at 100° for 2 hours to complete the reaction. The solution was cooled, acidified with sulphuric acid, and unchanged quinol extracted with ether (2 × 400 c.c.). The aqueous layer was adjusted to pH 10 with sodium hydroxide, and the product isolated with ether (2 × 500 c.c.). Distillation gave *p*-2-diethylaminoethoxyphenol (43·7 g.), b. p. 161°/2 mm., m. p. 81°. Its *picrate* separated from ethanol in yellow needles, m. p. 129° (Found: C, 49·5; H, 5·1. $C_{18}H_{22}O_9N_4$ requires C, 49·3; H, 5·0%).

Disproportionation of p-2-*Diethylaminoethoxyphenol.*—(*a*) This phenol (5·23 g.) and methyl iodide (7·1 g., 2 mols.) were added to a solution of sodium (0·575 g., 1 mol.) in absolute ethanol (50 c.c.), and the mixture was heated under reflux for 48 hours. Removal of the ethanol *in vacuo*, addition of water to the residue, and extraction with ether furnished a solid (1·3 g.), m. p. 50°, identified by mixed m. p., after recrystallisation, as quinol dimethyl ether. This corresponds to a 75% disproportionation of the diethylaminoethoxyphenol. Similarly, ethyl iodide gave quinol diethyl ether (2·0 g.), m. p. 66°, corresponding to a 96% disproportionation.

(*b*) Attempted alkylation with hexyl bromide as above afforded a liquid product (3·5 g.), b. p. 174°/2 mm., identified by formation of its picrate, m. p. 183—184° (Found: N, 14·7; Calc. for $C_{30}H_{38}O_{16}N_8$: N, 14·6%), as *p*-bis-2-diethylaminoethoxybenzene (see table, compound 6). This corresponds to a 90% disproportionation.

(*c*) *p*-2-Diethylaminoethoxyphenol (10·45 g.) and a solution of sodium (1·15 g.) in absolute ethanol (50 c.c.) were heated under reflux for 16 hours. The ethanol was removed *in vacuo*, the residue dissolved in water, and the solution made strongly alkaline with sodium hydroxide. Extraction with ether yielded an oily base (3·5 g.), identified as its picrate, m. p. 183—184° undepressed by *p*-bis-2-diethylaminoethoxybenzene picrate. This corresponds to a 45% disproportionation.

Preparation of Diethylaminoethyl Derivatives.

The following general methods were used as indicated in the table.

Method A.—Sodium (1 atom for each phenolic group) was dissolved in absolute ethanol, and the phenol and diethylaminoethyl chloride (1—1·2 mols. for each phenolic group) were added. The solution was refluxed with stirring for 1—10 hours (depending on the rate of separation of sodium chloride), the ethanol removed *in vacuo*, and water added. The oil was isolated with ether and purified either by distillation or by direct conversion into the hydrochloride or other derivative.

Method B.—The phenol was dissolved in 3·5N-sodium hydroxide (2·5 equivs.) and shaken at room temperature with diethylaminoethyl chloride (3—4 mols.) for 16—60 hours. The mixture was then made strongly alkaline with sodium hydroxide and extracted with ether. The product was isolated as in method A.

Method C.—The phenol was dissolved in methanol containing sodium methoxide (1 equiv.), and benzene added. The methanol was removed azeotropically, diethylaminoethyl chloride (1 mol.) added to the benzene suspension of the sodium salt, and the mixture heated under reflux for 24 hours. The benzene solution was washed with dilute aqueous sodium hydroxide, and the product extracted into dilute hydrochloric acid. The free base, isolated with ether after basification, was purified by distillation or as a derivative.

1 : 8-*Bis*-2′-*diethylaminoethoxyoctane.*—Sodium (1·7 g.) was dissolved in diethylaminoethanol (100 c.c.), and 1 : 8-dibromo-octane (10·0 g.) added. A white precipitate formed almost immediately. The mixture was heated at 100° overnight with stirring, and filtered, and the diethylaminoethanol removed *in vacuo*. The residual oil was dissolved in ether, the solution filtered, and the product fractionated through a short Vigreux column. The crude distillate (b. p. 140—180°/2 mm.) still contained bromine and was therefore reheated with diethylaminoethanol containing dissolved sodium. Again isolated as before, the product was bromine-free but still boiled over a wide range (120—160°/2 mm.), probably owing to superheating. A middle cut gave a correct analysis for the desired compound (see table).

Bis-2-*diethylaminoethyl Ether.*—Sodium (2·3 g.) was dissolved in warm diethylaminoethanol (50 c.c.), and diethylaminoethyl chloride (16·9 g., 1·25 mols.) added. The mixture was kept at room temperature for 2 days and then heated under reflux for 2 hours. Distillation of the filtered solution gave bis-2-diethylaminoethyl ether (see table). This compound was identical (m. p. and mixed m. p. of picrate) with the by-product obtained in 16% yield during the alkylation of *p*-ethoxyphenol with diethylaminoethyl chloride by method B above.

p-*Bis*-2-*diethylaminoethylaminobenzene.*—*NN′*-Diformyl-*p*-phenylenediamine (4·1 g.) (Wundt, *Ber.*, 1878, **11**, 828) was dissolved in a mixture of acetone (100 c.c.) and methanol (10 c.c.). Diethylaminoethyl chloride (13·55 g., 4 mols.) and an excess of potassium carbonate (10 g.) were added, and the mixture was heated under reflux with stirring for 5 hours. Solvents and low-boiling components were removed up to 100°/1—2 mm., and the residual oil was hydrolysed by heating it under reflux with 5N-hydrochloric acid (30 c.c.) for 2 hours. The solution was then cooled and basified, and the oil isolated with ether. Distillation gave *p*-bis-2-diethylaminoethylaminobenzene (see table).

p-*Dihexyloxybenzene* (*Quinol Dihexyl Ether*).—Quinol (5·5 g., 1 mol.) and hexyl bromide (20·6 g., 2·5 mols.) were added to a solution of potassium hydroxide (5·6 g., 2 mols.) in ethanol (50 c.c.), and the solution was heated under reflux for 3 hours. On cooling, p-*dihexyloxybenzene* (*quinol dihexyl ether*) (8 g.; m. p. 41—43°) separated. A further small crop (0·36 g.; m. p. 36°), together with a small amount of unchanged quinol, was obtained by evaporation of the filtrate. The product crystallised from methanol in plates, m. p. 45° (Found: C, 77·7; H, 10·85. $C_{18}H_{30}O_2$ requires C, 77·7; H, 10·8%).

Compound	Activity: * in absence of serum	Activity: * in presence of 10% serum	Method and yield, %	B. p. of base	Derivative	Solvent	Crystal form	M. p.	Formula	N, % Found	N, % Reqd.
(1) 3 : 4-Bis-*p*-2′-diethylamino-ethoxyphenylhex-3-ene	100 (10,000)	100 (500)	A, 49·5	—	Dihydro-chloride	EtOAc–EtOH	Needles	236°	$C_{30}H_{48}O_2N_2Cl_2$	5·0	5·2
(2) 1 : 3-Bis-2′-diethylamino-ethoxy-4-hexylbenzene	50—100	50—100	A, 25	183—187°/0·4 mm.	—	—	—	—	$C_{24}H_{44}O_2N_2$	7·0	7·1
(3) 3 : 4-Bis-*p*-2′-diethylamino-ethoxyphenylhexane	1000 (10,000)	100 (500)	A, 46	—	*Dihydro-chloride*	EtOAc–EtOH	Needles	222	$C_{30}H_{50}O_2N_2Cl_2$	5·15	5·2
(4) 3 : 4-Bis-(4-2′-diethylamino-ethoxy-3 : 5-di-iodo-phenyl)hexane	50—100	5—10	A, 35	—	*Dihydro-chloride*	EtOH	Needles	241	$C_{30}H_{46}O_2N_2Cl_2I_4$	2·9	2·7
(5) 4 : 4′-Bis-2″-diethylamino-ethoxydiphenyl	500	10—100	A, 38·5	—	*Dihydro-chloride*	EtOAc–EtOH	Needles	235	$C_{24}H_{38}O_2N_2Cl_2$	6·0	6·1
(6) *p*-Bis-2-diethylamino-ethoxybenzene	100—500	100	B, 47	182—183°/3 mm.	Dipicrate	EtOH	Rods	184	$C_{30}H_{38}O_{16}N_8$	14·7	14·6
(7) Bis-*p*-2′-diethylamino-ethoxyphenyl sulphone	1	—	A, 29	—	*Direineckate dihydrate*	30% $COMe_2$	Needles	130 †	$C_{32}H_{54}O_6N_{14}S_9Cr_2$	17·1	17·5
					Direineckate	—	—	165 †	$C_{32}H_{50}O_4N_{14}S_9Cr_2$	18·0	18·05
(8) 1 : 8-*Bis-2′-diethylamino-ethoxyoctane*	1	—	See p. 3289	140°/3 mm.	—	—	—	—	$C_{20}H_{44}O_2N_2$	8·25	8·1
(9) *Bis-2-diethylaminoethyl ether*	<1	—	See p. 3289	85°/0·5 mm.	—	—	—	—	$C_{12}H_{28}ON_2$	12·9	13·0
					Dipicrate	EtOH	Needles	132·5	$C_{24}H_{34}O_{15}N_8$	16·9	16·6
(10) *m*-Bis-2-diethylamino-ethoxy benzene	—	<1 (1)	B, 21	178°/0·15 mm.	—	—	—	—	$C_{18}H_{32}O_2N_2$	9·35	9·1
(11) *o*-Bis-2-diethylamino-ethoxybenzene	—	1	B, 44	160°/1·5 mm.	—	—	—	—	$C_{18}H_{32}O_2N_2$	9·1	9·1
(12) 1 : 4-Bis-2′-diethylamino-ethoxy-2-hexylbenzene	—	50	B, 71·5	169°/0·3 mm.	*Dipicrate*	MeOH	Prisms	125·5	$C_{36}H_{50}O_{16}N_8$	13·45	13·2
(13) p-*Bis-2-diethylaminoethyl-aminobenzene*	5—10	5 (10)	See p. 3289	180°/1 mm.	—	—	—	—	$C_{18}H_{34}N_4$	18·1	18·3
(14) 1-2′-Diethylaminoethoxy-4-methoxybenzene	5—10	1—5	B, 29	127—130°/3 mm.	*Picrate*	EtOH	Rods	110	$C_{19}H_{24}O_9N_4$	12·6	12·4
(15) 1-2′-*Diethylaminoethoxy-4-ethoxybenzene*	5	5	B, 71	183—186°/5 mm.	—	—	—	—	$C_{14}H_{23}O_2N$	6·1	5·9
					Picrate	EtOH	Needles	77—78	$C_{20}H_{26}O_9N_4$	—	—
(16) 4-*Butoxy*-1-2′-*diethylamino-ethoxybenzene*	100	50	B, 45	128°/0·5 mm.	—	—	—	—	$C_{16}H_{27}O_2N$	5·3	5·3

(17) 1-2′-*Diethylaminoethoxy*-4-*octyloxybenzene*	100	10—50	B, 54·5	190°/1·3 mm.	—	—	—	—	$C_{20}H_{35}O_2N$	4·4	4·4
(18) p-*Dihexyloxybenzene*	—	1 (10)	See p. 3289	—	—	MeOH	Plates	45	$C_{18}H_{30}O_2$	—	—
(19) *p*-2′-Diethylaminoethoxytoluene	10	—	A, 72	—	*Hydrochloride*	EtOH–Et_2O	Fine needles	107	$C_{13}H_{22}ONCl$	5·7	5·7
(20) 3 : 5-*Dichloro*-4-2′-*diethylaminoethoxytoluene*	10	10	C, 56	114—117°/1 mm.	—	—	—	—	$C_{13}H_{19}ONCl_2$	5·3	5·1
					Picrate	C_6H_6	Needles	155—156	$C_{19}H_{22}O_8N_4Cl_2$	11·0	11·1
(21) 3 : 5-Dichloro-2-2′-diethylaminoethoxytoluene	10	10	C, 79	132—134°/2 mm.	*Hydrochloride*	EtOH	Needles	153—154	$C_{13}H_{20}ONCl_3$	4·6	4·5
(22) 1-2′-Diethylaminoethoxy-4-propylbenzene	100	10	A, 90	—	*Hydrochloride*	EtOAc–EtOH	Needles	141—142	$C_{15}H_{26}ONCl$	5·2	5·15
(23) 1-2′-*Diethylaminoethoxy*-4-*hexylbenzene*	100	100	A, 75	140°/0·5 mm.	—	—	—	—	$C_{18}H_{31}ON$	5·0	5·05
(24) 2 : 6-*Dichloro*-1-2′-*diethylaminoethoxy*-4-*hexylbenzene*	10	10	A, 61	167—171°/1 mm.	—	—	—	—	$C_{18}H_{29}ONCl_2$	4·05	4·0
(25) 4-2′-Diethylaminoethoxypropiophenone	5	—	A, 64	152°/1 mm.	*Hydrochloride*	EtOAc–EtOH	Needles	149—150	$C_{15}H_{24}O_2NCl$	5·0	4·85
(26) 1-2′-Diethylaminoethoxy-4-(1-ethyl-1-hydroxy-*n*-butyl)benzene	50—100	50	See p. 3292	—	*Hydrochloride*	EtOAc	Needles	130—131	$C_{18}H_{32}O_2NCl$	4·4	4·25
(27) 1-2′-Diethylaminoethoxy-4-(1-ethyl-*n*-but-1-enyl)benzene	1000	50—100	See p. 3292	—	*Hydrochloride*	EtOAc	Needles	144	$C_{18}H_{30}ONCl$	4·7	4·5
(28) 1-2′-Diethylaminoethoxy-4-(1-ethyl-*n*-butyl)benzene	500—1000	10	See p. 3292	—	*Hydrochloride*	$COMe_2$	Needles	157—158	$C_{18}H_{32}ONCl$	4·7	4·5

* 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) (Croshaw and Dickinson, *loc. cit.*). 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.

† With decomposition.

Notes to table.

(1) Chapman *et al.* (*loc. cit.*) record m. p. 236—237° (slight decomp.). (2) Picrate, m. p. 108—109°. Chapman *et al.* (*loc. cit.*), who use a considerable deficiency of 2-diethylaminoethyl chloride, record b. p. 220—225°/11 mm. for the base contaminated with appreciable amounts of monoether, and m. p. 108—109·5° for the picrate. (6) Found for the dipicrate: C, 46·4; H, 4·6. Calc. for $C_{30}H_{38}O_{16}N_8$: C, 47·0; H, 5·0%. Protiva, Jilek, Kolinsky, Rericha, and Urban (*Coll. Czech. Chem. Comm.*, 1948, **13**, 1326) record b. p. 178—182°/1—2 mm. for the base and m. p. 184—185° for the dipicrate. (7) Found for the *dihydrate*: H_2O, 2·7. $C_{32}H_{50}O_4N_{14}S_9Cr_2,2H_2O$ requires H_2O, 3·2%. (8) Prepared by Mr. F. F. Whitmont. (9) Found for the *dipicrate*: C, 43·0; H, 4·9. $C_{24}H_{34}O_{15}N_8$ requires C, 42·7; H, 5·0%. (10) and (11) Protiva *et al.* (*loc. cit.*) record b. p. 194—200°/5 mm. and b. p. 165—175°/1—3 mm., respectively. (14) Found: C, 50·7; H, 5·7. $C_{19}H_{24}O_9N_4$ requires C, 50·45; H, 5·3%. (20) and (21) Prepared by Mr. F. F. Whitmont. (24) Prepared by Mr. D. J. Drain. A solid hydrochloride or picrate could not be prepared. (27) Found: C, 69·4; H, 9·2. $C_{18}H_{30}ONCl$ requires C, 69·3; H, 9·6%. (28) Found: C, 68·7; H, 10·0. $C_{18}H_{32}ONCl$ requires C, 68·9; H, 10·2%.

1-2′-*Diethylaminoethoxy*-4-(1-*ethyl*-1-*hydroxy*-n-*butyl*)*benzene* (3-p-2′-*Diethylaminoethoxyphenylhexan*-2-*ol*).—A solution of *p*-2-diethylaminoethoxypropiophenone (16 g.) in anhydrous ether (50 c.c.) was added slowly to a Grignard solution prepared from magnesium turnings (1·62 g., 1·1 atoms) and propyl bromide (8·3 g., 1·1 mols.) in ether (40 c.c.). The resulting green suspension was then heated under reflux for 45 minutes, and poured into a mixture of ice and hydrochloric acid. The aqueous phase was brought nearly to neutrality with sodium hydroxide solution and then excess of solid sodium hydrogen carbonate was added. The ethereal layer was separated, and the product isolated by distillation as a colourless oil, b. p. 146—151°/0·3 mm. The crude material was probably a mixture of the carbinol and its dehydration product, since a pure hydrochloride (see table) was obtained only by repeated fractional crystallisation.

1-2′-*Diethylaminoethoxy*-4-(1-*ethyl*-n-*but*-1-*enyl*)*benzene* (3-p-2′-*Diethylaminoethoxyphenylhex*-3-*ene*).—The foregoing crude product (15 g.) was boiled under reflux with 98% formic acid (50 g.) for 45 minutes. Most of the formic acid was removed *in vacuo*, and the free base isolated with sodium hydroxide and ether. The crude product (13·5 g.; b. p. 144—148°/0·9 mm.) still contained oxygenated impurities. It was purified by redistillation over sodium (2·0 g.), and the distillate (10·8 g.; b. p. 140—142°/0·7 mm.) converted into the hydrochloride (see table).

1-2′-*Diethylaminoethoxy*-4-(1-*ethyl*-n-*butyl*)*benzene* (3-p-2′-*Diethylaminoethoxyphenylhexane*).—The foregoing unsaturated base (8·2 g.) in methanol (80 c.c.) was hydrogenated at atmospheric pressure and temperature with Raney nickel catalyst. Absorption of the theoretical amount of hydrogen was rapid. Isolated in the usual manner, the product distilled at 135°/0·5 mm. (7·3 g.) and was further purified by conversion into its hydrochloride (see table).

RESEARCH LABORATORIES, BOOTS PURE DRUG CO. LTD.,
NOTTINGHAM.

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