ANALGESICS. PART II. SOME ARYLOXYALKYL OXAALKYLAMINES

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The synthesis is described of some structures formally related to aryloxypropanolamine in which the aryl and amine residues are joined by combinations derived from glycerol and ethylene glycol.

THE syntheses of aryloxypropanolamines (I) for study as analgesics, initiated in Part I[1], is herein extended to some formally related types in which the aryl and amine residues are joined by combinations derived from glycerol and ethylene glycol.

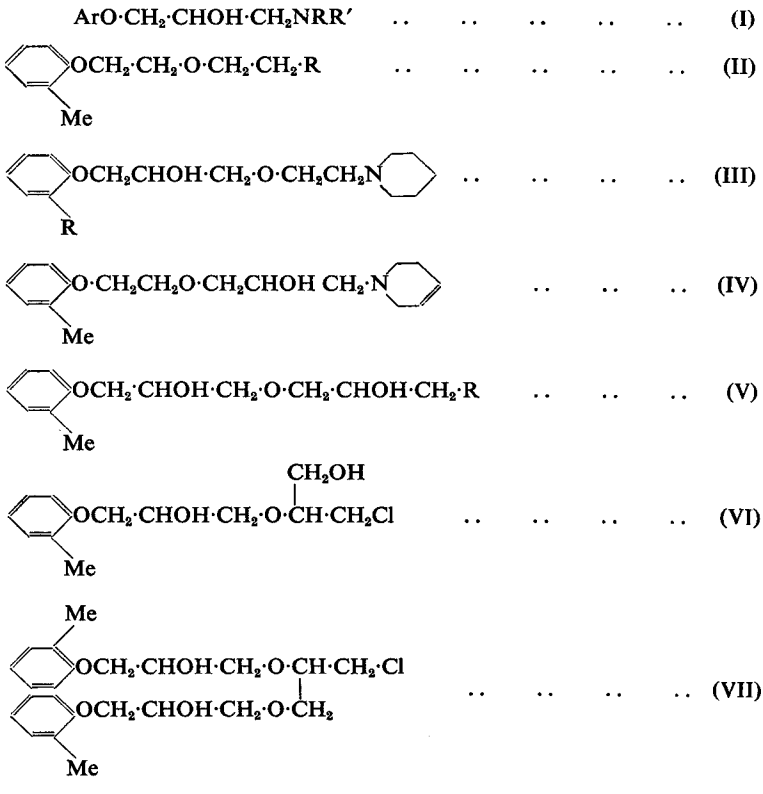
The 5-*o*-toloxy-3-oxapentylamines (II; R = NRR′) were readily prepared from 5-*o*-toloxy-3-oxapentyl chloride (II; R = Cl), in turn obtained by condensation of 2:2′-dichlorodiethyl ether with *o*-cresol. The last reaction invariably yielded some 1:5-bis-*o*-toloxy-ether (II; R = *o*-toloxy) as minor product, which was removed by fractional distillation under reduced pressure. *N*-(5-Hydroxy-6-phenoxy-3-oxahexyl)-piperidine (III; R = H) was obtained by condensing 3-phenoxy-1:2-epoxypropane with 2-hydroxyethylpiperidine in benzene solution under reflux. *N*-(5-Hydroxy-6-*o*-methoxyphenoxy-3-oxahexyl)-piperidine (III; R = OMe) was similarly prepared. The analogous *N*-(2-hydroxy-6-*o*-toloxy-4-oxahexyl)-Δ^3-piperideine (IV) was obtained by condensing 2-*o*-toloxyethanol with 2:3-epoxypropyl chloride in the presence of sodium methoxide to give 1:2-epoxy-6-*o*-toloxy-4-oxahexane, followed by reaction of the last compound with Δ^3-piperideine in benzene solution.

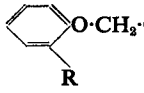
The synthesis of 2:6-dihydroxy-7-*o*-toloxy-4-oxaheptyl chloride (V; R = Cl), required for conversion to the piperidine derivative (V; R = piperidino) was next examined. Reaction of 3-*o*-toloxy-1:2-epoxypropane with 2:3-dihydroxypropyl chloride in the presence of sulphuric acid as catalyst[2] appeared to proceed normally with formation of a compound having the empirical formula of the chloride (V; R = Cl). The concomitant formation of 2-(3′-hydroxy-4′-*o*-toloxy-1-oxabutyl)-6-hydroxy-7-*o*-toloxy-4-oxaheptyl chloride (VII) as by-product, however, threw doubt upon the purity of the main product, which could well have contained some of the isomeric compound (VI). We therefore developed an unambiguous route to the piperidine derivative (V; R = piperidino). To this end 3-*o*-toloxy-1:2-epoxypropane was condensed with allyl alcohol in the presence of an acid catalyst to yield 6-hydroxy-7-*o*-toloxy-4-oxahept-1-ene (VIII; R = Me), additionally obtained by reaction between 2-hydroxy-3-*o*-toloxypropyl chloride and allyl alcohol in the presence of powdered potassium hydroxide. Epoxidation of the heptene (VIII; R = Me) with perbenzoic acid gave the epoxide (IX; R = Me) which passed smoothly into the required base (V; R = piperidino) on warming with piperidine in benzene solution. The diethylamine (V; R = NEt_2) was similarly prepared.

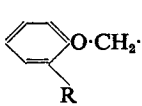
A variation on the above types resulted from the condensation of *o*- and *p*-alkoxyaniline and *o*- and *p*-alkoxy-*N*-alkylaniline with 2:6-dihydroxy-4-oxahexyl chloride when the novel amines (X) were obtained. 2:6-Dihydroxy-4-oxahexyl chloride was additionally condensed with morpholine, Δ^3-piperideine and pyrrolidine.

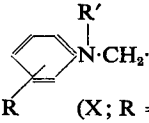
We next examined the condensation of *p*-anisidine and *p*-phenetidine with 2:6-dihydroxy-4-oxaheptyl chloride, which we had previously synthesised by the condensation of propane-1:2-diol with 2:3-epoxypropyl chloride[3]. In addition to the expected *p*-methoxy- and *p*-ethoxy-*N*-2:6-dihydroxy-4-oxaheptylaniline (XI) we obtained smaller quantities of isomeric bases formulated as *p*-methoxy- and *p*-ethoxy-*N*-2:6-dihydroxy-5-methyl-4-oxahexyl aniline (XII), which were readily separated from the isomeric compounds (XI) through their increased solubility in water. Concomitant formation of the last two compounds (XII) reveals the presence of appreciable quantities of 2:6-dihydroxy-5-methyl-4-oxahexyl chloride (XIII) in the 2:6-dihydroxy-4-oxaheptyl chloride (XIV) prepared by this route.

Finally, some unrelated derivatives based on but-2-yne were synthesised by condensing 4-phenoxy- and 4-*o*-toloxybut-2-yne chloride (XV) with diethylamine and Δ^3-piperideine to give the bases (XV*a*).

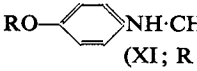



(VIII)

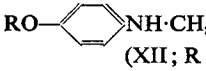

(IX)


(X)

(X; R = *o*- and *p*-alkoxy; R′ = H or lower alkyl)


(XI)

(XI; R = Me or Et)


(XII)

(XII; R = Me or Et)

$Cl{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2O{\cdot}CHMe{\cdot}CH_2OH$ .. .. (XIII)

$Cl{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CHOH{\cdot}Me$ .. .. .. (XIV)

$ArO{\cdot}CH_2{\cdot}C \equiv C{\cdot}CH_2R$ .. .. (XV)
(Ar = Ph or *o*-tolyl, R = Cl)

(Ar = Ph or *o*-tolyl, R = NEt_2 or Δ^3-piperideino) .. .. (XV*a*)

Experimental

Melting points are uncorrected.

5-o-*Toloxy*-3-*oxapentyl chloride* (II; R = Cl). To a solution of sodium hydroxide (40 g.) in ethanol (450 ml.) and water (40 ml.) was added *o*-cresol (108 g.) followed by 2:2′-dichlorodiethyl ether (143 g.) and the mixture heated under reflux for 5 hours. Excess of ethanol was boiled off, water added, and the separated oil extracted with chloroform. The chloroform extract was washed with water, the solvent removed and the residual oil distilled at 0·3 mm., yielding:

fraction (i) b.p. 36 to 95°, 52·4 g., fraction (ii) b.p. 100 to 120°, 111·9 g., and fraction (iii) b.p. 160°, 26·9 g.

Fraction (ii) was redistilled to give 5-o-*toloxy*-3-*oxapentyl chloride*, b.p. 92° at 0·3 mm. Found: C, 62·0; H, 7·1; Cl, 16·0. $C_{11}H_{15}O_3Cl$ requires C, 61·5; H, 7·1; Cl, 16·5 per cent. Fraction (iii) on redistillation yielded 1:5-*bis*-o-*toloxy*-3-*oxapentane* (II, R = *o*-tolyl), b.p. 156° at 0·3 mm. Found: C, 75·4; H, 7·8. $C_{18}H_{22}O_3$ requires C, 75·5; H, 7·8 per cent.

N-(5-o-*Toloxy*-3-*oxapentyl*)-*piperidine* (II; R = piperidino). The foregoing chloro-compound (21·45 g.) was heated with piperidine (25·5 g.) on the steam bath for 10 hours. Excess of piperidine was removed under reduced pressure, the residue was treated with water and the oil extracted with chloroform. The extract was washed with water, the chloroform removed and the residual oil distilled at 0·3 mm. to give the product, b.p. 132°, 25·5 g. Redistillation yielded N-(5-o-*toloxy*-3-*oxapentyl*)-*piperidine*, b.p. 130° at 0·3 mm. Found: C, 72·7; H, 9·2; N, 4·7.

$C_{16}H_{25}O_2N$ requires C, 73·0; H, 9·6; N, 5·3 per cent. It formed a *picrate* which separated from a mixture of ethyl acetate and light petroleum (b.p. 40 to 60°) in yellow nodules, m.p. 77 to 78°. Found: C, 53·7; H, 5·9; N, 11·2. $C_{22}H_{28}O_9N_4$ requires C, 53·6; H, 5·7; N, 11·4 per cent.

N-(5-o-*Toloxy*-3-*oxapentyl*)-*pyrrolidine* (II; R = pyrrolidino) was obtained as an oil, b.p. 122° at 0·3 mm. Found: N, 5·4. $C_{15}H_{23}O_2N$ requires N, 5·6 per cent.

N-(5-o-*Toloxy*-3-*oxapentyl*)-Δ^3-*piperideine* (II; R = Δ^3-piperideino) was obtained as an oil, b.p. 138°/0·3 mm. Found: C, 73·9; H, 8·9; N, 4·9. $C_{16}H_{23}O_2N$ requires C, 73·5; H, 8·9; N, 5·4 per cent. It formed a *picrate* which separated from a mixture of ethyl acetate and light petroleum (b.p. 60 to 80°) in yellow needles m.p. 92 to 94°. Found: C, 53·9; H, 5·2; N, 11·2. $C_{22}H_{26}O_9N_4$ requires C, 53·9; H, 5·3; N, 11·4 per cent.

N-(5-*Hydroxy*-6-*phenoxy*-3-*oxahexyl*)-*piperidine* (III; R = H). A mixture of 3-phenoxy-1:2-epoxypropane (30 g.) and 2-hydroxyethyl piperidine (25·8 g.) in benzene (100 ml.) was heated under reflux for 20 hours. The basic fraction was extracted with N hydrochloric acid, the acid extract basified and extracted with chloroform. The chloroform extract was washed with water, the chloroform removed and the residual oil distilled at 0·1 mm. to yield N-(5-*hydroxy*-6-*phenoxy*-3-*oxahexyl*)-*piperidine*, b.p. 150°. Found: C, 68·7; H, 9·0; N, 5·3. $C_{16}H_{25}O_3N$ requires C, 68·8; H, 9·0; N, 5·1 per cent.

N-(5-*Hydroxy*-6-o-*methoxyphenoxy*-3-*oxahexyl*)-*piperidine* (III; R = OMe) was similarly obtained as an oil, b.p. 160° at 0·1 mm. Found: C, 66·2; H, 8·9; N, 4·3. $C_{17}H_{27}O_4N$ requires C, 66·0; H, 8·8; N, 4·5 per cent.

2-*Hydroxy*-6-o-*toloxy*-4-*oxahexyl chloride*. To a mixture of 2-*o*-toloxyethanol (152 g., 3 mole equivs.) and 2:3-epoxypropylchloride (31 g.) was added polyphosphoric acid (2 g.) and the mixture heated on the steam bath for 20 hours. After cooling, the residue was taken up in chloroform, washed with aqueous sodium bicarbonate and then with water. After removal of the chloroform the residue was distilled at 0·2 mm. to yield a fraction b.p. 120 to 134°; 38·0 g. This on refractionation at 0·5 mm. gave 2-*hydroxy*-6-o-*toloxy*-4-*oxahexyl chloride*, b.p. 136°. Found: C, 58·6; H, 7·1; Cl, 14·7. $C_{12}H_{17}O_3Cl$ requires C, 58·9; H, 7·0; Cl, 14·5 per cent.

1:2-*Epoxy*-6-o-*toloxy*-4-*oxahexane*. Method I: 2-*o*-Toloxyethanol (88·7 g.) was added to a solution of sodium methoxide prepared by dissolving sodium (13·4 g.) in methanol (200 ml.). The mixture was heated under reflux for several minutes and the methanol distilled off, last traces being removed by heating at 100° at 0·3 mm. for 2 hours. The residue was suspended in dry benzene (300 ml.), 1-chloro-2:3-epoxypropane (64·8 g.) added and the mixture heated under reflux for 8 hours. It was cooled, poured into water and acidified with acetic acid (5 ml.). The benzene layer was separated, washed with water, the benzene removed and the residual oil distilled under reduced pressure. The main fraction, b.p. 98 to 130° at 0·4 mm., 39·0 g., was refractionated to yield 1:2-*epoxy*-6-o-*toloxy*-4-*oxahexane* as an oil, b.p. 100° at 0·05 mm., 31·2 g. Found: C, 69·3; H, 8·2. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7 per cent.

An appreciable amount of 5-*hydroxy*-1:9-*bis*-o-*toloxy*-3:7-*dioxanonane* was isolated from the top fraction and obtained as a viscous oil, b.p. 210° at 0·07 mm. Found: C, 69·5; H, 7·9. $C_{21}H_{28}O_5$ requires C, 70·0; H, 7·8 per cent.

Method II: Treatment of the foregoing chlorohydrin with an equivalent of methanolic potash at 0°, followed by dilution and extraction with chloroform yielded the required epoxide.

N-(2-*Hydroxy*-6-o-*toloxy*-4-*oxahexyl*)-Δ^3-*piperideine* (IV). The foregoing epoxide (15 g.) was dissolved in benzene (20 ml.), Δ^3-piperideine (7·2 g.) added and the mixture heated under reflux for 6 hours. After removal of the benzene the residual oil was refractionated at 0·3 mm. to yield N-(2-*hydroxy*-6-o-*toloxy*-4-*oxahexyl*)-Δ^3-*piperideine* as an oil, b.p. 162°. Found: N, 4·7. $C_{17}H_{25}O_3N$ requires N, 4·8 per cent. The *hydrochloride* was a hygroscopic solid, m.p. 50 to 60°. Found: C, 60·7; H, 8·2; N, 4·4; Cl, 10·5. $C_{17}H_{26}O_3NCl$; $\frac{1}{2}H_2O$, requires C, 60·6; H, 8·1; N, 4·2; Cl, 10·5 per cent. The *picrate*, which separated from a mixture of ethyl acetate and ether, had m.p. 81 to 83°. Found: C, 52·8; H, 5·6; N, 10·7. $C_{23}H_{28}O_{10}N_4$ requires C, 53·1; H, 5·4; N, 10·8 per cent.

Condensation of 3-o-*toloxy*-1:2-*epoxypropane with* 2:3-*dihydroxypropyl chloride*. A mixture of 3-*o*-toloxy-1:2-epoxypropane (82 g.) and 2:3-dihydroxypropyl chloride (166 g., 3 moles) was treated carefully with concentrated sulphuric acid (2 ml.) added dropwise with shaking. The mixture was heated on the steam bath for 20 hours, cooled, taken up in an equal volume of chloroform, washed with dilute aqueous sodium bicarbonate and then with water. After removal of the chloroform the residual oil was distilled at 0·5 mm. to yield:—fraction (i) b.p. 80 to 145° 7 g.; fraction (ii) b.p. 190 to 205°, 64 g.; fraction (iii) b.p. 270°. Fraction (ii) on redistillation yielded a constant fraction b.p. 176° at 0·4 mm. Found: C, 57·2; H, 7·5. $C_{13}H_{19}O_4Cl$ requires C, 56·8; H, 7·0 per cent. Fraction (iii) was not distilled completely owing to decomposition of the residue. Found: C, 63·3; H, 7·4. 2-(3′-Hydroxy-4′-*o*-toloxy-1′-oxabutyl)-6-hydroxy-7-*o*-toloxy-4-oxaheptyl chloride (VII) $C_{23}H_{31}O_6Cl$ requires C, 62·9; H, 7·1 per cent.

6-*Hydroxy*-7-o-*toloxy*-4-*oxahept*-1-*ene* (VIII; R = Me). Method I: A mixture of 3-*o*-toloxy-1:2-epoxypropane (164 g.) and allyl alcohol (174 g., 3 mole) was treated carefully with concentrated sulphuric acid (2 ml.) and heated on the steam bath for 20 hours. Excess of allyl alcohol was removed at reduced pressure, the residue was taken up in chloroform, washed acid-free, the chloroform removed and the residue distilled at reduced pressure to give fraction (i) b.p. 120° at 0·25 mm. and fraction (ii) b.p. 124 to 144° at 0·25 to 1·0 mm. Distillation had to be stopped due to decomposition of the residue. Fraction (i) was redistilled at 1·2 mm. to yield 6-*hydroxy*-7-o-*toloxy*-4-*oxahept*-1-*ene* b.p. 130 to 132°. Found: C, 70·5; H, 8·3. $C_{13}H_{18}O_3$ requires C, 70·2; H, 8·2 per cent. Fraction (ii) contained a high proportion of 3-*o*-toloxypropane-1:2-diol (mephenesin) which separated on standing.

Method II: To a mixture of 2-hydroxy-3-*o*-toloxypropyl chloride (100 g.) and allyl alcohol (232 g., 8 moles), powdered potassium hydroxide

(33·6 g., 1·2 mole) was added in portions with shaking over 10 minutes. The mixture was heated on the steam bath for 8 hours, excess of allyl alcohol removed at reduced pressure, the residue cooled, diluted with water and extracted with chloroform. The chloroform extract was neutralised with acetic acid, washed with water and the chloroform removed. The residue was distilled at 0·1 mm. to yield the product (97·8 g.), b.p. 113°. Found: C, 70·4; H, 8·3 per cent.

1:2-*Epoxy*-6-*hydroxy*-7-o-*toloxy*-4-*oxaheptane* (IX; R = Me). The foregoing allyl ether (63 g.) was added to a cold solution of perbenzoic acid (39·15 g.) in benzene (995 ml.). The solution was left at 0° for 2 days and then at room temperature for 2 days. It was washed with 10 per cent sodium hydroxide, then with water. After removal of the benzene the residual oil was distilled at 0·3 mm. The main fraction, b.p. 118 to 150° (37·7 g.), was refractionated to yield the *product* as an oil, b.p. 144° at 0·4 mm. Found: C, 65·7; H, 7·6. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6 per cent.

N-(2:6-*Dihydroxy*-7-o-*toloxy*-4-*oxaheptyl*)-*diethylamine* (V; R = NEt_2) was obtained as an oil, b.p. 174° at 0·3 mm. by condensation of the foregoing epoxide with diethylamine in benzene solution at reflux temperature for 5 hours. Found: N, 4·8. $C_{17}H_{29}O_4N$ requires N, 4·5 per cent.

N-(2:6-*Dihydroxy*-7-o-*toloxy*-4-*oxaheptyl*)-*piperidine* (V; R = piperidino) was obtained as an oil, b.p. 194° at 0·4 mm. Found: C, 66·6; H, 9·0; N, 4·3. $C_{18}H_{29}O_4N$ requires C, 66·8; H, 9·0, N, 4·3 per cent.

6-*Hydroxy*-7-*phenoxy*-4-*oxahept*-1-*ene* (VIII; R = H) was prepared from 3-phenoxy-1:2-epoxy propane and allyl alcohol as for the corresponding *o*-toloxy analogue and obtained as an oil, b.p. 110° at 0·05 mm. Found: C, 69·3; H, 7·7. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·8 per cent.

1:2-*Epoxy*-6-*hydroxy*-7-*phenoxy*-4-*oxaheptane* (IX; R = H) was prepared by reaction of the foregoing allyl ether with perbenzoic acid. It was obtained as an oil, b.p. 140° at 0·4 mm. Found: C, 64·5; H, 7·2. $C_{12}H_{16}O_4$ requires C, 64·3; H, 7·2 per cent.

N-(2:6-*Dihydroxy*-4-*oxahexyl*)-p-*anisidine* (X; R = *p*-OMe, R′ = H). A mixture of *p*-anisidine (123 g.), 2:6-dihydroxy-4-oxahexyl chloride (77 g.) and anhydrous sodium carbonate (31·8 g.) in ethanol (500 ml.) was heated under reflux for 6 hours. After removal of most of the ethanol, the residue was diluted with water, extracted with chloroform, the extracts washed with water and the chloroform removed. The residue was distilled at 0·4 mm. yielding unchanged *p*-anisidine (70 g.) and the *product* (44 g.), b.p. 190 to 200°. The latter solidified and had m.p. 65 to 67° after crystallisation from a mixture of ethyl acetate and light petroleum (b.p. 60 to 80°). Found: C, 59·0; H, 8·2; N, 6·2. $C_{12}H_{19}O_4N$ requires C, 59·4; H, 8·1; N, 5·8 per cent.

N-*Methyl*-N-(2:6-*dihydroxy*-4-*oxahexyl*)-p-*anisidine* (X; R = *p*-OMe, R′ = Me). The foregoing amine (6 g.) was dissolved in methanol (100 ml.), methyl iodide (4·3 g.) and anhydrous sodium carbonate (2·7 g.) added and the mixture heated under reflux for 5 hours. The solvent was removed, the residue diluted with water and the oil extracted with ethyl acetate. After drying the ethyl acetate was distilled off and the residual

oil distilled at 0·1 mm. yielding the *product* as an oil, b.p. 180°. Found: C, 60·9; H, 7·9; N, 6·0. $C_{13}H_{21}O_4N$ requires C, 61·0; H, 8·2; N, 5·5 per cent.

N-*Ethyl*-N-(2:6-*dihydroxy*-4-*oxahexyl*)-p-*anisidine* (X; R = *p*-OMe, R′ = Et) was prepared as for the corresponding *N*-methyl analogue and obtained as an oil, b.p. 185° at 0·1 mm. Found: C, 61·8; H, 8·2; N, 4·8. $C_{14}H_{23}O_4N$ requires C, 62·2; H, 8·6; N, 5·2 per cent.

N-(2:6-*Dihydroxy*-4-*oxahexyl*)-p-*phenetidine* (X; R = *p*-OEt, R′ = H). To a mixture of *p*-phenetidine (82·2 g., 1·5 moles) and 2:6-dihydroxy-4-oxahexyl chloride (61·8 g.) dissolved in methanol (100 ml.) was added a solution of potassium hydroxide (22·4 g.) in methanol (100 ml.) and the mixture heated on the steam bath for 3 hours. After removal of solvent the residue was diluted with water, extracted with chloroform and the extracts washed with a small volume of brine solution. The chloroform was removed and the residual oil distilled under reduced pressure giving unchanged *p*-phenetidine together with the product (62 per cent) as an oil, b.p. 220° at 0·4 mm., which solidified rapidly. It crystallised from a mixture of ethyl acetate and light petroleum (b.p. 40 to 60°) in light yellow prisms, m.p. 70 to 72°. Found: C, 61·2; H, 8·4; N, 5·3. $C_{13}H_{21}O_4N$ requires C, 61·4; H, 8·3; N, 5·5 per cent. The *picrate* separated from ethanol in bright yellow needles, m.p. 127 to 128°. Found: C, 47·1; H, 4·9; N, 11·7. $C_{19}H_{24}O_{11}N_4$ requires C, 47·1; H, 5·0; N, 11·6 per cent.

N-*Ethyl*-N-(2:6-*dihydroxy*-4-*oxahexyl*)-p-*phenetidine* (X; R = *p*-OEt, R′ = Et). When the foregoing base was ethylated with ethyl iodide in ethanol in the presence of sodium carbonate at reflux temperature for 10 hours the *product* was obtained as an oil, b.p. 180° at 0·3 mm. Found: C, 63·6; H, 9·0; N, 4·6. $C_{15}H_{25}O_4N$ requires C, 63·6; H, 8·9; N, 4·9 per cent.

N-(2:6-*Dihydroxy*-4-*oxahexyl*)-p-n-*propoxyaniline* (X; R = *p*-OPr, R′ = H). It was prepared by condensation of *p*-*n*-propoxyaniline with 2:6-dihydroxy-4-oxahexyl chloride as described for the *p*-methoxy analogue. It was obtained in 61 per cent yield as an oil, b.p. 192 to 198° at 0·1 mm. The product solidified rapidly and crystallised from a mixture of ethyl acetate and light petroleum (b.p. 40 to 60°) in light yellow needles, m.p. 71 to 73°. Found: C, 61·9; H, 8·5; N, 4·8. $C_{14}H_{23}O_4N$ requires C, 62·2; H, 8·6; N, 5·2 per cent.

N-(2:6-*Dihydroxy*-4-*oxahexyl*)-p-n-*butoxyaniline* (X; R = *p*-OBu, R′ = H) was obtained as an oil, b.p. 195 to 200° at 0·4 mm. which solidified rapidly and crystallised from a mixture of ethyl acetate and light petroleum (b.p. 40 to 60°) in yellow needles, m.p. 69 to 71°. Found: C, 63·0; H, 8·6; N, 4·9. $C_{15}H_{25}O_4N$ requires C, 63·3; H, 8·8; N, 5·0 per cent.

N-(2:6-*Dihydroxy*-4-*oxahexyl*)-o-*phenetidine* (X; R = *o*-OEt, R′ = H) was isolated as an oil, b.p. 182 to 186°/0·4 mm. which solidified and crystallised from a mixture of ethyl acetate and light petroleum (b.p. 40 to 60°) in pale yellow needles, m.p. 57 to 58°. Found: C, 61·5; H, 8·2; N, 5·0. $C_{13}H_{21}O_4N$ requires C, 61·2; H, 8·2; N, 5·5 per cent.

N-(2:6-*Dihydroxy*-4-*oxahexyl*)-*morpholine* was obtained as an oil, b.p. 144° at 0·5 mm. Found: C, 52·0; H, 9·1; N, 7·0. $C_9H_{19}O_4N$ requires C, 52·4; H, 9·3; N, 6·8 per cent.

N-(2:6-*Dihydroxy*-4-*oxahexyl*)-Δ^3-*piperideine* formed an oil, b.p. 140° at 0·3 mm. Found: C, 59·5; H, 9·1. $C_{10}H_{19}O_3N$ requires C, 59·6; H, 9·5 per cent.

N-(2:6-*Dihydroxy*-4-*oxahexyl*)-*pyrrolidine* was an oil, b.p. 118° at 0·1 mm. Found: C, 57·2; H, 9·9. $C_9H_{19}O_3N$ requires C, 57·1; H, 10·0 per cent.

N-(2:9-*Dihydroxy*-4:7-*dioxanonyl*)-p-*phenetidine*. A mixture of 2:9-dihydroxy-4:7-dioxanonyl chloride (19·85 g.), *p*-phenetidine (27·4 g., 2 moles) and potassium hydroxide (5·6 g.) in methanol (30 ml.) was heated on the steam bath for 3 hours. Isolation in the usual manner gave the *product* as an oil (16·5 g.), which after refractionation had b.p. 220° at 0·5 mm. Found: C, 59·7; H, 8·5; N, 4·5. $C_{15}H_{25}O_5N$ requires C, 60·2; H, 8·4; N, 4·7 per cent. The *picrate* separated from ethyl acetate in bright yellow needles, m.p. 120 to 121°. Found: C, 47·8; H, 5·5; N, 10·4. $C_{21}H_{28}O_{12}N_4$ requires C, 47·7; H, 5·3; N, 10·6 per cent.

The compound (50·6 g.), previously stated by us[3] to be 2:6-dihydroxy-4-oxaheptyl chloride, was dissolved in ethanol (125 ml.) and *p*-phenetidine (82·2 g., 2 mole) added, followed by anhydrous sodium carbonate (21 g.). The mixture was heated on the steam bath for 8 hours when the solvent was removed, water added and the product extracted with chloroform. The chloroform extract was washed with water, the chloroform removed, and the residue distilled to yield:—fraction (i) b.p. 70° at 0·5 mm. (46 g.), mainly unchanged *p*-phenetidine, and (ii) b.p. 200 to 205° at 0·4 to 0·5 mm. (57 g.). Fraction (ii) crystallised on treatment with ethyl acetate and light petroleum (b.p. 40 to 60°) to yield a white solid (A), m.p. 92 to 97° (21 g.) which had m.p. 102 to 104° after repeated crystallisation from a mixture of ethyl acetate and light petroleum (b.p. 60 to 80°). It was soluble in hot water, the *product* crystallising on cooling. Found: C, 62·4; H, 8·5; N, 5·2. $C_{14}H_{23}O_4N$ requires C, 62·4; H, 8·6; N, 5·2 per cent.

The *picrate* separated from ethyl acetate in yellow fluffy needles, m.p. 130 to 132°. Found: C, 48·6; H, 5·4; N, 10·6. $C_{20}H_{26}O_{11}N_4$ requires C, 48·2; H, 5·3; N, 11·2 per cent.

The mother-liquors from solid (A) were concentrated and the gummy residue distilled at 0·8 mm. to yield a main fraction, b.p. 210°. This solidified and crystallised from a mixture of ether and light petroleum (b.p. 40 to 60°) to yield fluffy white needles, m.p. 45° (12·5 g.) (B), which after repeated crystallisation from the same solvent mixture had m.p. 54 to 56°. It was much more soluble in cold water than (A). Found: C, 62·2; H, 8·5; N, 5·1. $C_{14}H_{23}O_4N$ requires C, 62·4; H, 8·6; N, 5·2 per cent.

Because of the sharp differences in water solubilities, and relative yields, compound (A) is tentatively assigned structure (XI; R = Et) and compound (B) the structure (XII; R = Et).

In a similar experiment the mixed chlorohydrin (33·7 g.) was condensed with *p*-anisidine (49·2 g., 2 mole) in methanol (150 ml.) containing potassium hydroxide (11·2 g.). After working up as in the previous example a fraction was obtained b.p. 200 to 220° at 0·5 mm. This yielded two

isomers again, the less soluble isomer (C) crystallised from water in white fluffy needles, m.p. 92 to 93°. Found: C, 60·6; H, 8·1. $C_{13}H_{21}O_4N$ requires C, 61·1; H, 8·3 per cent. It formed a *picrate* which separated from a mixture of ethyl acetate and light petroleum (b.p. 60 to 80°) in bright yellow crystals, m.p. 134 to 136°. Found: C, 47·1; H, 5·0. $C_{19}H_{24}O_{11}N_4$ requires C, 47·1; H, 5·0 per cent.

The second more soluble *isomer* (D) had m.p. 64 to 66° after crystallisation from a mixture of ether and light petroleum (b.p. 60 to 80°). Found: C, 60·9; H, 8·2; N, 5·2. $C_{13}H_{21}O_4$ requires C, 61·1; H, 8·3; N, 5·5 per cent. Its *picrate* separated from a mixture of ethyl acetate and light petroleum (b.p. 60 to 80°) in yellow needles, m.p. 125 to 126°. Found: C, 47·4; H, 5·0; N, 11·9. $C_{19}H_{24}O_{11}N_4$ requires C, 47·1; H, 5·0; N, 11·6 per cent.

Isomer (C) is tentatively assigned structure (XI; R = Me), and isomer (D) the structure (XII; R = Me).

N-p-*Ethoxyphenylmorpholine*. A mixture of 2:2′-dichlorodiethyl ether (36 g.), *p*-phenetidine (34·5 g.) and potassium hydroxide (28 g.) in 50 per cent aqueous ethanol (200 ml.) was heated on the steam bath for 6 hours. Excess of ethanol was boiled off, the oil was taken up in chloroform, the chloroform layer washed, concentrated and the residue distilled at 0·5 mm. The product had b.p. 120° at 0·5 mm. and solidified rapidly. It crystallised from aqueous ethanol in white shining plates, m.p. 75 to 76°. Found: C, 69·6; H, 8·5. $C_{12}H_{17}O_2N$ requires C, 69·5; H, 8·3 per cent.

The bulk of the product was converted to the *hydrochloride*, which separated from a mixture of ethanol and ether in small colourless prisms (17 g.), m.p. 170 to 171°. Found: C, 59·4; H, 6·9; N, 6·2. $C_{12}H_{18}O_2NCl$ requires C, 59·1; H, 7·5; N, 5·8 per cent.

3-(3′:4′:5′-*Trimethoxyphenyl*)*aminopropan*-1:2-*diol* was obtained by condensation of 3:4:5-trimethoxyaniline (18·3 g.) with 2:3-epoxypropanol (7·4 g.) in ethanol (40 ml.) on the steam bath for 8 hours. It had b.p. 210° at 0·2 mm. Found: C, 55·7; H, 7·8; N, 5·8. $C_{12}H_{19}O_5N$ requires C, 56·0; H, 7·4; N, 5·5 per cent. The *hydrochloride* separated from a mixture of ethanol and ether in white needles with a blue-green tinge, m.p. 148 to 150°. Found: C, 49·0; H, 6·9; N, 4·8. $C_{12}H_{20}O_5NCl$ requires C, 49·0; H, 6·9; N, 4·8 per cent.

4-o-*Toloxy-but*-2-*yne chloride* (XV; Ar = *o*-tolyl). Potassium hydroxide (75 g.) was dissolved by warming in a mixture of *iso*propanol (550 ml.) and *o*-cresol (172 g.) and 1:4-dichloro-but-2-yne (172 g.) was added rapidly with stirring to the warm solution. Reaction was completed by heating the mixture on the steam bath for 30 minutes. After cooling, potassium chloride was removed, the neutral residue distilled at reduced pressure to remove excess of *iso*propanol and the *product* isolated by distillation at 0·3 mm. It formed an oil, b.p. 110°. Found: C, 67·8; H, 5·8; Cl, 18·2. $C_{11}H_{11}OCl$ requires C, 67·8; H, 5·7; Cl, 18·2 per cent.

1-Chloro-4-phenoxy-but-2-yne was prepared similarly.

1-*Diethylamino*-4-*phenoxy-but*-2-*yne hydrochloride*. A mixture of 4-phenoxy-but-2-yne chloride (24 g.) and diethylamine (36 ml.) was heated on the steam bath under reflux for 30 minutes. It was then cooled,

poured into water, made alkaline with concentrated sodium hydroxide solution and the separated oil extracted with ether. The ethereal layer was washed with water, dried over anhydrous sodium sulphate and the ether removed. The residual oil was distilled to yield the *base* as an oil, b.p. 110 to 115° at 0·2 mm.

The base was converted to the *hydrochloride* in ethereal solution and the latter was purified by crystallisation from a mixture of ethanol and ether, forming white needles of m.p. 138 to 139°. Found: C, 66·5; H, 8·1; N, 5·4; Cl, 13·6. $C_{14}H_{20}ONCl$ requires C, 66·2; H, 7·9; N, 5·5; Cl, 14·0 per cent.

1-*Diethylamino*-4-o-*toloxy-but*-2-*yne* had b.p. 126 to 128° at 0·6 mm. The *hydrochloride* separated from a mixture of ethanol and ether in white crystals of m.p. 116 to 117°. Found: C, 66·7; H, 8·3; N, 4·8; Cl, 13·6. $C_{15}H_{22}ONCl$ requires C, 67·2; H, 8·3; N, 5·2; Cl, 13·3 per cent.

1-Δ^3-*Piperideino*-4-o-*toloxy-but*-2-*yne* had b.p. 130° at 0·5 mm. The *hydrochloride* separated from a mixture of *iso*propanol and ether in white needles, m.p. 126 to 127°. Found: C, 69·0; H, 7·0; N, 4·8; Cl, 13·1. $C_{16}H_{20}ONCl$ requires C, 69·1; H, 7·3; N, 5·0; Cl, 12·8 per cent.

References

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