ANALGESICS. PART IV. SOME 3-ARYLOXY-1-Δ^3-PIPERIDEINOPROPAN-2-OL DERIVATIVES

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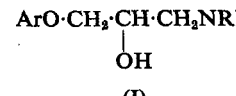
From the Chemical Research Laboratories, The British Drug Houses, Ltd., London, N.1

Received August 6, 1957

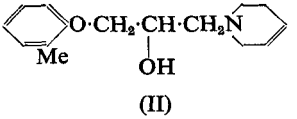
The synthesis of some 3-aryloxy-1-Δ^3-piperideinopropan-2-ol derivatives and related types is described. Their biological study has led to the selection of 1-Δ^3-piperideino-3-*o*-toloxypropan-2-ol hydrochloride, Tolpronine, for fuller evaluation as an analgesic agent.

BIOLOGICAL study of the aryloxypropanolamines (I) described in Part I (preceeding paper) showed that, in general, analgesic activity increased in passing from alkyl- and dialkylamino-derivatives (I; R = H or alkyl, R′ = alkyl) to cyclic structures in which NRR′ was piperidino, pyrrolidino or morpholino. The fortuitous observation that a still more active compound resulted from replacement of piperidino by Δ^3-piperideino in one of the more potent earlier types led to the preparation of the 3-aryloxy-1-Δ^3-piperideinopropan-2-ol derivatives (V) described herein and to the ultimate selection of 1-Δ^3-piperideino-3-*o*-toloxypropan-2-ol hydrochloride (Tolpronine)[1] (II*a*) for detailed pharmacological study.

The required 3-aryloxy-1-Δ^3-piperideinopropan-2-ol derivatives (V) were prepared by condensation of the appropriate 3-aryloxy-1:2-epoxypropane (III) with a slight excess of Δ^3-piperideine (IV) in an organic

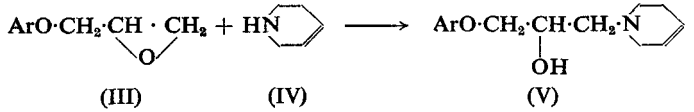


(I)

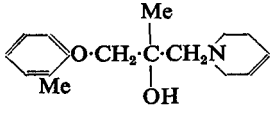


(II)

[II*a*; hydrochloride of (II)]



(III) (IV) (V)



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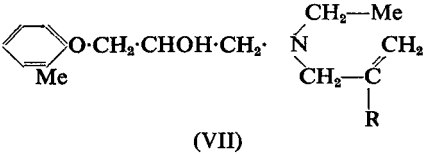


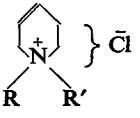
(VII)

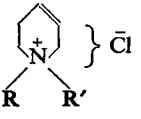
solvent like benzene, toluene, light petroleum or ethanol. Reaction was exothermic and rapid, but was readily controlled by water cooling or by controlled addition of the glycide ether to the Δ^3-piperideine. The products were isolated by distillation under reduced pressure or directly by crystallisation. The phenyl-, *o*-chlorophenyl-, *o*-fluorophenyl-, *o*-allylphenyl-, *o*-*n*-butoxyphenyl, 2-methoxy-4-propenylphenyl- and 2-methoxy-4-allylphenyl analogues of (II) were all obtained in this way.

In addition, 2-methyl-1-Δ^3-piperideino-3-*o*-toloxypropan-2-ol (VI), the 2-methyl homologue of the active base (II), was prepared by the condensation of 1:2-epoxy-2-methyl-3-*o*-toloxypropane with Δ^3-piperideine (IV).

Some compounds of type (VII) in which the Δ^3-piperideino-moiety characteristic of (II) is replaced by an open-chain type of structure were also prepared. These were synthesised by condensing 1:2-epoxy-3-*o*-toloxypropane with ethyl allylamine, ethyl 2-methallylamine and diallylamine, respectively. The first two compounds were also obtained from 1-ethylamino-3-*o*-toloxypropan-2-ol by reaction with allyl chloride and with 2-methallyl chloride.

Quaternation of 1-Δ^3-piperideino-3-*o*-toloxypropan-2-ol (II) with 3-*o*-chlorophenoxy-2-hydroxypropyl chloride surprisingly led to the formation of two isomeric compounds which are probably geometrical isomers of type (VIII; R = *o*-Me·C_6H_4·O·CH_2·CHOH·CH_2·, R′ = *o*-Cl·C_6H_4·O·CH_2·CHOH·CH_2·).





(VIII)

Quaternation of the base (II) with benzyl chloride led likewise to the formation of two isomers (VIII; R = *o*-Me·C_6H_4·O·CH_2·CHOH·CH_2·, R′ = Ph·CH_2·), also formed, albeit in low yield, by the condensation of *N*-benzyl-Δ^3-piperideine with 2-hydroxy-3-*o*-toloxypropyl chloride.

1-Δ^3-Piperideino-3-*o*-toloxypropan-2-ol (II) (*vide supra*) crystallised from light petroleum in white needles, m.p. 62 to 64°. It was converted into its salts with inorganic and organic acids and further transformed into its *O*-esters which were isolated as their hydrochlorides. Biological study of these derivatives led to the selection of the hydrochloride, Tolpronine (II*a*), for fuller evaluation. This salt crystallised from ethylene dichloride or from mixtures of ethanol and ether in white needles, m.p. 136 to 137°. It was readily soluble in half its weight of water to give solutions of pH about 5. These could be neutralised with sodium bicarbonate solution without precipitation of the base.

Experimental

Melting points are uncorrected.

1-Δ^3-*Piperideino*-3-o-*toloxypropan*-2-*ol* (II). (1) A mixture of 3-*o*-toloxy-1:2-epoxypropane (246 g.) and Δ^3-piperideine (137 g.; 1·1 mole equiv.) in toluene (400 ml.) was heated under reflux on the steam bath until the exothermic reaction had started when slight cooling was applied as required. The reaction was completed by heating for 30 minutes. The mixture was cooled, washed twice with water to remove excess of Δ^3-piperideine and taken to dryness under reduced pressure. The solid residue was crystallised from light petroleum (b.p. 40 to 60°) to give 1-Δ^3-*piperideino*-3-o-*toloxypropan*-2-*ol*, needles, m.p. 62 to 64°, b.p. 136° at 0·3 mm. Found: C, 72·8; H, 8·2; N, 5·9. $C_{15}H_{21}O_2N$ requires C, 72·8; H, 8·6; N, 5·7 per cent.

(2) 3-Δ^3-Piperideino-1:2-epoxypropane (13·9 g.) and *o*-cresol (10·8 g.) were heated on the steam bath for 10 hours and the product distilled directly at reduced pressure. The main fraction (15 g.) b.p. 134 to 138° at 0·3 mm. was redistilled to yield the base (II), b.p. 134° at 0·3 mm. (12·1 g.).

The *hydrochloride* separated from ethanol:ether in plates, m.p. 136 to 137°. Found: C, 63·5; H, 7·6; N, 4·6; Cl, 13·0. $C_{15}H_{22}O_2NCl$ requires C, 63·5; H, 7·8; N, 4·9; Cl, 12·5 per cent. The *picrate*, m.p. 134 to 135°, crystallised from ethyl acetate containing a trace of ethanol. Found: N, 11·8. $C_{21}H_{24}O_9N_4$ requires N, 11·8 per cent. The *hydrobromide* had m.p. 124 to 126° after crystallisation from ethyl acetate containing a trace of ethanol. Found: N, 4·4. $C_{15}H_{22}O_2NBr$ requires N, 4·3 per cent. The *benzoate*, m.p. 108 to 110°, separated from ethanol:ether. Found: N, 3·5. $C_{22}H_{27}O_4N$ requires N, 3·8 per cent. The *salicylate*, crystallised from ethanol in needles, m.p. 144 to 145°. Found: C, 68·1; H, 6·9; N, 3·4. $C_{22}H_{27}O_5N$ requires C, 68·5; H, 7·1; N, 3·6 per cent. The *acetylsalicylate*, separated from ethyl acetate:light petroleum (b.p. 60 to 80°) in needle clusters, m.p. 119°. Found: C, 67·7; H, 6·7; N, 3·3. $C_{24}H_{29}O_6N$ requires C, 67·4; H, 6·8; N, 3·3 per cent.

The 4-*hydroxy*-iso*phthalate* crystallised from ethyl acetate:ether in needles, m.p. 78 to 80°. Found: C, 63·7; H, 6·4; N, 3·1. $C_{23}H_{27}O_7N$ requires C, 64·3; H, 6·3; N, 3·3 per cent. The *acid malonate* crystallised from ethyl acetate in needles, m.p. 105 to 106°. Found: C, 61·7; H, 7·2. $C_{18}H_{25}O_6N$ requires C, 61·5; H, 7·2 per cent. The *ethyl hydrogen malonate salt* separated from ethanol:ether in prisms m.p. 136 to 137°. Found: C, 63·7; H, 7·8; N, 3·7. $C_{20}H_{29}O_6N$ requires C, 63·3; H, 7·7; N, 3·7 per cent.

1-Δ^3-*Piperideino*-2-*acetoxy*-3-o-*toloxypropane*. A solution of 1-Δ^3-piperideino-3-*o*-toloxypropan-2-ol (49·4 g.) in acetic anhydride (200 ml.) was heated under reflux for 5 hours when excess of acetic anhydride was distilled off at reduced pressure. The residue was fractionated at 0·5 mm. to yield the *product* (37·1 g.) as an oil, b.p. 126° at 0·1 mm. Found: C, 70·8; H, 7·9; N, 4·7. $C_{17}H_{23}O_3N$ requires C, 70·5; H, 8·0; N, 4·8 per cent.

1-Δ^3-*Piperideino*-2-*acetoxy*-3-o-*toloxypropane hydrochloride*. A solution of 1-Δ^3-piperideino-3-*o*-toloxypropan-2-ol (49·4 g.) in benzene (200 ml.) was treated with shaking with acetyl chloride (15·7 g.). Rapid and copious separation of solids occurred. These were collected, washed with ether and purified from ethylene dichloride, to give the *hydrochloride*, needles, m.p. 175°. Found: C, 63·1; H, 7·1; N, 3·9; Cl, 10·8. $C_{17}H_{24}O_3NCl$ requires C, 62·6; H, 7·4; N, 4·3; Cl, 10·9 per cent.

The product was readily soluble in water yielding a neutral solution. Its (10 g.) hydrolysis with 0·1N ethanolic hydrochloric acid (105 ml.) for 2 hours on the steam bath yielded after concentration 1-Δ^3-piperideino-3-*o*-toloxypropan-2-ol hydrochloride, m.p. 133 to 135° not depressed on admixture with an authentic specimen.

1-Δ^3-*Piperideino*-2-*propionoxy*-3-o-*toloxypropane hydrochloride*. A solution of 1-Δ^3-piperideino-3-*o*-toloxypropan-2-ol (49·4 g.) in benzene

(300 ml.) was treated gradually with a solution of propionyl chloride (20·4 g., 1·1 mole equiv.) in benzene (30 ml.). The mixture was heated under reflux for 2 hours. The *product* which separated on cooling was collected, washed with ether and purified by crystallisation from ethylene dichloride:ethyl acetate, forming plates, m.p. 139 to 140°. Found: C, 64·1; H, 7·8; N, 4·3. $C_{18}H_{26}O_3NCl$ requires C, 63·6; H, 7·7; N, 4·1 per cent.

1-Δ^3-*Piperideino*-2-n-*butyroxy*-3-o-*toloxypropane hydrochloride* separated from ethanol:ether in white needles, m.p. 114 to 115°. Found: C, 64·5; H, 7·8; N, 4·0; Cl, 10·2. $C_{19}H_{28}O_3NCl$ requires C, 64·5; H, 8·0; N, 4·0; Cl, 10·0 per cent.

1-Δ^3-*Piperideino*-2-iso*butyroxy*-3-o-*toloxypropane hydrochloride* crystallised from ethyl acetate containing a trace of ethanol, in needles, m.p. 122 to 124°. Found: C, 64·3; H, 7·9; N, 3·9; Cl, 10·1. $C_{19}H_{28}O_3NCl$ requires C, 64·5; H, 8·0; N, 4·0; Cl, 10·0 per cent.

Bis carbonate ester of 1-Δ^3-*piperideino*-3-o-*toloxypropan*-2-*ol*. To 1-Δ^3-piperideino-3-*o*-toloxypropan-2-ol (28·6 g.) in dry benzene (150 ml.) was added, in portions with shaking, a solution of phosgene (5·8 g.) in dry benzene (50 ml.). Reaction was completed by heating the mixture on the steam bath for 30 mins. After cooling, the solid was collected and washed with ether (24·9 g., m.p. 198 to 200° [decomp.]). Crystallisation from methanol:ether gave the *ester*, m.p. 204 to 205°. Found: C, 62·6; H, 7·3; N, 4·9. $C_{31}H_{42}O_5N_2Cl_2$ requires C, 62·7; H, 7·1; N, 4·7 per cent.

1-Δ^3-*Piperideino*-2-*phenylacetoxy*-3-o-*toloxypropane hydrochloride* crystallised from ethylene dichloride:ethyl acetate and had m.p. 129 to 130°. Found: C, 68·4; H, 7·0; N, 3·1. $C_{23}H_{28}O_3NCl$ requires C, 68·7; H, 7·0; N, 3·5 per cent.

1-Δ^3-*Piperideino*-2-*ethoxycarbonyloxy*-3-o-*toloxypropane hydrochloride* was prepared by reaction of 1-Δ^3-piperideino-3-*o*-toloxypropan-2-ol with ethyl chloroformate in benzene solution and crystallised from ethyl acetate in needles, m.p. 143 to 144°. Found: C, 60·7; H, 7·3; N, 3·9; Cl, 9·9. $C_{18}H_{26}O_4NCl$ requires C, 60·7; H, 7·4; N, 3·9; Cl, 10·0 per cent.

1-*Piperidino*-2-*ethoxycarbonyloxy*-3-o-*toloxypropane hydrochloride* needles from ethyl acetate, m.p. 131 to 133° were prepared by reaction of 1-piperidino-3-*o*-toloxypropan-2-ol with ethyl chloroformate. Found: C, 60·8; H, 7·9; N, 3·6; Cl, 9·7. $C_{18}H_{28}O_4NCl$ requires C, 60·4; H, 7·9; N, 3·9; Cl, 9·9 per cent.

1-Δ^3-*Piperideino*-3-*phenoxypropan*-2-*ol* (V; Ar = Ph) formed a pale yellow oil, b.p. 132° at 0·2 mm. Found: C, 72·0; H, 8·1; N, 5·8. $C_{14}H_{19}O_2N$ requires C, 72·0; H, 8·2; N, 6·0 per cent. The *hydrochloride* crystallised from ethanol:ether in needles, m.p. 132°. Found: C, 62·4; H, 8·0; N, 4·9; Cl, 12·9. $C_{14}H_{20}O_2NCl$ requires C, 62·3; H, 7·5; N, 5·2; Cl, 13·2 per cent.

1-Δ^3-*Piperideino*-3-o-*chlorophenoxypropan*-2-*ol* (V; Ar = *o*-Cl·C_6H_4) crystallised from light petroleum (b.p. 60 to 80°) in needles, m.p. 69 to 71°. Found: N, 4·9. $C_{14}H_{18}O_2NCl$ requires N, 5·2 per cent. The *acetylsalicylate* separated from ethanol:ether and had m.p. 97 to 98°. Found: C, 62·2; H, 5·8; N, 2·9; Cl, 7·6. $C_{23}H_{26}O_6NCl$ requires C, 61·6; H, 5·9;

N, 3·1; Cl, 7·9 per cent. The *salicylate* had m.p. 118 to 119° after crystallisation from ethyl acetate. Found: N, 3·4; Cl, 8·4. $C_{21}H_{24}O_5NCl$ requires N, 3·5; Cl, 8·8 per cent.

1-Δ^3-*Piperideino*-3-o-*fluorophenoxypropan*-2-*ol* (V; Ar = *o*-F·C_6H_4) of b.p. 132° at 0·5 mm. it had m.p. 46 to 48° after crystallisation from light petroleum (b.p. 40 to 60°). Found: C, 67·5; H, 7·2; N, 5·4. $C_{14}H_{18}O_2NF$ requires C, 66·9; H, 7·2; N, 5·6 per cent. The *hydrochloride* crystallised from ethanol:ether in needles, m.p. 115 to 117°. Found: N, 5·0. $C_{14}H_{19}O_2NClF$ requires N, 4·9 per cent.

3-o-*Butoxyphenoxy*-1:2-*epoxypropane* (III; Ar = *o*-BuO·C_6H_4) formed an oil, b.p. 100 to 102° at 0·05 mm. Found: C, 70·1; H, 8·6. $C_{13}H_{18}O_3$ requires C, 70·2; H, 8·2 per cent.

1-Δ^3-*Piperideino*-3-o-*butoxyphenoxypropan*-2-*ol* (V; Ar = *o*-BuO·C_6H_4) was prepared by condensation of the foregoing epoxide with Δ^3-piperideine in benzene solution. After crystallisation from light petroleum (b.p. 60 to 80°) the *product* formed in prisms, m.p. 46°, b.p. 146° at 0·05 mm. Found: C, 71·0; H, 9·1; N, 4·7. $C_{18}H_{27}O_3N$ requires C, 70·8; H, 8·9; N, 4·6 per cent.

3-o-*Allylphenoxy*-1:2-*epoxypropane*. Prepared by condensation of *o*-allylphenol with 2:3-epoxypropyl chloride in aqueous alkali, it formed an oil, b.p. 99 to 100° at 0·6 mm. Found: C, 75·8; H, 7·8. $C_{12}H_{14}O_2$ requires C, 75·8; H, 7·4.

2-*Hydroxy*-3-o-*allylphenoxypropyl chloride*. Isolated in low yield from the same reaction, it had b.p. 122 to 124° at 0·5 mm. Found: C, 63·6; H, 6·5; Cl, 15·4. $C_{12}H_{15}O_2Cl$ requires C, 63·6; H, 6·7; Cl, 15·6 per cent.

1-Δ^3-*Piperideino*-3-o-*allylphenoxypropan*-2-*ol* (V; Ar = *o*-C_3H_5O·C_6H_4) had b.p. 164 to 166° at 0·8 mm. Found: N, 5·0. $C_{17}H_{23}O_2N$ requires N, 5·1 per cent. The *hydrochloride* crystallised from ethyl acetate containing a trace of methanol in needles, m.p. 125 to 126°. Found: C, 66·1; H, 7·8; N, 4·3; Cl, 11·1. $C_{17}H_{24}O_2NCl$ requires C, 65·9; H, 7·8; N, 4·5; Cl, 11·4 per cent.

1-Δ^3-*Piperideino*-3-p-*aminophenoxypropan*-2-*ol* (V; Ar = *p*-NH_2·C_6H_4). To a solution of 3-*p*-acetamidophenoxy-1:2-epoxypropane (20·7 g.) in warm ethanol (40 ml.) was added Δ^3-piperideine (8·3 g.). A slight exothermic reaction occurred which was completed by heating the mixture for 1 hour. Removal of volatile material at reduced pressure left a *gum* which was hydrolysed by heating under reflux with ethanol (25 ml.) and concentrated hydrochloric acid (20 ml.) for 2 hours. Concentration at reduced pressure and treatment with ethanol gave the *hydrochloride*, buff-coloured nodules, m.p. 252 to 253° (decomp.) from methanol:ethyl acetate. Found: C, 52·0; H, 7·0; N, 8·7; Cl, 22·2. $C_{14}H_{22}O_2N_2Cl_2$ requires C, 52·3; H, 6·9; N, 8·7; Cl, 22·1 per cent.

3-(2′-*Methoxy*-4′-*propenyl*)-*phenoxy*-1:2-*epoxypropane*. 2:3-Epoxypropyl chloride (139 g., 1·5 mole) was added in one portion to a stirred solution of *iso*eugenol (164 g.) in N potassium hydroxide (1 litre) at 20° and the mixture stirred for 4 hours. A further quantity of potassium hydroxide (11·2 g.) in water (100 ml.) was then added and stirring continued for a further 4 hours. The oily layer was removed, the aqueous

layer extracted with chloroform and the combined extracts washed with water. After removal of the chloroform the residual oil was distilled at 0·6 mm. to yield fractions: (i) 136·2 g., b.p. 134°; (ii) 34·8 g., b.p. 134 to 190°; (iii) 23·5 g., b.p. 240°. The yield of the last fraction was greater than indicated but distillation was stopped owing to the high boiling point.

Fraction (i) was purified from ethyl acetate: light petroleum (b.p. 40 to 60°) to give 3-(2′-*methoxy*-4′-*propenyl*)-*phenoxy*-1 : 2-*epoxypropane*, small needles, m.p. 59 to 60°. Found: C, 71·4; H, 7·5. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3 per cent.

Fraction (iii) crystallised from ethyl acetate to give 1 : 3-bis-(2′-*methoxy*-4′-*propenyl*)-*phenoxypropan*-2-*ol* in nodules of needles, m.p. 86 to 87°. Found: C, 71·8; H, 7·3. $C_{23}H_{28}O_5$ requires C, 71·9; H, 7·4 per cent.

Fraction (ii) was a mixture of the foregoing epoxide and the corresponding chlorohydrin. It was hydrolysed by heating under reflux with sodium carbonate (20 g.) in water (300 ml.) for 12 hours. The resulting oil was isolated with chloroform and distilled at 0·1 mm. to yield 3-(2′-*methoxy*-4′-*propenyl*)-*phenoxypropane*-1 : 2-*diol*, b.p. 164°, needles, m.p. 90 to 91° after crystallisation from ethyl acetate. Found: C, 65·3; H, 7·7. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6 per cent.

1-Δ^3-*Piperideino*-3-(2′-*methoxy*-4′-*propenyl*)-*phenoxypropan*-2-*ol* was prepared by condensation of the foregoing epoxide with Δ^3-piperideine, b.p. 200° at 0·6 mm., needles, m.p. 71 to 72° after crystallisation from light petroleum (b.p. 60 to 80°). Found: C, 70·9; H, 8·2; N, 4·5. $C_{18}H_{25}O_3N$ requires C, 71·3; H, 8·3; N, 4·6 per cent.

3-(2′-*Methoxy*-4′-*allyl*)*phenoxy*-1 : 2-*epoxypropane*. Prepared by condensation of 2 : 3-epoxypropyl chloride with eugenol, it formed an oil, b.p. 110° at 0·05 mm., which solidified on standing. Found: C, 71·1; H, 7·3. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3 per cent.

1-Δ^3-*Piperideino*-3-(2′-*methoxy*-4′-*allyl*)-*phenoxypropan*-2-*ol* separated from light petroleum (b.p. 40 to 60°) in needles, m.p. 51 to 52°, b.p. 182 to 184° at 0·4 mm. Found: C, 71·1; H, 8·2; N, 4·5. $C_{18}H_{25}O_3N$ requires C, 71·3; H, 8·3; N, 4·6 per cent.

1-Δ^3-*Piperideino*-2-*methyl*-3-o-*toloxypropan*-2-*ol* (VI) was obtained by condensation of 3-*o*-toloxy-2-methyl-1 : 2-epoxypropane (10 g.) with Δ^3-piperideine (5·1 g.) in light petroleum (50 ml., b.p. 60 to 80°) under reflux for 3 hours. The *product* formed an oil, b.p. 128 to 130° at 0·5 mm. Found: C, 73·1; H, 8·9; N, 5·2. $C_{16}H_{13}O_2N$ requires C, 73·5; H, 8·9; N, 5·4 per cent. The *hydrochloride* had m.p. 155 to 157° after crystallisation from ethanol: ether. Found: C, 64·5; H, 8·2; N, 4·6; Cl, 12·1. $C_{16}H_{24}O_2NCl$ requires C, 64·5; H, 8·1; N, 4·7; Cl, 11·9 per cent.

1-(N-*Allyl*-N-*ethyl*)*amino*-3-o-*toloxypropan*-2-*ol* (VII; R = H). (*a*) Condensation of 3-*o*-toloxy-1 : 2-epoxypropane with *N*-allyl-*N*-ethylamine in benzene solution yielded the *base* as an oil, b.p. 112° at 0·05 mm. Found: C, 71·8; H, 8·9; N, 5·8. $C_{15}H_{23}O_2N$ requires C, 72·2; H, 9·3; N, 5·6 per cent. The *hydrochloride* crystallised from benzene: ether in hygroscopic needles m.p. 60°. Found: C, 62·6; H, 8·5; N, 4·9. $C_{15}H_{24}O_2NCl$ requires C, 63·0; H, 8·5; N, 4·9 per cent. The *picrate*

crystallised from ethyl acetate, had m.p. 123°. Found: C, 53·1; H, 5·6; N, 12·2. $C_{21}H_{26}O_9N_4$ requires C, 52·7; H, 5·5; N, 11·7 per cent.

(*b*) To a solution of 1-ethylamino-3-*o*-toloxypropan-2-ol (41·8 g.) in ethanol (100 ml.) was added allyl chloride (23 g.) and anhydrous sodium carbonate (21·2 g.) and the mixture heated on the steam bath for 15 hours. After concentration and addition of water the residual oil was isolated with chloroform, and distilled at reduced pressure to yield the base b.p. 135° to 140° at 1·0 mm., identified by conversion to the *picrate* m.p. 123° not depressed in admixture with a sample prepared by method (*a*).

N-*Ethyl*-N-2-*methallylamine*, b.p. 102° formed a *hydrochloride* which crystallised from ethyl acetate in shining leaflets, m.p. 182 to 183°. Found: C, 53·5; H, 10·3; N, 10·0; Cl, 25·7. $C_6H_{14}NCl$ requires C, 53·1; H, 10·4; N, 10·3; Cl, 26·2 per cent.

1-(N-*Ethyl*-N-2′-*methallyl*)*amino*-3-o-*toloxypropan*-2-*ol* (VII; R = Me). (*a*) Condensation of 3-*o*-toloxy-1:2-epoxypropane with *N*-ethyl-*N*-2-methallylamine yielded the *base* as an oil b.p. 118° at 0·1 mm. Found: C, 72·5; H, 9·2; N, 5·0. $C_{16}H_{25}O_2N$ requires C, 72·9; H, 9·6; N, 5·3 per cent. The *hydrochloride* had m.p. 102 to 103° after crystallisation from ethyl acetate:light petroleum (b.p. 60 to 80°). Found: C, 63·8; H, 8·5. $C_{16}H_{26}O_2NCl$ requires C, 64·1; H, 8·8 per cent. The *picrate* separated from ethyl acetate:light petroleum (b.p. 40 to 60°) in yellow crystals, m.p. 93 to 95°. Found: C, 53·2; H, 5·5; N, 11·2. $C_{22}H_{28}O_9N_4$ requires C, 53·6; H, 5·7; N, 11·4 per cent.

(*b*) To 1-ethylamino-3-*o*-toloxypropan-2-ol (41·8 g.) and 2-methallyl chloride (19·9 g.) in ethanol (125 ml.) was added potassium hydroxide (11·2 g.) in water (10 ml.) and the mixture heated for 10 hours. The product, isolated with chloroform formed an oil, b.p. 120° at 0·5 mm., identified by conversion to the *hydrochloride* identical with that described under (*a*).

1-*Diallylamino*-3-o-*toloxypropan*-2-*ol*. Prepared by condensation of 3-*o*-toloxy-1:2-epoxypropane with diallylamine, it had b.p. 119° at 0·1 mm. Found: N, 5·4. $C_{16}H_{23}O_2N$ requires N, 5·4 per cent. The *hydrochloride* had m.p. 86 to 87° after crystallisation from a mixture of benzene:ether. Found: C, 64·5; H, 8·1; N, 4·7. $C_{16}H_{24}O_2NCl$ requires C, 64·5; H, 8·0; N, 5·1 per cent.

1-*Diallylamino*-3-o-*allylphenoxypropan*-2-*ol*. Prepared by condensation of 3-*o*-allylphenoxy-1:2-epoxypropane with diallylamine, it had b.p. 148 to 151° at 0·3 mm. Found: C, 75·0; H, 8·8; N, 4·8. $C_{18}H_{25}O_2N$ requires C, 75·2; H, 8·8; N, 4·9 per cent.

N-*bis*-(2-*Hydroxy*-3-o-*toloxypropyl*)-Δ^3-*piperideino chloride*. A mixture of 2-hydroxy-3-*o*-toloxypropyl chloride (8 g.) and 1-Δ^3-piperideino-3-*o*-toloxypropan-2-ol (10 g.) was heated on the steam bath for 20 hours. The resultant gum was dissolved in a minimum of ethanol and the solution diluted to turbidity with ethyl acetate, when the *product* separated on cooling. After crystallisation from a mixture of ethanol and ethyl acetate it had m.p. 188 to 189°. Found: C, 66·6; H, 7·4; N, 2·7. $C_{25}H_{34}O_4NCl$ requires C, 67·0; H, 7·7; N, 3·1 per cent. The *iodide* had m.p. 170° after

crystallisation from a mixture of ethanol and ether. Found: C, 55·6; H, 6·0; N, 2·8. $C_{25}H_{34}O_4NI$ requires C, 55·6; H, 6·4; N, 2·6 per cent.

N - (2 - *Hydroxy* - 3 - o - *chlorophenoxypropyl*) - N - (2 - *hydroxy* - 3 -o-*toloxypropyl*)-Δ^3-*piperideino chloride.* A mixture of 2-hydroxy-3-*o*-chlorophenoxypropyl chloride (22·1 g.) and 1-Δ^3-piperideino-3-*o*-toloxypropan-2-ol (24·7 g.) was heated on the steam bath for 10 hours. The resultant gum was dissolved in the minimum of hot ethanol and the solution diluted to turbidity with ethyl acetate. The first crop of solid which separated (A) had m.p. (144°) 152 to 154° (12·7 g.). Concentration of the filtrate and cooling yielded a second crop of solid (B), m.p. (156°) 160 to 166° (7·5 g.). *Isomer A*, after four crystallisations from ethanol: ethyl acetate had m.p. 172 to 174°. The m.p. was not raised by a further crystallisation from ethylene dichloride in which the salt was sparingly soluble. Found: C, 61·9; H, 6·7; N, 2·9. $C_{24}H_{31}O_4NCl_2$ requires C, 61·5; H, 6·7; N, 3·0 per cent. It formed a *picrate* which separated from a small volume of ethanol in minute yellow needles, m.p. 139 to 141°. Found: C, 54·3; H, 4·9; N, 8·2. $C_{30}H_{33}O_{11}N_4Cl$ requires C, 54·5; H, 5·0; N, 8·5 per cent. *Isomer B* had m.p. 176 to 178° after three recrystallisations from ethanol:ethyl acetate and one crystallisation from ethylene dichloride. Found: C, 61·8; H, 6·7; N, 3·0. $C_{24}H_{31}O_4NCl_2$ requires C, 61·5; H, 6·7; N, 3·0 per cent. The *picrate* separated from ethanol in light yellow nodules of needles, m.p. 166 to 167° C. Found: C, 54·7; H, 4·9; N, 8·1. $C_{30}H_{33}O_{11}N_4Cl$ requires C, 54·5; H, 5·0; N, 8·5 per cent. Mixtures of isomers A and B had m.p. 152 to 160°.

N-*Benzyl*-N-(2-*hydroxy*-3-o-*toloxypropyl*)-Δ^3-*piperideino chloride.* (*a*) 1-Δ^3-Piperideino-3-*o*-toloxypropan-2-ol (49·4 g.) and benzyl chloride (25·3 g.) were warmed on the steam bath. The temperature of the mixture rose rapidly to 135° and ethanol (60 ml.) was stirred in carefully at this stage, followed by ethyl acetate (200 ml.). The mixture was left at room temperature for 24 hours when it deposited solid (A) m.p. 172 to 176° (54·7 g.). Concentration of the mother liquors yielded a solid (B) m.p. 162 to 168° (11·7 g.).

Solid (*A*) dissolved in ethylene dichloride (1200 ml.) and left at 0 to 5° overnight deposited a product (23 g.; m.p. 188 to 190°) which after crystallisation from the same solvent had m.p. 190 to 191° (isomer "A"). Found: C, 70·6; H, 7·7; N, 3·6; Cl, 9·3. $C_{22}H_{28}O_2NCl$ requires C, 70·7; H, 7·6; N, 3·8; Cl, 9·5 per cent., λmax 264 mμ (1580), 270 mμ (1947) and 277 mμ (1525) (in ethanol).

It formed an *iodide* which crystallised as the hemihydrate from ethanol in prisms, m.p. 157 to 159°. Found: C, 55·6, 55·4; H, 6·5, 6·1; N, 3·1; I, 27·5. $C_{22}H_{28}O_2NI$; $\frac{1}{2}H_2O$ requires C, 55·7; H, 6·2; N, 3·0; I, 26·8 per cent.

The original mother liquors after the removal of *isomer A* were concentrated to about 250 ml. and diluted with an equal volume of ethyl acetate. After standing at room temperature for one day, the product (m.p. 170 to 175°; 30·2 g.) was collected. Repeated crystallisation from ethylene dichloride gave *isomer B*, m.p. 171 to 173° (11·2 g.). *Solid* (*B*) crystallised twice from ethylene dichloride yielded a further crop of

isomer B m.p. 171 to 173° (4·3 g.), λmax 264 mμ (1525), 270 mμ (1898) and 277 mμ (1476) (in ethanol). Found: C, 70·4; H, 7·6; N, 3·6; Cl, 9·2. $C_{22}H_{28}O_2NCl$ requires C, 70·7; H, 7·6; N, 3·8; Cl, 9·5 per cent. The *iodide* separated from ethanol in small crystals, m.p. 176 to 177°. Found: C, 56·3; H, 6·3; N, 3·1; I, 27·2. $C_{22}H_{28}O_2NI$ requires C, 56·7; H, 6·1; N, 3·0; I, 27·3 per cent. Mixtures of isomers A and B had m.p. $< 160°$.

(*b*) A mixture of *N*-benzyl-Δ^3-piperideine (17·3 g.) and 2-hydroxy-3-*o*-toloxypropyl chloride (20·1 g.) was heated on the steam bath for 40 hours. The semicrystalline residue was dissolved in a small amount of ethanol and diluted with hot ethyl acetate. After allowing to stand overnight the solid was collected, m.p. 170 to 180° (7·5 g.). Fractionation from ethylene dichloride yielded *isomer A* (2·6 g., m.p. 188 to 190°) and *isomer B* (2·0 g., m.p. 171 to 173°).

References

1. Petrow and Stephenson, B.P. Prov. Spec. 24277/55.