ARYLOXYPROPANE DERIVATIVES

PART II. THE SYNTHESIS OF SOME ARYLOXYPROPANOLAMINES FOR STUDY AS LOCAL ANÆSTHETICS

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FOLLOWING studies[1–3] on 1-aryloxypropane-2:3-diols such as mephenesin, attention was turned in these laboratories to the derived 3-aryloxy-2-hydroxypropylamines (IV; see p. 668)[4]. Compounds of this type had previously been prepared by Boyd[5,6] in 1909 and by Fourneau[7,8] in 1910, the French worker drawing attention to their antipyretic and analgesic properties. Some years later Pyman[9] discovered the local anæsthetic activity of 3-diethylamino-1-phenoxypropan-2-ol (IV; Ar = Ph; R = R′ = Et), thereby extending the range of biological properties shown by this versatile group of compounds. More recently Ing and Ormerod[10] have described 16 propylamines based on (IV), some of which were more active than procaine in the guinea-pig weal test.

Work outlined below was directed to the preparation of 3 main types (i) simple aryloxyhydroxypropylamines (IV); these were synthesised and examined prior to the independent studies of Ing and Ormerod[10], (ii) 3-(2′:6′-xylyloxy)-2-hydroxypropylamines (IV; Ar = 2:6-xylyl), which bear a formal resemblance to the lignocaine group of local anæsthetics[11,12] and (iii) the hitherto unknown 3-diphenylmethoxy-2-hydroxypropylamines (IV; Ar = Ph_2CH).

The simpler aryloxyhydroxypropylamines listed in Table I were readily prepared by condensing the 3-aryloxy-1:2-epoxypropanes (I) with the appropriate amines (II) (route a). Their biological study, kindly undertaken by Dr. S. W. F. Underhill and his staff showed that most of them had appreciable local anæsthetic activity when tested on the rabbit's cornea. Maximum potency was shown by 1-propylamino-(IV; Ar = *o*-tolyl; R = Pr; R′ = H) and 1-*iso*propylamino-2-hydroxy-3-*o*-toloxypropane (IV; Ar = *o*-tolyl; R = *iso*Pr; R′ = H). The *iso*propyl-derivative was examined further when it was found to be superior to procaine in local anæsthetic activity using the guinea-pig weal method. Unfortunately it proved to be somewhat more toxic than procaine and its development was not proceeded with.

Following the discovery of lignocaine [2-diethylamino-acetamido-*m*-xylene (hydrochloride monohydrate)] by Löfgren[11,12] we turned to the synthesis of the analogous 3-(2′:6′-xylyloxy)-2-hydroxypropylamines (IV; Ar = 2:6-xylyl). These (see Table II) were prepared not only by reaction (*a*) (above), but also by route (*b*) employing the chlorohydrin (III; Ar = 2:6-xylyl). Their biological study, for which we are indebted to Dr. A. David and Mr. B. G. Cross, B.Sc., F.P.S., revealed a high order of potency, 1-diethylamino-2-hydroxy-3:2′:6′-xylyloxy) propane

TABLE I

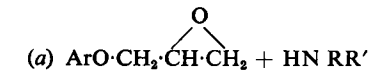
ARYLOXYPROPANOLAMINE DERIVATIVES

$ArOCH_2CHOHCH_2 \cdot NRR'$

Ar	R	R'	Base (B) Hydrochloride (H)	M.pt. ° C. B.pt. ° C.	Formula	Found per cent. C	H	N	Cl	Required per cent. C	H	N	Cl
PHENYL	H	H	H*	—	$C_9H_{14}O_2NCl$	—	—	—	—	—	—	—	—
	H	Et	H*	126	$C_{11}H_{16}O_2NCl$	56·9	7·7	5·9	—	57·0	7·8	6·1	—
	H	*n*-Pr	H	141–2	$C_{12}H_{20}O_2NCl$	58·1	7·4	5·8	14·5	58·6	8·2	5·7	14·5
	H	*i*-Pr	H	115	$C_{12}H_{20}O_2NCl$	58·3	8·0	5·6	—	58·6	8·2	5·7	—
	H	*n*-Bu	H	140	$C_{13}H_{22}O_2NCl$	60·4	8·4	5·2	13·6	60·1	8·5	5·4	13·7
	H	Bz	H	185	$C_{16}H_{20}O_2NCl$	—	—	—	12·0	—	—	—	12·1
	Et	Et	B	128/1 mm.	$C_{13}H_{21}O_2N$	—	—	6·3	—	—	—	6·3	—
o-TOLYL	H	Et	H*	115	$C_{13}H_{20}O_2NCl$	58·9	8·3	—	—	58·6	8·2	—	—
	H	*n*-Pr	H	116	$C_{13}H_{22}O_2NCl$	60·0	8·3	5·2	13·7	60·1	8·5	5·4	13·7
	H	*i*-Pr	H	135	$C_{13}H_{22}O_2NCl$	60·1	8·4	—	13·6	60·1	8·5	5·4	13·7
	H	*n*-Bu	H	101	$C_{14}H_{24}O_2NCl$	61·3	8·7	—	12·9	61·4	8·8	—	13·0
	Me	Me	B	132/1·5 mm.	$C_{12}H_{19}O_2N$	69·1	8·7	—	—	68·9	9·2	—	—
	Et	Et	H*	115	$C_{14}H_{24}O_2NCl$	61·5	8·7	5·3	—	61·4	8·8	5·1	—
	n-Bu	*n*-Bu	B	170/1 mm.	$C_{17}H_{29}O_2N$	73·9	10·5	4·7	—	73·1	10·5	5·0	—
p-TOLYL	H	Et	B	76	$C_{12}H_{19}O_2N$	69·1	8·8	6·7	—	68·9	9·2	6·7	—
	H	Et	H*	170	$C_{13}H_{20}O_2NCl$	59·1	8·0	—	—	58·6	8·2	—	—
	H	*n*-Pr	H	170	$C_{13}H_{22}O_2NCl$	60·0	8·5	5·3	—	60·1	8·5	5·4	—
	H	*n*-Bu	H*	174	$C_{14}H_{24}O_2NCl$	61·8	8·8	—	—	61·4	8·8	—	—
o-CHLOROPHENYL	Et	Et	B	106–110/0·1 mm.	$C_{13}H_{20}O_2NCl$	60·9	7·6	—	—	60·5	7·8	—	—
p-CHLOROPHENYL	Et	Et	B	120/0·1 mm.	$C_{13}H_{20}O_2NCl$	60·3	8·1	5·3	13·8	60·5	7·8	5·4	13·8
	n-Bu	*n*-Bu	B*	140/0·05 mm.	$C_{17}H_{28}O_2NCl$	65·3	8·9	4·4	11·6	65·0	9·0	4·5	11·3
p-METHOXYCARBONYL PHENYL	H	*n*-Pr	H	180	$C_{14}H_{21}O_4NCl$	55·5	6·7	4·8	11·8	55·3	7·3	4·6	11·7
	H	*n*-Bu	H	185	$C_{15}H_{24}O_4NCl$	56·9	7·6	—	—	56·7	7·6	—	—
p-ETHOXYCARBONYL-PHENYL	H	*n*-Pr	H	153	$C_{15}H_{24}O_4NCl$	56·7	7·6	4·2	11·3	56·7	7·6	4·4	11·2
	H	*n*-Bu	H	157	$C_{16}H_{26}O_4NCl$	57·8	7·8	4·5	10·7	57·9	7·9	4·2	10·7
p - BUTOXYCARBONYL-PHENYL	H	*n*-Pr	H	114	$C_{17}H_{26}O_4NCl$	59·6	7·8	—	10·3	59·0	8·2	—	10·3
1-NAPHTHYL	H	*n*-Pr	B	104	$C_{16}H_{21}O_2N$	—	—	5·4	—	—	—	5·4	—
	H	*n*-Pr	H*	138	$C_{16}H_{22}O_2NCl$	—	—	4·7	12·0	—	—	4·7	12·0
	H	*n*-Bu	B	82	$C_{17}H_{23}O_2N$	74·9	8·7	—	—	74·7	8·5	—	—
	H	*n*-Bu	H	161–2	$C_{17}H_{26}O_2NCl$	—	—	4·4	11·5	—	—	4·5	11·5

*Inactive.

(IV; Ar = 2:6-xylyl; R = R′ = Et) being 3 times more active than lignocaine using the guinea-pig corneal reflex method. All members of this series, however, produced some evidence of local necrosis on subcutaneous injection, thus rendering them unsuitable for clinical trial (*cf.* also Fosdick and Carbon)[13]. Their high biological potency led us to examine their deoxy-analogues (V) (see Table II), which were readily obtained by condensing trimethylene dibromide with sodium 2:6-xylenoxide to give ω-2:6-xylenoxypropyl bromide, followed by reaction with (II) in the usual way. This structural modification, however, failed to eliminate the irritant properties shown by the parent group (IV; Ar = 2:6-xylyl).



(*a*) $ArO{\cdot}CH_2{\cdot}\underset{\diagdown\,\diagup}{O}CH{\cdot}CH_2 + HN\,RR'$

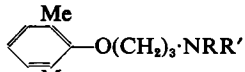
(I) (II)

$ArO{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2NRR'$

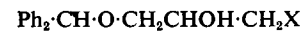
(IV)

(*b*) $ArO{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2{\cdot}Hal + (II)$

(III)

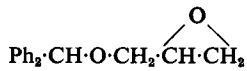


(V)

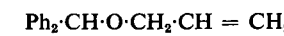


$Ph_2{\cdot}CH{\cdot}O{\cdot}CH_2CHOH{\cdot}CH_2X$

(VI)

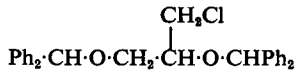


(VII)



$Ph_2{\cdot}CH{\cdot}O{\cdot}CH_2{\cdot}CH = CH_2$

(VIII)

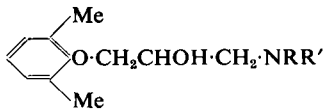


(IX)

Extension of the work to the hitherto unknown 3-diphenylmethoxy-2-hydroxypropylamine series (VI; X = NRR′) offered initial difficulty. 1:2-Epoxy-3-diphenylmethoxypropane (VII), required as an intermediate in route (*a*) was not obtained by heating diphenylcarbinol with epichlorohydrin in the presence of basic catalysts such as pyridine. The required epoxide (VII) was ultimately obtained in 40 per cent. yield by condensing sodium diphenyl methoxide with epichlorohydrin in benzene solution. For small scale work, however, epoxidation of diphenylmethyl allyl ether (VIII) proved a more convenient route to (VII). The allyl ether (VIII) had previously been described by D'yakonov[14], who obtained it in 32 per cent. yield by condensing diphenyldiazomethane with allyl alcohol. We now find that (VIII) is readily prepared in high yield by (i) heating diphenylmethyl bromide with excess allyl alcohol in the presence of powdered potassium hydroxide and (ii) by heating diphenylcarbinol with allyl alcohol in benzene solution under reflux in the presence of toluene *p*-sulphonic acid as catalyst and with continuous removal of the water formed during the reaction. Its epoxidation with perbenzoic acid

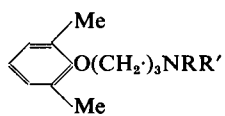
TABLE II

1-AMINO-2-HYDROXY-3(2′:6′-XYLYLOXY) PROPANE DERIVATIVES



R	R′	Base/Salt	M.pt. ° C. B.pt. ° C.	Formula	Found per cent. C	H	N	Cl	Required per cent. C	H	N	Cl
H	Et	B	76	$C_{13}H_{21}O_2N$	70·3	9·5	6·0	—	69·9	9·5	6·3	—
H	Et	H	145–7	$C_{13}H_{22}O_2NCl$	60·5	8·8	5·3	—	60·1	8·5	5·4	13·7
H	*n*-Pr	B	79	$C_{14}H_{23}O_2N$	70·8	9·9	6·0	—	70·8	9·8	5·9	—
H	*n*-Pr	H	152–3	$C_{14}H_{24}O_2NCl$	61·1	9·0	5·2	12·8	61·4	8·8	5·1	13·0
H	*i*-Pr	B	75–7	$C_{14}H_{23}O_2N$	71·0	9·6	—	—	70·8	9·8	5·9	—
H	*i*-Pr	H	141–2	$C_{14}H_{24}O_2NCl$	61·5	8·7	4·5	—	61·4	8·8	5·1	—
Et	Et	B	121/0·2 mm.	$C_{15}H_{25}O_2N$	71·3	10·3	5·4	—	71·6	10·1	5·6	—
Et	Et	H	114–5	$C_{15}H_{26}O_2NCl$	62·4	9·2	4·7	12·5	62·5	9·1	4·9	12·3
PIPERIDINE		H	164–6	$C_{16}H_{26}O_2NCl$	63·8	8·9	4·8	11·7	64·1	8·7	4·7	11·9

1-AMINO-3(2′:6′-XYLYLOXY) PROPANE DERIVATIVES



H	*n*-Pr	H	162–3	$C_{14}H_{21}ONCl$	65·3	9·8	5·3	13·4	65·2	9·3	5·4	13·8
MORPHOLINE		H	170–1	$C_{15}H_{24}O_2NCl$	—	—	5·1	—	—	—	4·9	—
Δ^3-PIPERIDEINE		H	177–8	$C_{16}H_{24}ONCl$	67·8	8·5	4·4	13·0	68·2	8·5	5·0	12·6

in benzene solution furnished (VII) in yields greater than 90 per cent. Reaction of (VII) with (II) gave the propanolamines listed in Table III.

Attempts to prepare (VI; X = NRR′) by route (*b*) were only partly successful. Reaction of diphenylcarbinol with epichlorohydrin in the presence of sulphuric acid as catalyst[7,8] led to the formation of *sym*-tetraphenyl methyl ether in place of the expected (VI; X = Cl).

The required intermediate was ultimately obtained by making use of an earlier observation that diphenylmethylcarbinol reacts smoothly with ethylene chlorohydrin or cyanohydrin in the presence of toluene *p*-sulphonic acid as catalyst [*cf.* the preparation of (VIII) by method (ii) (above)] to give diphenylmethoxyethyl chloride and diphenylmethoxyethyl cyanide, respectively. Extending this reaction to diphenylcarbinol and α-monochlorohydrin in equimolar ratio led only to the formation of the bimolecular condensation product (IX). By using 3 molar proportions of α-monochlorohydrin, however, a 25 per cent. yield of 1-chloro-2-hydroxy-3-diphenylmethoxypropane (VI; X = Cl) was obtained, together with larger quantities of (IX). Reaction of (VI; X = Cl) with (II) gave (VI; X = NRR′) in the usual way.

Biological study of the diphenylmethoxypropanolamines listed in Table III was kindly undertaken by Dr. A. David and Mr. B. G. Cross, B.Sc., F.P.S. The compounds, in general, showed marked local anæsthetic activity by the guinea-pig corneal reflex method, and on application to an exposed human nerve ending stimulated by the Newton Victor electronic nerve stimulator. In common with the lignocaine analogues, however, they produced necrosis at the site of injection.

Experimental

M.pts. are uncorrected.

The following example illustrates the method used for the preparation of the simpler 3-aryloxy-2-hydroxypropylamines listed in Table I.

Preparation of 1-iso*Propylamino*-2-*hydroxy*-3-*o*-*toloxypropane* (IV; Ar = *o*-tolyl; R = *iso*Pr; R′ = H). Glycide *o*-tolyl ether (23 g.) and *iso*propylamine (30 g.) were slightly warmed until reaction commenced and the mixture then water-cooled to moderate the exothermic condensation. Reaction was then completed by heating on the steam bath for 1 hour. After distilling off excess amine, the residual solids were dissolved in benzene and the solution treated with hydrogen chloride. The precipitated *hydrochloride* was collected and purified by crystallisation from methanol/ether.

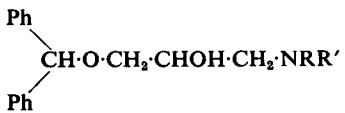
The following examples indicate the methods used for the preparation of the 3-(2′:6′-xylyloxy)-2-hydroxypropylamines listed in Table II.

Preparation of 1-*Diethylamino*-2-*hydroxy*-3-(2′:6′-*xylyloxy*)-*propane* (IV, Ar = 2:6-xylyl; R = R′ = Et). (*a*) Glycide 2:6-xylyl-ether was obtained in 70 per cent. yield by condensation of 2:6-xylenol with epichlorohydrin[15]. It had b.pt. 84° C. at 0·5 mm. Found: C, 73·5; H, 8·0. $C_{11}H_{14}O_2$ requires C, 74·1; H, 7·9 per cent.

The glycide ether (44·5 g.) was heated with diethylamine (21·9 g.) under reflux for 5 hours. Excess diethylamine was removed by distillation and

TABLE III

1-AMINO-2-HYDROXY-3-DIPHENYLMETHOXYPROPANE DERIVATIVES



R	R′	Base or Salt	M.pt. ° C. B.pt. ° C.	Formula	Found per cent.				Required per cent.			
					C	H	N	Cl	C	H	N	Cl
H	Me	B	83	$C_{17}H_{21}O_2N$	75·0	8·1	5·2	—	75·2	7·8	5·2	—
H	Me	H	135–6	$C_{17}H_{22}O_2NCl$	66·0	6·8	4·6	11·8	66·3	7·2	4·6	11·5
H	Et	B	90–1	$C_{18}H_{23}O_2N$	76·3	8·2	4·9	—	75·8	8·1	4·7	—
H	Et	H	117–9	$C_{18}H_{24}O_2NCl$	—	—	4·6	11·4	—	—	4·4	11·0
H	*n*-Pr	B	61–3	$C_{19}H_{25}O_2N$	76·2	8·5	4·7	—	76·2	8·4	4·7	—
H	*n*-Pr	H	106–9	$C_{19}H_{26}O_2NCl$	—	—	4·2	11·3	—	—	4·2	10·6
H	*i*-Pr	B	55–60	$C_{19}H_{25}O_2N$	76·0	8·2	4·8	—	76·2	8·4	4·7	—
H	*i*-Pr	H	199–201	$C_{19}H_{26}O_2NCl$	67·8	7·8	4·1	10·6	68·0	7·8	4·2	10·6
Me	Me	B	154/0·3 mm.	$C_{18}H_{23}O_2N$	75·7	7·9	4·7	—	75·8	8·1	4·9	—
Et	Et	B	156/0·4 mm.	$C_{20}H_{27}O_2N$	76·7	8·9	4·1	—	76·6	8·7	4·5	—
PIPERIDINE		B	57–9	$C_{21}H_{27}O_2N$	77·7	7·9	4·4	—	77·5	8·4	4·2	—
		Salicylate	136–8	$C_{28}H_{33}O_5N$	72·5	6·5	3·1	—	72·5	7·2	3·0	—
N-BENZYL PIPERAZINE		H	218–220	$C_{27}H_{34}O_2N_2Cl_2$	—	—	6·0	—	—	—	5·7	—
PIPERAZINE (BIS)		B	116–8	$C_{36}H_{42}O_4N_2$	76·2	7·6	4·9	—	76·3	7·5	5·0	—
PIPERAZINE (BIS)		H	216–8 (d)	$C_{36}H_{44}O_4N_2Cl_2$	—	—	4·4	11·5	—	—	4·4	11·1

the product fractionally distilled at 0·2 mm. to give a nearly quantitative yield of the required *base* as an oil.

(*b*) 1-*Chloro*-2-*hydroxy*-3-(2′ : 6′-*xylyloxy*)-*propane* was prepared by the method described earlier[16] and obtained in high yield as an oil, b.pt. 91° C. at 0·1 mm. Found: C, 61·3; H, 7·2; Cl, 16·7. $C_{11}H_{15}O_2Cl$ requires, C, 61·5; H, 7·0; Cl, 16·5 per cent.

The chlorohydrin (21·5 g.) in benzene (40 ml.) was treated with diethylamine (15 g.) and the mixture heated on the steam bath for 5 hours. After washing with water to remove diethylamine hydrochloride, the benzene solution was dried and treated with hydrogen chloride. The precipitated 1-*diethylamino*-2-*hydroxy*-3-(2′ : 6′-*xylyloxy*)*propane hydrochloride* was purified by crystallisation from ethyl acetate containing a trace of methanol.

Preparation of 1-*Bromo*-3-(2′ : 6′-*xylyloxy*)*propane.* Sodium (34·5 g.) dissolved in ethanol (750 ml.) was added to 2 : 6-xylen-1-ol (183 g.). 1 : 3-Dibromopropane (909 g.) was then added and the mixture heated under reflux on the steam bath for 4 hours. Excess alcohol was removed on the steam bath and the residue treated with water and thoroughly extracted with chloroform. The chloroform extracts were washed with water, dried and the solvent removed. The residue was purified by distillation under reduced pressure to give 1-*bromo*-3-(2′ : 6′-*xylyloxy*)*propane* as an oil, b.pt. 80° C. at 0·5 mm. Found: C, 54·5; H, 6·51; Br, 32·6. $C_{11}H_{15}OBr$ requires C, 54·3; H, 6·2; Br, 32·9 per cent.

Reaction of the foregoing compound with (II) is illustrated by the following example.

Preparation of 1-n-*Propylamino*-3-(2′ : 6′-*xylyloxy*)*propane.* 1-Bromo-3(2′ : 6′-xylyloxy)propane (11·7 g.) was treated with *n*-propylamine (6·0 g.) when an exothermic reaction occurred. The mixture was heated under reflux for 2 hours. After allowing to stand overnight, the separated propylamine hydrobromide was collected and washed with ether, which was subsequently used to isolate the product in the usual way. The base so obtained was purified as the hydrochloride.

Preparation of diphenylmethyl allyl ether (VIII). (*a*) Diphenylcarbinol (87 g.) and allyl alcohol (32 g.) in benzene (250 ml.) were treated with toluene *p*-sulphonic acid (200 mg.) and the mixture refluxed for 20 hours in a Dean-Stark apparatus. The cooled solution was washed with sodium carbonate solution and then with water and the solvent removed. Fractionation under reduced pressure gave (VIII), b.pt. 120° C. at 0·2 mm. Found: C, 85·8; H, 6·9. Calc. for $C_{16}H_{16}O$: C, 85·7; H, 7·2 per cent.

(*b*) Diphenylmethyl bromide (160 g.) in allyl alcohol (200 g.) was heated under reflux on the steam bath and finely powdered potassium hydroxide (40 g.) added in 5 g. portions at 10 minute intervals with occasional shaking. Heating was continued for a further 8 hours, when the mixture was poured into water and the product isolated with chloroform. Fractionation under reduced pressure furnished (VIII), b.pt. 101° C. at 0·2 mm. Found: C, 85·7; H, 7·2. Calc. for $C_{16}H_{16}O$: C, 85·7; H, 7·2 per cent.

1:2-*Epoxy*-3-*diphenylmethoxypropane* (VIII). (*a*) The foregoing compound (26·4 g.) was added to a cold solution of perbenzoic acid (18·32 g.) in benzene (490 ml.) and the mixture left at 0° to 5° C. for 4 days. The benzene solution was then washed consecutively with dilute aqueous solutions of sodium hydroxide, sodium iodide and sodium thiosulphate and then with water, when the benzene was removed by distillation. Fractionation under reduced pressure gave 1:2-*epoxy*-3-*diphenylmethoxypropane*, b.pt. 114° C. at 0·1 mm. Found: C, 80·0; H, 6·5. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7 per cent. The product solidified on standing.

(*b*) Diphenylcarbinol (92 g.) in methanol (100 ml.) was added to sodium methoxide (11·6 g. sodium in 160 ml. methanol) and the mixture taken to dryness under reduced pressure at 100° C. The resulting sodium salt was suspended in dry benzene (400 ml.), epichlorohydrin (92·5 g.) added and the mixture heated under reflux for 16 hours. After acidification with acetic acid, filtration and water washing, the benzene was removed by distillation and the residue purified by fractionation to yield (VII), b.pt. 130° to 134° C. at 0·4 mm.

(*c*) Experiment (*b*) was repeated with the addition of sodium iodide (2 g.). After filtration, the benzene layer was treated with hydrogen chloride to convert any (VII) present into (VI; X = Cl). The benzene solution was then washed with sodium thiosulphate solution and with water and the solvent removed. Distillation of the complex mixture under reduced pressure gave a fraction (24 g.), b.pt. 210° C. at 0·4 mm. which solidified and yielded $\alpha\alpha\beta\beta$-tetraphenylethane[17], m.pt. 207° to 209° C. on crystallisation from acetone. Found: C, 93·1; H, 6·8. Calc. for $C_{26}H_{22}$: C, 93·4; H, 6·6 per cent.

The condensation of 1:2-epoxy-3-diphenylmethoxypropane with (II) to give the propanolamines listed in Table (III) is typified by the following example.

Preparation of 1-*diethylamino*-2-*hydroxy*-3-*diphenylmethoxypropane* (VI; X = NEt_2). The epoxide (VII) (crude, 15 g.) in benzene (30 ml.) was treated with anhydrous diethylamine (7·9 g.) and the mixture heated under reflux for 6 hours. The product was isolated with chloroform and purified by fractionation under reduced pressure, a small fore-run being rejected. The main fraction (b.pt. 150° C. at 0·4 mm.) was identified as the required propanolamine, which was characterised as indicated in Table III.

sym-*Tetraphenylmethyl ether*. Diphenylcarbinol (23 g.) in epichlorohydrin (23·2 g.) was treated with conc. sulphuric acid (0·3 ml.) with swirling, when a slight exothermic reaction occurred. The mixture was heated on the steam bath for 24 hours, cooled and the product extracted with chloroform, which was washed with aqueous sodium bicarbonate and then with water. Removal of the chloroform followed by fractionation under reduced pressure yielded (i) unchanged diphenylcarbinol, b.pt. 110° to 114° C. at 0·5 mm., (ii) a fraction (11 g.), b.pt. 200° C. at 0·5 mm., which was crystallised from light petroleum (b.pt. 60 to 80° C.) to yield *sym*-tetraphenylmethyl ether[18], needles, m.pt. 109° C. Found: C, 89·4; H, 6·0. Calc. for $C_{26}H_{22}O$: C, 89·1; H, 6·3 per cent.

2-*Diphenylmethoxyethyl chloride.* Diphenylcarbinol (61·3 g.) ethylene chlorohydrin (54 g.), toluene *p*-sulphonic acid (500 mg.) and toluene (250 ml.) was heated under reflux in the Dean-Stark apparatus for 30 minutes. After washing with sodium bicarbonate solution and with water the solvent was removed and the residue fractionated under reduced pressure to give 2-diphenylmethoxyethyl chloride[19], b.pt. 122° C. at 0·3 mm. Found: C, 73·3; H, 6·2; Cl, 14·7. Calc. for $C_{15}H_{15}OCl$: C, 73·0; H, 6·1; Cl, 14·4 per cent.

By employing ethylene cyanohydrin (28·5 g.), 2-*diphenylmethoxyethyl cyanide* was obtained, b.pt. 158° C. at 0·3 mm., m.pt. 58° C. (after crystallisation from light petroleum). Found: C, 80·6; H, 6·2; N, 6·0. $C_{16}H_{15}ON$, requires C, 81·0; H, 6·4; N, 5·9 per cent.

Preparation of 1-*chloro*-2-*hydroxy*-3-*diphenylmethoxypropane* (VI, X = Cl). (*a*) A solution of 1:2-epoxy-3-diphenylmethoxypropane in benzene was saturated with hydrogen chloride. After standing 24 hours at room temperature the solution was washed free from acid, the solvent removed and the residue fractionated under reduced pressure to give 1-*chloro*-2-*hydroxy*-3-*diphenylmethoxypropane*, b.pt. 140° C. at 0·05 mm. Found: C, 69·7; H, 6·3; Cl, 12·6. $C_{16}H_{17}O_2Cl$ requires C, 69·4; H, 6·2; Cl, 12·8 per cent.

(*b*) Diphenylcarbinol (61·3 g.) α-monochlorhydrin (46·3 g.) and toluene *p*-sulphonic acid (500 mg.) in toluene (250 ml.) were heated under reflux in the Dean-Stark apparatus for 2½ hours when water (6 ml. 100 per cent. theory) had collected. The toluene solution was washed with aqueous sodium carbonate and with water and the solvent removed. Fractionation of the residue under reduced pressure gave a small fore-run (2·7 g.), b.pt. 130° to 190° at 0·3 mm. and a main fraction (58·3 g.), b.pt. 230° C. at 0·4 mm. On crystallisation from light petroleum it yielded 1-*chloro*-2:3-bis-(*diphenylmethoxy*)*propane* (IX), crystals, m.pt. 85° to 87° C. Found: C, 78·0; H, 6·1; Cl, 8·4. $C_{29}H_{27}O_2Cl$, requires C, 78·6; H, 6·2; Cl, 8·0 per cent.

When the reaction was repeated using three molar equivalents of α-monochlorohydrin (110·5 g.) condensation took place within 1 hour. Fractionation of the product yielded the required chlorohydrin (19 g.), b.pt. 140° at 0·05 mm. and (IX) (40 g.) m.pt. 85° to 87° C.

Preparation of 1-(4′-*Benzylpiperazino*)-2-*hydroxy*-3-*diphenylmethoxypropane* (VI; X = NC_2H_4NBz). The following example illustrates the method used for condensing (VI; X = Cl) with (II): (VI; X = Cl] (2·8 g.) in ethanol was treated with sodium hydroxide (400 mg.) dissolved in the minimum volume of water and benzylpiperazine (1·8 g.) added. After 1 hour at room temperature the mixture was heated on the steam bath for 3 hours, after which it was diluted with water and the product isolated with chloroform. Conversion to the hydrochloride and crystallisation from ethanol containing a little water furnished 1-(4′-benzylpiperazino)-2-hydroxy-3-diphenylmethoxypropane dihydrochloride.

Summary

1. Propane derivatives of types $ArO{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2NRR'$,  and $Ph_2{\cdot}CH{\cdot}O{\cdot}CH_2CHOHCH_2NRR'$ have been prepared for examination as local anæsthetic agents.
2. Though active, the compounds proved irritant.

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