ANALGESICS. PART I. SOME ARYLOXYPROPANOLAMINES

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The synthesis is described of some 3-aryloxy-2-hydroxypropylamines and *N*-(ω-aryloxyalkyl)-piperidines, which were required for study as analgesics.

OUR object was the preparation of an orally active generally useful analgesic agent free from the limitations of acetylsalicylic acid. To this end we selected the aryloxypropanolamine type (II) for initial study. Some compounds of this class had previously been examined in these Laboratories for local anaesthetic activity[1] (cf. Ing and Ormerod[2]), when the marked analgesic properties of certain members had become apparent (cf. Fourneau[7,8]). The series was therefore extended as indicated in the present communication. Some miscellaneous types bearing a formal resemblance to the aryloxypropanolamines (II) were also prepared and form the subject of Part II. At this stage a publication appeared by Way and others[3] describing the analgesic activity of some substituted salicylamides, which led us to extend our studies to the salicylic acid derivatives described in Part III. Finally, the preparation of aryloxypropanolamines from $\triangle^3$-piperideine was undertaken. These proved superior in analgesic activity to the earlier compounds and one of them, 1-$\triangle^3$-piperideino-3-*o*-toloxypropan-2-ol hydrochloride ("Tolpronine") was selected for fuller evaluation. Biological studies were conducted by Dr. A. David and his colleagues, who kindly provided the analgesic data.

Work on the aryloxypropanolamines began with a study of 3-*o*-chlorophenoxy-2-hydroxypropylamine as a model compound. Mono-alkyl and alkaryl derivatives (II; Ar = *o*-Cl·C_6H_4–, R = H, R′ = alkyl or alkaryl) were first prepared and the series thereafter extended to the dialkyl derivatives (R and R′ = alkyl) and to compounds in which the primary amino-group was replaced by a cyclic structure such as piperidine or morpholine. *o*-Methoxyphenylhydroxypropylamines were next synthesised, as well as two 3:4:5-trimethoxyphenoxypropylamines which contained the trimethoxyphenyl group, characteristic of mescaline. The series (see Table II) was completed with some *o*-toloxy- and substituted phenoxyhydroxypropylamines.

The preferred route to the foregoing compounds (II) lay in the condensation of the 3-aryloxy-1:2-epoxypropanes (I) with the appropriate amines:

$$\underset{\text{(I)}}{ArO{\cdot}CH_2{\cdot}CH\overset{O}{\diagdown\!\diagup}CH_2} + HNRR' \longrightarrow \underset{\text{(II)}}{ArO{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2NRR'} \quad .. \quad (i)$$

The synthesis of the intermediate 3-aryloxy-1:2-epoxypropanes (I) needed for this purpose required initial study. Though generally obtained by condensing the phenol with 2:3-epoxypropyl chloride in aqueous alkali,

their preparation is by no means as simple as is implied in the literature[4,5], in that the products obtained depend not only upon the experimental conditions employed for the condensation, but also upon the nature of the phenol. We have, therefore, studied the condensation in some detail.

Reaction between a phenol and 2:3-epoxypropyl chloride is slow and incomplete in aqueous solutions containing a catalytic quantity (0·1 mole) of sodium hydroxide. The main product in this case is the 3-aryloxy-2-hydroxypropyl chloride (III) (cf. reaction (ii)), admixed with much starting material and only minimal quantities of the required epoxide (I).

$$\mathrm{Ar{\cdot}OH + CH_2 \cdot CH{\cdot}CH_2Cl \longrightarrow ArO{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2Cl} \quad \text{(ii)}$$

(III)

The reaction thus resembles that which obtains with basic catalysts in non-aqueous media[6] when the chlorides (III) are obtained, though in much higher yields.

Increase in the amount of alkali employed leads to increased condensation between the phenol and 2:3-epoxypropyl chloride to give the chloride (III) which then undergoes partial conversion to the epoxide (I). The yield of epoxide obtained reaches a maximum for many phenols when 1·2 moles of alkali hydroxide are present. Reaction presumably occurs between the phenolate ion and 2:3-epoxypropyl chloride in the following way:

$$\mathrm{ArO^- + CH_2{-}CH{\cdot}CH_2{-}Cl \longrightarrow ArO{\cdot}CH_2{\cdot}CH{-}CH_2 + Cl^-} \quad \text{(iii)}$$

Still higher concentrations of alkali lead to the formation of appreciable quantities of the bis-1:3-aryloxypropan-2-ols (IV), which are otherwise obtained in only small amounts.

$$\mathrm{ArO^- + CH_2 \cdot CH{\cdot}CH_2{\cdot}OAr \longrightarrow ArO{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2{\cdot}OAr} \quad \text{(iv)}$$

(IV)

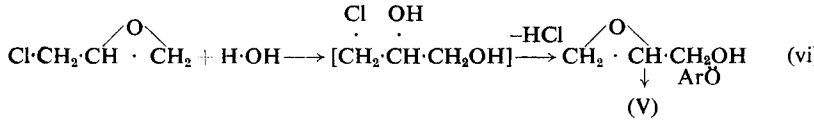
Their (IV) formation is facilitated by increase of reaction temperature.

The glyceryl ether (V) forms a further product of the condensation. Its production is unlikely to proceed *via* the epoxide (I) (reaction (i)) as we have found that the latter (I; Ar = *o*-tolyl) is hydrolysed only to the extent of about 1·5 per cent after 16 hours treatment with 0·4N aqueous sodium hydroxide.

$$\mathrm{ArO{\cdot}CH_2{\cdot}CH \cdot CH_2 + H{\cdot}OH \longrightarrow ArO{\cdot}CH_2{\cdot}CHOH{\cdot}CH{\cdot}OH} \quad \text{(v)}$$

(V)

Its (V) formation may well take place through condensation of the phenol with 2:3-epoxypropyl alcohol ("glycidol"), itself formed by hydrolysis of the 2:3-epoxypropyl chloride (reaction (vi)).



(V)

The rates at which the foregoing transformations occur are influenced by the substituents in the aryl nucleus of the phenol and varying proportions of by-products (III, IV and V) are obtained from different phenols under the same reaction conditions. Thus for example electron-releasing substituents such as methyl, which lower the pseudo-acidic character of the phenol, depress reactivity. This is illustrated by the condensation of phenol and *o*-cresol with 2:3-epoxypropyl chloride in normal aqueous

TABLE I

CONDENSATION OF PHENOL (2·0 MOLES) WITH 2:3-EPOXYPROPYL CHLORIDE (2·2 MOLES) IN ALKALINE SOLUTION. YIELDS OF PRODUCTS IN G.

Mole equiv. of potassium hydroxide	3-Phenoxy-1:2-epoxypropane b.p. 80° at 1·0 mm.	3-Phenoxy-2-hydroxypropyl chloride b.p. 112° at 1·0 mm.	1:3-Bis-phenoxy propane-2-ol m.p. 81°
0·1	103 b.p. 90 to 115° at 1·0 mm.		0
0·5	230 b.p. 96 to 112° at 1·0 mm.		8
1·0	162	58	9
1·2	195	3	25
2·0	113·5	0	42·5

sodium carbonate solution at room temperature for 48 hours. The former gives a 30 per cent and the latter only a 6 per cent yield of the corresponding 3-aryloxy-2-hydroxypropyl chloride. Here however the retarding steric effect of the *ortho* methyl group must also be taken into consideration.

The 3-aryloxy-1:2-epoxypropanes (I), prepared as described above, condense readily with amines (see reaction (i)) to give the required aryloxyhydroxypropylamines[7–11]. Primary amines additionally give low yields of tertiary bases of type (VI) as by-products.

$$(Ar{\cdot}O{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2)_2N\ R$$

(VI)

Secondary bases such as piperidine may give complex products of unknown constitution if excess of epoxide (I) is present in the mixture. In addition, quaternary salts of type (VII) may be isolated. These result from reaction between the product (II) and the 3-aryloxy-2-hydroxypropyl chloride (III). The last compound is generally present to the extent of about 5 per cent in samples of the epoxide (I) unless these have been specially purified by further distillation. This additional purification step, however, is not regarded as necessary.

TABLE II

ARYLOXYPROPANOLAMINES

$Ar{\cdot}O{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2{\cdot}NR\,R'$

Ar	R	R′	Base (B) Hydrochloride (H)	m.p. or b.p. ° C.	Formula	Found per cent				Required per cent			
						C	H	N	Cl	C	H	N	Cl
Phenyl	Et	Ph	B	156/0·1 mm.	$C_{17}H_{21}O_2N$	74·8	7·9			75·2	7·8		
	Piperidine		B	55	$C_{14}H_{21}O_2N$	71·6	8·9	6·0		71·4	9·0	6·0	
			O-Acetyl	124/0·1 mm.	$C_{16}H_{23}O_3N$	69·7	8·3	4·9		69·3	8·4	5·1	
	Pyrrolidine		B	124/0·4 mm.	$C_{13}H_{19}O_2N$			5·9				6·3	
			H	121–122	$C_{13}H_{20}O_2NCl$	60·1	7·7	5·4		60·5	7·8	5·4	
o-Tolyl	H	*iso* Bu	H	132	$C_{14}H_{24}O_2NCl$	61·4	8·5	5·4		61·4	8·8	5·1	
	H	*sec.*-Octyl	H	98	$C_{18}H_{32}O_2NCl$	65·7	9·5	4·4		65·5	9·8	4·2	
	H	Allyl	B	68	$C_{13}H_{19}O_2N$	70·0	8·5	6·3		70·5	8·7	6·3	
	H	Allyl	H	93	$C_{13}H_{20}O_2NCl$	60·6	7·8			60·5	7·8		
	H	Benzyl	B	84	$C_{17}H_{21}O_2N$	75·2	7·9			75·2	7·8		
	H	β-Phenylethyl	H	130	$C_{18}H_{24}O_2NCl$	67·7	7·1	4·5		67·2	7·5	4·4	
	H	*cyclo*Hexyl	H	166	$C_{16}H_{30}O_2NCl$	64·6	8·7			64·1	8·4		
	H	2-Pyridyl	B	138	$C_{15}H_{18}O_2N_2$	69·9	7·2	11·4		69·8	7·0	10·9	
	Benzyl	Benzyl	B	206/0·4 mm.	$C_{24}H_{27}O_2N$	80·2	7·5	3·7		79·7	7·5	3·9	
	β-Hydroxyethyl	β-Hydroxyethyl	B	230/0·1 mm.	$C_{14}H_{23}O_4N$	63·2	8·6	5·6		62·4	8·6	5·2	
	Piperidine		B	56–58	$C_{15}H_{23}O_2N$			5·5				5·6	
			H	128–130	$C_{15}H_{24}O_2NCl$	63·1	8·5	4·9	12·2	63·0	8·5	4·9	12·4
	2-Methylpiperidine		B	80–82	$C_{16}H_{25}O_2N$	73·5	9·4	5·2		73·0	9·6	5·3	
			H	162–164	$C_{16}H_{26}O_2NCl$	64·2	8·5	4·5	11·9	64·1	8·7	4·7	11·8
	4-Methylpiperidine		B	54–55	$C_{16}H_{25}O_2N$	73·3	9·5	5·1		73·0	9·6	5·3	
	3-Ethoxycarbonylpiperidine		H	139–140	$C_{18}H_{28}O_4NCl$	60·4	7·9	3·6		60·4	7·9	3·9	
	Morpholine		B	68–69	$C_{14}H_{21}O_3N$	67·0	8·5	5·6		66·9	8·4	5·6	
	Pyrrolidine		B	126/0·4 mm. solidified	$C_{14}H_{21}O_2N$	71·2	9·2	5·8		71·4	9·0	6·0	
			H	108–110	$C_{14}H_{22}O_2NCl$	61·8	8·1	5·4		61·8	8·2	5·2	
(β-Methyl) {	Pyrrolidine		B	120/0·6 mm.	$C_{15}H_{23}O_2N$	72·2	9·2	5·6		72·2	9·3	5·6	
			H	161–163	$C_{15}H_{24}O_2NCl$	62·9	8·4	4·9	12·2	63·0	8·5	4·9	12·4
	H	3:4:5-Trimethoxy	H	154–156	$C_{19}H_{26}O_5NCl$	59·2	6·9			59·4	6·8		
p-Tolyl	Et	Et	B	132/0·5 mm.	$C_{14}H_{23}O_2N$	71·4	9·3	5·8		70·8	9·8	5·9	
2:4-Xylyl	H	Et	B	103	$C_{13}H_{21}O_2N$	70·1	9·7	6·2		69·9	9·5	6·3	
			H	118	$C_{13}H_{22}O_2NCl$	60·3	8·6	5·4	13·2	60·1	8·5	5·4	13·7
	H	*n*-Pr	B	102	$C_{14}H_{23}O_2N$	70·4	9·7	5·8		70·8	9·8	5·9	
			H	111	$C_{14}H_{24}O_2NCl$				13·0				13·0
	H	*n*-Bu	B	75	$C_{15}H_{25}O_2N$	71·7	9·7	5·6		71·7	10·0	5·6	
			H	134	$C_{15}H_{26}O_2NCl$	62·8	8·9		12·4	62·6	9·1		12·3

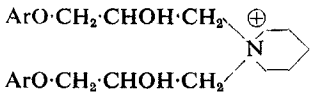
TABLE II—*continued*

Ar	R	R′	Base (B) Hydrochloride (H)	m.p. or b.p. ° C.	Formula	Found per cent				Required per cent			
						C	H	N	Cl	C	H	N	Cl
o-Chorophenyl	H	Me	B	85–88									
			Picrate	139	$C_{16}H_{17}O_9N_4Cl$	43·6	4·0	12·2	7·7	43·2	3·9	12·6	8·0
	H	Et	B	85–88	$C_{11}H_{16}O_2NCl$			5·7	15·3			6·1	15·5
	H	*n*-Pr	B	93–95	$C_{12}H_{18}O_2NCl$			5·8				5·8	
	H	*iso*Pr	B	88–90									
			Picrate	170–171	$C_{18}H_{21}O_9N_4Cl$	45·8	4·3	11·5	7·6	45·7	4·5	11·9	7·5
	H	*n*-Bu	B	64–68	$C_{13}H_{20}O_2NCl$	60·2	7·8	5·4	13·4	60·5	7·8	5·4	13·8
			H	100–102	$C_{13}H_{21}O_2NCl_2$				24·2				24·1
	H	*sec.*-Bu	B	140/0·5 mm.									
			H	150–152	$C_{13}H_{21}O_2NCl_2$	53·5	7·6	4·6	24·1	53·0	7·2	4·8	24·1
	H	*n*-Amyl	B	64–68	$C_{14}H_{22}O_2NCl$	62·2	8·0	5·2	13·0	61·8	8·2	5·2	13·1
	H	*iso*Amyl	B	137/0·2 mm.									
			H	119–121	$C_{14}H_{22}O_2NCl_2$	54·6	7·4	4·5	23·2	54·5	7·5	4·5	23·0
	H	Allyl	B	62–65	$C_{12}H_{16}O_2NCl$			6·0				5·8	
	H	Phenyl	B	184/0·1 mm.	$C_{15}H_{16}O_2NCl$			5·2				5·0	
	H	*p*-Tolyl	B	75–78									
			Picrate	130–133	$C_{22}H_{21}O_9N_4Cl$	50·5	4·2	10·5	6·6	50·7	4·1	10·8	6·8
	H	Benzyl	B	85–87	$C_{16}H_{18}O_2NCl$	65·8	6·1	4·6	12·2	65·9	6·2	4·8	12·2
	H	β-Phenyl *iso*Propyl	B	184–188/0·3 mm.	$C_{18}H_{22}O_2NCl$			4·4	11·5			4·4	11·1
	H	*cyclo*Hexyl	B	81–84									
			Picrate	204–205	$C_{21}H_{23}O_9N_4Cl$	49·2	4·7	10·8	7·0	49·2	4·9	10·9	6·9
			H	178–179	$C_{15}H_{23}O_2NCl_2$			4·4	21·5			4·4	22·2
	H	$-CONH_2$	B	113–115	$C_{10}H_{13}O_3N_2Cl$	49·4	5·2	11·2	14·5	49·1	5·4	11·5	14·5
	Me	Me	B	110–114/0·4 mm.	$C_{11}H_{16}O_2NCl$			5·9	15·1			6·1	15·5
	n-Bu	*n*-Bu	B	136–140/0·1 mm.	$C_{17}H_{28}O_2NCl$			4·4				4·5	
	n-Hexyl	*n*-Hexyl	B	192–194/0·5 mm.	$C_{21}H_{36}O_2NCl$			4·2	10·1			3·8	9·6
	n-Octyl	*n*-Octyl	B	206/0·3 mm.	$C_{25}H_{44}O_2NCl$			3·4	7·9			3·3	8·3
	Piperidine		B	71–73	$C_{14}H_{20}O_2NCl$			5·0 }	13·2 }			5·2	13·2
								5·1 }	12·9 }				
			H	145–147	$C_{14}H_{21}O_2NCl_2$	54·6	6·9	4·5	23·7	54·9	6·9	4·6	23·2
			Aspirin Salt	114–116	$C_{29}H_{29}O_6NCl$	61·8	6·1	3·2		61·4	6·3	3·1	
			Salicylate	119	$C_{21}H_{28}O_5NCl$			3·4	9·2			3·4	8·7
			"O" acetyl	136/0·1 mm.	$C_{16}H_{22}O_3NCl$			4·6				4·5	
	Morpholine		B	66–69	$C_{13}H_{18}O_3NCl$	57·3	6·4	4·8		57·4	6·7	5·2	
	Pyrrolidine		B	132/0·5 mm.; 60–61	$C_{15}H_{18}O_2NCl$	60·8	6·8	5·4		61·0	7·1	5·5	
p-Chlorophenyl	H	*n*-Bu	B	74	$C_{13}H_{20}O_2NCl$	60·8	7·8	5·4	13·9	60·5	7·8	5·4	13·8
	H	*iso*Amyl	H	182	$C_{14}H_{22}O_2NCl_2$	54·9	7·4	4·1	23·0	54·5	7·5	4·5	23·0
	H	Benzyl	B	100	$C_{16}H_{18}O_2NCl$	66·4	6·2	4·7		65·9	6·2	4·8	
	H	β-Phenyl *iso*Propyl	H	163	$C_{18}H_{22}O_2NCl_2$	61·1	6·5	3·5		60·7	6·5	3·9	
	H	*Cyclo*Hexyl	B	109	$C_{15}H_{22}O_2NCl$	63·0	7·8	4·5		63·5	7·8	4·9	
	Me	Phenyl	B	180/0·3 mm.	$C_{16}H_{18}O_2NCl$	66·2	6·3	4·9		65·9	6·2	4·8	
	Piperidine		B	73–75	$C_{14}H_{20}O_2NCl$	62·1	7·5	5·1	13·3	62·3	7·5	5·2	13·2
	Morpholine		B	68	$C_{13}H_{18}O_3NCl$	56·9	6·6	4·8		57·4	6·7	5·2	

TABLE II—*continued*

Ar	R	R′	Base (B) hydrochloride (H)	m.p. or b.p. ° C.	Formula	Found per cent				Required per cent			
						C	H	N	Cl	C	H	N	Cl
2:4-Dichlorophenyl	Piperidine		B	94–96	$C_{14}H_{19}O_2NCl_2$	55·8	5·7	4·8	23·2	55·3	6·3	4·6	23·4
2:4:6-Trichlorophenyl	H	*n*-Bu	B	109	$C_{13}H_{18}O_2NCl_3$	48·3	5·7	3·9	33·3	47·8	5·6	4·3	32·6
o-Bromophenyl	Piperidine		B	72	$C_{14}H_{20}O_2NBr$	53·1	6·3	4·4	25·1[1]	53·2	6·4	4·5	25·5[1]
			H	146–149	$C_{14}H_{21}O_2NClBr$	48·3	6·1	3·9	32·7[2]	47·9	6·1	4·0	32·9[2]
			Acetyl Salicylate	119–121	$C_{23}H_{26}O_6NBr$	55·8	5·9	3·0		55·9	5·7	2·8	
o-Iodophenyl	Piperidine		H	163–165	$C_{14}H_{21}O_2NClI$	42·2	5·3			42·3	5·3		
2-Chloro-4-ethoxycarbonylphenyl	Piperidine		H	158–160	$C_{17}H_{23}O_4NCl_2$			3·6	18·6			3·7	18·8
2:6-Dichloro-4-ethoxycarbonylphenyl	Piperidine		B	74–76	$C_{17}H_{23}O_4NCl_2$			4·0				3·7	
			H	143–145	$C_{17}H_{24}O_4NCl_3$	48·8	5·7	3·4		48·3	5·9	3·3	
p-Methoxycarbonylphenyl	H	Benzyl	B	121	$C_{18}H_{21}O_4N$	68·8	6·8	4·4		68·5	6·7	4·4	
	Piperidine		H	179	$C_{16}H_{24}O_4NCl$	58·0	7·0	4·7		58·2	7·3	4·3	
o-Hydroxyphenyl	Piperidine		B	140/0·1 mm.	$C_{14}H_{21}O_2N$	67·6	8·6	6·0		66·9	8·4	5·6	
			H	188	$C_{14}H_{22}O_2NCl$	58·0	7·4	4·9	12·3	58·4	7·7	4·9	12·5
p-Acetamidophenyl	Piperidine		H	174–176	$C_{16}H_{23}O_3N_2Cl$	58·5	7·4	8·3	10·6	58·4	7·7	8·5	10·8
2-Naphthyl	H	Et	B	100	$C_{16}H_{19}O_2N$	73·5	7·7	5·7		73·5	7·8	5·7	
			H	187	$C_{15}H_{20}O_2NCl$	63·4	7·2		12·5	64·0	7·1		12·6
2-(1-Chloronaphthyl)-	Piperidine		H	174–175	$C_{18}H_{23}O_2NCl_2$	60·5	5·8	3·9	20·3	60·7	6·5	3·9	19·9
*cyclo*Hexyl	Piperidine		B	110/0·3 mm.	$C_{14}H_{27}O_2N$	69·0	11·2	5·9		69·7	11·3	5·8	
Benzyl	Piperidine		H	138–140	$C_{16}H_{24}O_2NCl$	63·2	8·2	5·1	12·4	63·0	8·5	4·9	12·4
o-Methoxyphenyl	H	Et	B	71	$C_{12}H_{17}O_2N$	64·1	8·5	6·3		64·0	8·5	6·2	
			H	94	$C_{12}H_{18}O_2NCl$	55·2	7·4		13·5	55·0	7·7		13·6
	H	*n*-Pr	B	86	$C_{13}H_{21}O_2N$	65·0	8·8	5·8		65·2	8·9	5·9	
			H	100	$C_{13}H_{22}O_2NCl$	56·6	8·1		12·9	56·6	8·0		12·9
	H	*n*-Bu	B	67–70	$C_{14}H_{23}O_2N$	66·2	9·0	5·6		66·4	9·2	5·5	
	H	*iso*-Bu	B	135/0·3 mm.	$C_{14}H_{23}O_2N$	66·3	9·2	5·5		66·4	9·2	5·5	
	H	Benzyl	B	94	$C_{17}H_{21}O_2N$	71·1	7·3	4·7		71·0	7·4	4·9	
	Piperidine		B	134–136/0·1 mm.	$C_{15}H_{23}O_2N$	67·5	8·6			67·9	8·7		
	Et	Et	B	122/0·1 mm.	$C_{14}H_{23}O_2N$	66·2	9·2	5·7		66·4	9·2	5·5	
	n-Bu	*n*-Bu	B	140/0·05 mm.	$C_{16}H_{31}O_2N$	70·2	10·0	4·2		69·9	10·1	4·5	
p-Methoxyphenyl	H	Et	B	75	$C_{12}H_{17}O_2N$	64·1	8·1			64·0	8·5		
			H	167	$C_{12}H_{18}O_2NCl$	54·9	7·7	5·4	13·6	55·0	7·7	5·4	13·6
	H	*n*-Bu	B	78	$C_{14}H_{23}O_2N$	66·2	8·8	5·1		66·4	9·2	5·5	
			H	175	$C_{14}H_{24}O_2NCl$	58·0	8·5		12·1	58·0	8·4		12·3
	H	Benzyl	B	101	$C_{17}H_{21}O_2N$			4·7				4·9	
	Piperidine		B	50	$C_{15}H_{23}O_2N$	68·1	8·5			67·9	8·7		
			H	164	$C_{15}H_{24}O_2NCl$	59·7	7·7			59·7	8·0		
3:4:5-Trimethoxyphenyl	Piperidine		H	143–145	$C_{17}H_{26}O_5NCl$	56·1	7·8	3·6	9·8	56·4	7·8	3·9	9·8
	Morpholine		H	192–194	$C_{16}H_{24}O_6NCl$	52·3	7·0	4·0	9·7	52·8	7·2	3·9	9·8

1 = Bromine 2 = Total halogen



(VII)

A heterocyclic base such as piperazine gives mono (VIII; R — N N—R'; R = $ArO{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2$; R' = H) and bis (IX; R = R' = ArO $CH_2{\cdot}CHOH{\cdot}CH_2$) products, the former being readily separated from the latter by distillation or *via* the solid condensation products (X) obtained from (VIII) and carbon bisulphide.

Biological study of the compounds listed in Table II showed that in general monoalkylamino- and dialkylamino-derivatives (I; R and/or R' = alkyl) were weakly analgesic only. Increase in analgesic activity occurred, however, on replacing the primary amino-group by cyclic structures such as piperidine, pyrrolidine and morpholine, but not by piperazine. Although 3-*o*-chlorophenoxy-, 3-phenoxy- and 3-*o*-toloxy-2-hydroxypropylpiperidine proved effective by the subcutaneous route, their analgesic potency fell to low levels on oral administration. This may well have been associated with the presence of secondary hydroxyl groups in the compounds which might be expected to undergo oxidation in the body. We therefore prepared the aryloxyamines (XI) (see Table III)

$ArO{\cdot}(CH_2)_n{\cdot}N$ (XI) Ar = *o*–Cl– and *p*–$Cl{\cdot}C_6H_4$. n = 3, 4 and 5

but these proved only weakly active.

Experimental

Condensation of phenols with 2:3-*epoxypropyl chloride.* Condensations were carried out at room temperature for 8 to 20 hours. 10 to 20 per cent excess of 2:3-epoxypropyl chloride was generally employed, although the yield of 3-aryloxy-1:2-epoxypropane obtained was increased by using a 50 to 100 per cent excess of the chloroepoxide. The products were normally isolated for use by fractional distillation under reduced pressure through a 12″ to 18″ Vigreux column. They were generally contaminated with about 5 per cent of the corresponding 3-aryloxy-2-hydroxypropyl chloride, which could be removed, if desired, by a second fractionation.

Condensation of o-*cresol with* 2:3-*epoxypropyl chloride.* A typical condensation is described below. The conditions used do not lead to an optimum yield of 3-*o*-toloxy-1:2-epoxypropane.

2:3-Epoxypropyl chloride (305 g., 3·3 mole) was added over 10 minutes to a stirred solution of *o*-cresol (324 g., 3·0 mole) in N potassium hydroxide (3 litres) which had been cooled to 15°. After the addition was complete the mixture was allowed to warm to 20° and stirred at this temperature for 16 hours. The oil was separated and the aqueous layer extracted with three 300 ml. portions of chloroform. The combined extracts were washed with water, neutralised by the addition of a few drops of glacial acetic acid and rewashed with water. The chloroform extract was concentrated and the residue distilled at 2 mm. to yield:

Fraction (i) b.p. 104 to 107°. 343 g. (70 per cent). (ii) b.p. 107 to 140°. 97 g. (iii) b.p. 156 to 174°. 40 g. (iv) <10 g. residue.

TABLE III

ARYLOXYALKYLAMINES

$Ar{\cdot}O{\cdot}(CH_2)_n{\cdot}N$⟨⟩

Ar	n	Base (B) Hydrochloride (H)	m.p. or b.p. ° C.	Formula	Found per cent				Required per cent			
					C	H	N	Cl	C	H	N	Cl
o-Chlorophenyl	3	B	115/0·1 mm.									
		H	157	$C_{14}H_{21}ONCl_2$	57·9	6·8	4·8	24·6	57·9	7·3	4·8	24·5
	4	B	120/0·1 mm.									
		H	128	$C_{15}H_{23}ONCl_2$	59·6	7·6	4·4	23·2	59·2	7·6	4·6	23·3
	5	B	122/0·01 mm.	$C_{16}H_{24}ONCl$	68·2	8·4	4·9	12·8	68·2	8·6	5·0	12·6
p-Chlorophenyl	3	B	114–116/0·1 mm.	$C_{14}H_{20}ONCl$	65·9	7·7	5·4	14·2	66·2	8·0	5·5	14·0
	4	B	132–134/0·1 mm.	$C_{15}H_{22}ONCl$			4·9				5·2	
	5	B	142–144/0·1 mm. (solidified)	$C_{16}H_{24}ONCl$	67·8	8·4			68·2	8·6		
o-Methoxyphenyl	3	B	124/0·2 mm.									
		H	155–156	$C_{15}H_{24}O_2NCl$	62·3	8·5	5·1	12·6	63·0	8·5	4·9	12·4
		Picrate	157	$C_{21}H_{26}O_9N_4$	52·7	5·5	11·8		52·7	5·5	11·7	
	5	B	136–138/0·2 mm.	$C_{17}H_{27}O_2N$	73·6	9·5	5·1		73·6	9·8	5·1	
		H	140–143	$C_{17}H_{28}O_2NCl$			4·8	11·7			4·5	11·3

Fraction (i) contained 0·68 per cent of chlorine, corresponding to a chlorohydrin content of about 3·8 per cent. Fraction (ii) contained 7·2 per cent of chlorine corresponding to a chlorohydrin content of about 40·7 per cent.

Fraction (i). A sample (27 g.) was suspended in water (300 ml.) containing sodium carbonate (17·5 g.), and the mixture heated under reflux for 6 hours. The product crystallised after cooling to 0° for several hours. It was collected and purified by crystallisation from carbon tetrachloride yielding white fluffy needles of 3-*o*-toloxy-propane-1 : 2-diol (22 g.), m.p. 70 to 72°, unchanged on admixture with an authentic specimen.

Fraction (ii). 87 g. was treated with diethylamine (64 g.) and the mixture heated under reflux for 4 hours. After cooling the product was dissolved in chloroform and washed well with water. The chloroform was distilled off and the residue distilled at 1 mm. to give 1-*diethylamino*-3-o-*toloxypropan*-2-*ol*, b.p. 138° (93·5 g.). The product formed a *methiodide* which separated from a mixture of ethanol and ether in white prisms, m.p. 151 to 153°. Found: C, 47·5; H, 6·8. $C_{15}H_{26}O_2NI$ requires C, 47·5; H, 6·9 per cent.

Fraction (iii), on trituration with ether yielded 3-*o*-toloxypropane-1 : 2-diol (24 g.) which had m.p. 70 to 72° after crystallisation from carbon tetrachloride.

Fraction (iv) consisted of 1 : 3-bis-*o*-toloxy-propan-2-ol, b.p. 170° at 0·5 mm. on refractionation.

Condensation of phenol with 2 : 3-*epoxypropyl chloride in aqueous potassium hydroxide solution.* The method used is illustrated below: Phenol (188 g., 2 moles) and 2 : 3-epoxypropyl chloride (204 g., 2·2 moles) were suspended in water (2 litres) containing varying amounts of potassium hydroxide and stirred for 16 hours at 20 to 23°. After extraction with chloroform, unchanged material was distilled off and the residue distilled at reduced pressure. The results obtained are summarised in Table I.

Condensation of phenol with 2 : 3-*epoxypropyl chloride in aqueous sodium carbonate solution.* A mixture of phenol (188 g., 2 moles), 2 : 3-epoxypropyl chloride (204 g., 2·2 moles) and sodium carbonate (106 g., 1 mole) in water (2 litres) was stirred for 20 hours at 22°. After extraction with chloroform and washing, the residue was distilled at 0·5 mm. to yield 3-*phenoxy*-2-*hydroxypropyl* chloride (116·5 g., 31 per cent) b.p. 106°. Found: Cl, 18·6. $C_9H_{11}O_2Cl$ requires Cl, 19·0 per cent. No other product was isolated apart from unchanged phenol).

When the reaction was repeated and stirring continued for 70 hours, the yield of chlorohydrin was 35 per cent (b.p. 118 to 120° at 1·3 mm.).

Condensation of o-*cresol with* 2 : 3-*epoxypropyl chloride in aqueous sodium carbonate solution.* A mixture of *o*-cresol (216 g., 2 moles), 2 : 3-epoxypropyl chloride (204 g., 2·2 moles) and sodium carbonate (116·6 g., 1·1 mole) in water (1 litre) was stirred at 20° for 46 hours. After removal of unchanged material, distillation at 0·5 mm. yielded only 23 g. (6 per cent) of 3-*o*-toloxy-2-hydroxypropyl chloride, b.p. 110°.

Condensation of 3-*aryloxy*-1 : 2-*epoxypropane with amines.* (*a*) Pressure apparatus, as recommended in earlier publications, proved unnecessary and low boiling amines such as methylamine were condensed in ethanolic or benzene solution for about 16 hours at room temperature. Propylamine and higher amines were condensed in the absence of solvent in a reflux apparatus. The reaction mixture was maintained at 20° by water cooling, when the product usually crystallised after several hours.

(*b*) Cyclic amines such as piperidine reacted so vigorously that it was necessary to employ a diluent such as light petroleum or ethanol.

Condensation of 3-o-*toloxy*-1 : 2-*epoxypropane with ethylamine.* 3-*o*-Toloxy-1 : 2-epoxypropane (164 g., 1 mole) was added to a solution of ethylamine (100 g., 2·2 moles) in benzene (250 ml.) cooled in ice-water. The mixture was left overnight under reflux and surrounded by cold water (15 to 20°). The mixture was heated for 2 hours to remove excess of ethylamine and on cooling deposited 1-*ethylamino*-3-o-*toloxypropane*-2-*ol*, m.p. 87° (150 g.). Found: N, 6·8. $C_{12}H_{19}O_2N$ requires N, 6·9 per cent.

The mother liquors were concentrated and the residue distilled at 0·2 mm. to yield N-*ethyl*-*bis*-(2-*hydroxy*-3-o-*toloxypropyl*)-*amine* (42 g.) as a clear viscous oil, b.p. 210° after refractionation. Found: C, 70·8; H, 8·3; N, 3·7. $C_{22}H_{31}O_4N$ requires C, 70·8; H, 8·4; N, 3·8 per cent.

N-(2-*Hydroxy*-3-o-*chlorophenoxy*)-*propylpiperazine* and NN′-*bis*-(2-*Hydroxy*-3-o-*chlorophenoxy*)-*propylpiperazine.* To a solution of piperazine hexahydrate (155·2 g., 2 moles equivs.) in ethanol (200 ml.) was added 3-*o*-chlorophenoxy-1 : 2-epoxypropane and the mixture heated under reflux for 30 minutes. It was diluted with water to near turbidity and allowed to stand overnight. The solid which separated (23 g.) was NN′-*bis*-(2-*hydroxy*-3-o-*chlorophenoxy*)-*propylpiperazine* which had m.p. 182° after washing with boiling ethanol. Found: C, 58·0; H, 6·0; N, 6·0; Cl, 15·7. $C_{22}H_{28}O_4N_2Cl_2$ requires C, 58·0; H, 6·2; N, 6·2; Cl, 15·6 per cent. Its *dihydrochloride* had m.p. 230 to 233° after crystallisation from aqueous ethanol. Found: C, 50·1; H, 5·5; N, 5·4; Cl, 26·9. $C_{22}H_{30}O_4N_2Cl_4$ requires C, 50·0; H, 5·7; N, 5·3; Cl, 26·9 per cent.

After removal of the bis compound, the original filtrate was diluted with water and extracted with chloroform. The extract was washed with water, the chloroform distilled off and the residue distilled at 0·3 mm. to yield a viscous oil, b.p. 164 to 170°.

Part of the gum (10 g.) was dissolved in ethanol (40 ml.), stirred at room temperature and treated with carbon disulphide (5 ml.). A gum separated which solidified after standing overnight. The solid was collected, drained, suspended in ethanol and treated with hydrochloric acid gas. The solid dissolved after heating under reflux for 30 minutes. The ethanolic solution was concentrated to yield the dihydrochloride of N-(2-*hydroxy*-3-o-*chlorophenoxy*)-*propyl piperazine* which had m.p. 205 to 208° after crystallisation from ethanol. Yield 8·6 g. Found: C, 46·0; H, 6·0; N, 7·7. $C_{13}H_{21}O_2N_2Cl_3$ requires C, 45·4; H, 6·2; N, 8·1 per cent The original gummy base yielded a mono*picrate* which separated from ethyl acetate and had m.p. 195 to 197°. Found: C, 45·8; H, 4·3; N, 14·3. $C_{19}H_{22}O_9N_5Cl$ requires C, 45·6; H, 4·4; N, 14·0 per cent.

3-cyclo*Hexyloxy-2-hydroxy-propyl chloride.* To a mixture of *cyclo*hexanol (300 g., 3 moles) and 2:3-epoxypropyl chloride (92·5 g., 1 mole), concentrated sulphuric acid (2·3 ml.) was added dropwise with intermittent shaking over 10 minutes. The mixture was heated on the steam bath for 40 hours. It was then cooled, washed with water, dilute sodium carbonate solution and again with water and distilled at reduced pressure.

After recovery of unchanged *cyclo*hexanol (176 g.) there was obtained:

Fraction (i) 19 g., b.p. 38 to 76° at 0·25 mm.

„ (ii) 72 g., b.p. 76 to 80° at 0·25 mm.

Fraction (ii) was redistilled to give the *product* as an oil, b.p. 84° at 0·5 mm. Found: C, 55·8; H, 8·6; Cl, 18·7. $C_9H_{17}O_2Cl$ requires C, 56·1; H, 8·9; Cl, 18·4 per cent.

3-cyclo*Hexyloxy-1-piperidinopropan-2-ol.* The foregoing chlorohydrin (9·6 g.) was heated with piperidine (9·3 g., 2·2 moles) on the steam bath for 16 hours. After addition of chloroform (50 ml.) piperidine hydrochloride was removed by washing with water. The chloroform extract was concentrated and the residue distilled at reduced pressure to yield the *product* as an oil, b.p. 110° at 0·3 mm.

3-(3′:4′:5′-*Trimethoxyphenoxy*)-2-*hydroxypropyl chloride.* 3:4:5-Trimethoxyphenol was dissolved by warming in 2:3-epoxypropyl chloride (24 g. = 4·5 moles). Pyridine (5 drops) was added and the mixture heated on the steam bath. Heating was stopped when an exothermic reaction occurred and was then continued for 6 hours. Excess of 2:3-epoxypropyl chloride was removed at reduced pressure, the residual oil was dissolved in chloroform (50 ml.), shaken with concentrated hydrochloric acid[6], and then washed acid-free with water. After removal of the solvent, the residue was distilled at reduced pressure yielding an oil, b.p. 180° at 0·5 mm. which solidified on standing. It was purified by crystallisation from a mixture of ethyl acetate and light petroleum (b.p. 40 to 60°) to give white needles, m.p. 87 to 89°. Found: C, 52·0; H, 5·9; Cl, 13·4. $C_{12}H_{17}O_5Cl$ requires C, 52·1; H, 6·2; Cl, 12·8 per cent.

3-(3′:4′:5′-*Trimethoxyphenoxy*)-2-*hydroxypropylamine hydrochloride.* The foregoing chlorohydrin was dissolved in ethanol (50 ml.), concentrated ammonia (50 ml., d = 0·880) was added, the solution warmed on the steam bath for several hours, and then evaporated to dryness. The residue was treated with alcoholic hydrochloric acid, filtered, and the filtrate diluted with ether. The *product* separated on cooling and was purified by crystallisation from a mixture of ethanol and ether. It had m.p. 198 to 200°. Found: C, 49·2; H, 7·1; N, 5·1; Cl, 12·1. $C_{12}H_{20}O_5NCl$ requires C, 49·0; H, 6·9; N, 4·8; Cl, 12·1 per cent.

3:4:5-*Trimethoxyphenol and* 3:4:5-*Trimethoxyaniline.* 2:6-Dimethoxybenzoquinone and 3:4:5-trimethoxynitrobenzene were prepared as follows by a variation of the published method[12].

A solution of 1:2:3-trimethoxy benzene (42 g., 0·25 mole) in ethanol (200 ml.) was heated to boiling under reflux. Sodium nitrite (1 g.) was added, followed immediately by 60 per cent (v/v) nitric acid (100 ml.). Heating was stopped until the vigorous exothermic reaction was complete, when the mixture was heated for 10 minutes. It was cooled rapidly to

25° and the 2:6-dimethoxybenzoquinone collected. It was purified by boiling with a little ethanol and had m.p. 262 to 263°. Yield 24 g. The combined filtrate and washings by concentration and cooling yielded 3:4:5-trimethoxynitrobenzene (10·2 g., m.p. 98 to 100°). One crystallisation from methanol raised the m.p. to 104° (8·7 g.). This product was identical with that obtained by nitration of 3:4:5-trimethoxybenzoic acid[13].

3:4:5-Trimethoxyphenol was prepared *via* 2:6-dimethoxybenzoquinone by the method of Chapman, Perkin and Robinson[14].

3:4:5-Trimethoxyaniline was prepared by reduction of the nitro compound with iron powder[13] or by catalytic reduction in ethanol using Raney nickel. By the latter method it was obtained in 97 per cent yield in fawn coloured needles, m.p. 112 to 114°.

The *hydrochloride* separated from ethanol in white needles, m.p. 256° (decomp.). Found: C, 49·5; H, 6·4. $C_9H_{14}O_3NCl$ requires C, 49·2; H, 6·4 per cent.

Treatment of the hydrochloride (2·2 g.) in water (20 ml.) with sodium cyanate (0·8 g.) furnished the *urea*, which separated from water in small white needles, m.p. 178°. Found: C, 53·2; H, 6·1; N, 12·1. $C_{10}H_{14}O_4N_2$ requires C, 53·1; H, 6·2; N, 12·4 per cent.

3-*o*-*Chlorophenoxy*-1-*piperidinopropan*-2-*ol*. (*a*) A mixture of 3-*o*-chlorophenoxy-1:2-epoxypropane (184·5 g.) and piperidine (89 g., 1·05 mole) in light petroleum (500 ml., b.p. 60 to 80°) was heated on the steam bath for 2 hours, heating being controlled in the early stages when an exothermic reaction occurred. The product crystallised after cooling. Yield 233·5 g. m.p. 72 to 73° after crystallisation from light petroleum (b.p. 60 to 80°).

Alternatively, after cooling, the solution was washed with water, the solvent removed and the base purified by distillation at reduced pressure. (*b*) A mixture of *o*-chlorophenol (12·85 g.) and 3-piperidino-1:2-epoxypropane (14·1 g.) was warmed to 90° when an exothermic reaction occurred. Heating was discontinued to keep the reaction temperature below 105°. The mixture was warmed for a further 2 hours and was then distilled directly at reduced pressure. The product was obtained as an oil, b.p. 128° at 0·1 mm. which solidified and was purified by crystallisation from light petroleum (b.p. 60 to 80°). It had m.p. 72 to 73° and was identical with the material obtained under (*a*).

A solution of the foregoing base (2·7 g.) in ethanol (5 ml.) was treated with a solution of acetylsalicylic acid (1·8 g.) in ethanol (5 ml.). The mixture was warmed for a few minutes and then diluted with light petroleum (b.p. 40 to 60°). The solid obtained was crystallised from light petroleum (b.p. 60 to 80°) containing a trace of ethanol. The *acetylsalicylate* formed white needles, m.p. 114 to 116°.

3-(o-*Methylcarbonylphenoxy*)-1:2-*epoxypropane* was prepared by condensation of 2:3-epoxypropyl chloride with *o*-hydroxyacetophenone in aqueous alkaline solution. It was obtained as an oil, b.p. 120° at 0·3 mm. which solidified. The *product* separated from a mixture of ether and light petroleum (b.p. 40 to 60°) in white needles, m.p. 46 to 48°. Found: C, 68·5; H, 6·3. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·3 per cent.

1-(o-*Methylcarbonylphenoxy*)-3-*piperidinopropane*-2-*ol* was prepared by condensation of the foregoing epoxide with piperidine. It was isolated as its *hydrochloride* which separated from a mixture of ethanol and ether in pink tinged crystals, m.p. 126 to 128°. Found: C, 60·6; H, 7·4; N, 4·3; Cl, 11·2. $C_{16}H_{24}O_3NCl$ requires C, 61·2; H, 7·7; N, 4·5; Cl, 11·3 per cent.

NN′-*Bis*-(2-*hydroxy*-3-o-*toloxy*)-*propyl*-4:4′-*dipiperidyl* was prepared by condensation of 3-*o*-toloxy-1:2-epoxypropane (2 moles equiv.) with 4:4′-dipiperidyl in benzene containing a trace of ethanol. The *base* crystallised from ethanol in small white needles, m.p. 153 to 156°. Found: C, 72·9; H, 8·7; N, 5·7. $C_{30}H_{44}O_4N_2$ requires C, 72·5; H, 8·9; N, 5·6 per cent.

The *dihydrochloride* separated from aqueous ethanol in shining microcrystals, m.p. 293° (decomp.). Found: C, 63·3; H, 8·1; N, 5·0; Cl,12·5. $C_{30}H_{46}O_4N_2Cl_2$ requires C, 63·2; H, 8·2; N, 4·9; Cl, 12·5 per cent.

N:N′-*Bis*-(3-o-*allylphenoxy*-2-*hydroxy*)-*propyl*-4:4′-*dipiperidyl* crystallised from a mixture of ethyl acetate and light petroleum (b.p. 60 to 80°) in small cream coloured needles m.p. 106 to 107°. Found: C, 74·1; H, 8·7; N, 4·7. $C_{34}H_{48}O_4N_2$ requires C, 74·4; H, 8·8; N, 5·1 per cent. The *dihydrochloride* crystallised from a mixture of ethanol and ether in white needles, m.p. 244 to 246°. Found: C, 65·4; H, 8·3; N, 4·6. $C_{34}H_{50}O_4N_2Cl_4$ requires C, 65·7; H, 8·1; N, 4·5 per cent.

5-o-*Chlorophenoxypentyl bromide*, b.p. 200 to 204° at 20 mm., was prepared by condensation of *o*-chlorophenol with pentamethylene dibromide (3 mole equivs.) in ethanol containing 1 equivalent of sodium ethoxide. 3-p-*Chlorophenoxypropyl bromide* had b.p. 185 to 190° at 85 to 90 mm. 4-p-*Chlorophenoxybutyl bromide* had b.p. 198 to 200° at 20 mm. Found: Total halogen, 43·8. $C_{10}H_{12}OCl\,Br$ requires total halogen 43·8 per cent. 5-p-*Chlorophenoxypentyl bromide* had b.p. 226 to 228° at 30 mm. 3-o-*Methoxyphenoxypropyl bromide* had b.p. 98° at 0·25 mm. Found: C, 49·4; H, 5·3; Br, 32·2. $C_{10}H_{13}O_2$ requires C, 49·0; H, 5·4; Br, 32·6 per cent. It formed a low-melting solid. 5-o-*Methoxyphenoxypropyl bromide* b.p. 118° at 0·25 mm.

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