RESEARCH PAPERS

THE SYNTHESIS AND LOCAL ANÆSTHETIC PROPERTIES OF ARYLOXYPROPANOLAMINES

BY H. R. ING and W. E. ORMEROD

From the Department of Pharmacology, Oxford University

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IT is well known that alkamines which contain a sufficiently hydrophobic radical (e.g., an aryl group or a long-chain alkyl group) possess local anæsthetic properties. Quinine is the classical example but MacIntosh and Work[1] described a series of alkamines of the general type $RR'COH{\cdot}CH_2NR''_2$, where R contained an aryl nucleus (or in one compound was *n*-undecyl), R′ was usually H and NR''_2 usually NC_5H_{10}; most of these compounds had about the same order of activity as procaine in the guinea-pig weal test, but were much more active than procaine on the guinea-pig cornea. Fourneau and Samdahl[2] had previously prepared a series of dialkamines, derivatives of piperazine of the type

$$ROCH_2CHOH{\cdot}CH_2N{<}C_4H_8{>}NCH_2CHOH{\cdot}CH_2OR,$$

and had found that high local anæsthetic activity appeared when R was *n*-hexyl or *n*-heptyl. Although alkamines of the general types mentioned are unsuitable for clinical use, because they usually cause irritation at the site of injection, it seemed of interest to study another series in the hope that light would be thrown on the structural features which govern high local anæsthetic activity in this type of compound. We have prepared a series of aryloxypropanolamines of the general type: $ArOCH_2CHOH{\cdot}CH_2NR_2$, where NR_2 was piperidine (NC_5H_{10}) and Ar was an unsubstituted or substituted aryl nucleus; we have also prepared a short series of the same type in which Ar was α-naphthyl and R was H, C_2H_5, *n*-C_3H_7 *iso*-C_3H_7 and *n*-C_4H_9.

LOCAL ANÆSTHETIC ACTIVITY

Method. The local anæsthetic activities of our compounds were compared with that of procaine by the guinea-pig weal method of Bulbring and Wajda.[3] Two modifications of their method were introduced.

(1) Bulbring and Wajda divided the animal's back into 4 areas and gave each animal 4 injections, 2 concentrations of the standard drug and 2 of the compound of unknown potency. Since we wished to test the linearity of the log dose-response regression lines we used a device introduced by Somers and Edge[4] whereby 3 concentrations of a compound were compared with 3 concentrations of the standard in each of 6 animals, the locus of injection of each dose being changed from animal to animal. The use of 6 injections per animal probably sacrificed some accuracy in the method, since the area of maximum sensitivity on the animal's back is limited, but it was felt that this device was likely to be more satisfactory

for obtaining three-point regression lines than the use of different animals, of unknown variability, for a third point.

(2) Bulbring and Wajda used doses which gave a linear relation between log dose and response. The complete curve over the whole range of effective doses would of course be sigmoid and it is not always easy to arrange the dosage so that linearity is obtained. Somers and Edge used a probit scale, which improves the linearity but is based on the assumption that the responses are distributed normally. We used the method of Angular Transformation, whereby the percentage response is expressed as an angle from 0° to 90°. This method merely transforms the results from one arbitrary scale into another without involving any assumption about the normal distribution of responses. In practice we found that plotting the results on a degree scale gave better linearity than plotting them on a probit scale.

RESULTS

The compounds tested and their molar potencies in terms of procaine are listed in Table I. The potencies were estimated graphically from the

TABLE I

MOLAR ACTIVITIES IN THE GUINEA-PIG WEAL TEST IN TERMS OF PROCAINE = 100

$ArOCH_2CHOH{\cdot}CH_2NR_2$

Ar	NR_2	Salt	Molar potency, procaine = 100
phenyl	piperidino	HCl	105
m-tolyl	,,	,,	130
p-tolyl	,,	,,	95
o-chlorophenyl	,,	,,	(90)
m-chlorophenyl	,,	,,	(95)
p-chlorophenyl	,,	,,	110
p-nitrophenyl	,,	free base	(70)
p-aminophenyl	,,	di-HCl	0
o-diphenyl	,,	free base	185 (approx.)
p-diphenyl	,,	HCl	140
α-naphthyl	,,	,,	(95)
β-naphthyl	,,	,,	170
α-naphthyl	NH_2	,,	56
,,	$N(C_2H_5)_2$	,,	140
,,	$N(n\text{-}C_3H_7)_2$	,,	200
,,	$N(iso\text{-}C_3H_7)_2$	,,	200

regression lines, the log dose corresponding to the ordinate of 45° being taken as the "median effective dose." A few compounds gave regression lines which were not parallel to that for procaine; for these compounds the molar potencies are recorded in parentheses in Table I, since compounds which do not bear a constant log dose-effect relationship with procaine cannot strictly be compared with it. Departure of the regression lines from parallelism with that of procaine was always associated with lesser slope, a result which suggests that the compounds had some vasodilator action, but this possibility was not investigated further. Aryloxyethylamine derivatives are well-known to have vasodilator actions, and our compounds might be expected to share this property.

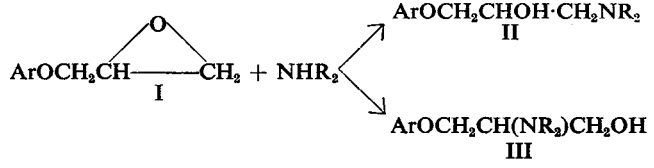
The potencies vary over a relatively narrow range from a half to twice that of procaine, except for *p*-aminophenoxypropanolpiperidine, which

was inactive. The *p*-amino group in this compound is, however, more strongly basic than that in procaine, as is shown by the fact that the *p*-aminophenoxy compound was isolated as its dihydrochloride. Apart from this, no clear-cut correlation between structure and action emerges other than the expected increase in potency in the α-naphthoxy series as the size of the N-alkyl group increases.

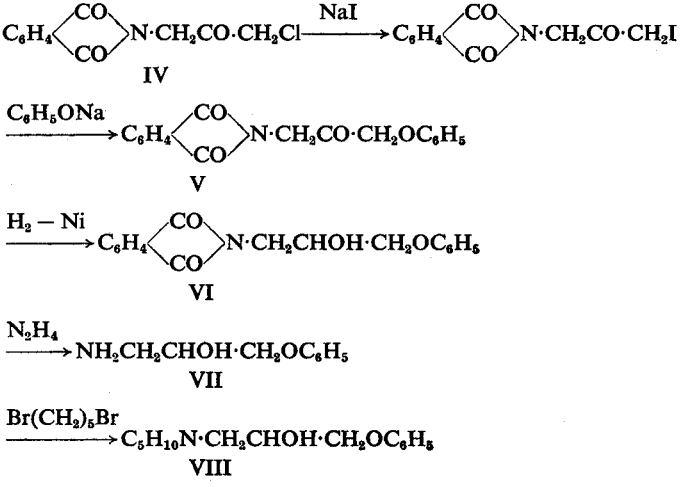
None of the compounds produced noticeable irritation at the site of injection except *o*-phenylphenoxypropanolpiperidine and α-naphthoxypropanolamine.

Chemical Section

The aryloxypropanolamines were all prepared by the condensation of the appropriate aryloxypropylene epoxide (I) with a secondary amine. Theoretically this reaction could give two products, (II) and (III),



of which (II) is the more likely. However, 3-phenoxy-2-hydroxypropylpiperidine was synthesised by an alternative route, the stages of which are outlined below:



The hydrochloride of the product (VIII) was identical with that of the base formed from phenoxypropylene epoxide and piperidine and consequently there seems to be no doubt that the general method (reaction of and aryloxypropylene epoxide with a secondary amine) gives products of the general structure (II).

Also 3-phenoxy-2-hydroxypropylphthalimide (VI) was prepared by three methods: from phenoxyphthalimido-acetone (V) as shown above,

from phenoxypropylene epoxide and phthalimide, and from 3-phenoxy-2-hydroxypropyl chloride and potassium phthalimide. Each method gave the same product, which after treatment with hydrazine (Ing and Manske)[5] gave the same phenoxypropanolamine hydrochloride (HCl salt of VII). This salt displayed a curious "double melting point": it melted at 135° to 136° C. to an opaque liquid which only became clear at 228° C. The hydrobromide behaved similarly, melting at 141° to 142° C. to an opaque liquid which became clear at 162° C.

Although epichlorhydrin reacts with phthalimide at 140° to 150° C. to give phthalimidopropylchlorhydrin, the structure of which is settled by its oxidation to phthalimido-chloro-acetone (IV) (Gabriel and Ohle[6]), phenoxypropylene epoxide can be heated with phthalimide at 180° C. for several hours without condensation occurring. If, however, a trace of potassium phthalimide is added to the mixture, condensation occurs rapidly and exothermically at 180° C., a result which suggests that it is the phthalimide anion which attacks the epoxide ring.

The aryloxypropanolamine salts prepared are listed in Table II, together with their melting-points and analyses. It will be noticed that few of them gave sharp melting-points although the analytical figures show them to have been substantially pure compounds. Fourneau,[7] who prepared a number of aryloxypropanoldimethylamines, found that these bases did not give crystalline hydrochlorides and we found it impossible to isolate a pure hydrochloride of α-naphthoxypropanoldimethylamine, although it gave a pure methiodide (Table II).

TABLE II

ARYLOXYPROPANOLAMINE SALTS

$ArOCH_2CHOH{\cdot}CH_2NR_2$

Ar	NR_2	Salt	M.pt. °C.	Formula	Found C per cent.	Found H per cent.	Theory C per cent.	Theory H per cent.
phenyl	NH_2	HCl	228	$C_9H_{14}O_2NCl$	53·0	7·0	53·1	6·9
		HBr	162	$C_9H_{14}O_2NBr$	43·5	5·6	43·6	5·6
phenyl	NC_5H_{10}	HCl (*a*)	150 to 152	$C_{14}H_{22}O_2NCl$	62·0	8·2		
		,, (*b*)	151 to 153	,,	61·7	8·0	62·0	8·2
m-tolyl	,,	,,	126 to 128	$C_{15}H_{24}O_2NCl$	63·1	8·3	63·2	8·3
p-tolyl	,,	,,	171 to 173	$C_{15}H_{24}O_2NCl$	62·8	8·0	63·2	8·3
o-chlorophenyl	,,	,,	148 to 150		54·8	6·8		
m-chlorophenyl	,,	,,	155 to 156	$C_{14}H_{21}O_2NCl_2$	55·4	7·0	54·9	6·9
p-chlorophenyl	,,	,,	156 to 158		54·6	6·8		
p-nitrophenyl	,,	free base	79 to 80	$C_{12}H_{20}O_4N_2$[1]	60·0	6·8	60·0	7·1
p-aminophenyl	,,	di HCl	262 decomp.	$C_{14}H_{24}O_2N_2Cl_2$	52·0	7·4	52·0	7·4
o-diphenyl	,,	free base	b.p. 240 to 250°/10 to 15 min.	$C_{20}H_{25}O_2N$	75·5	8·0	77·2	8·0
p-diphenyl	,,	HCl	197 to 199	$C_{20}H_{26}O_2NCl$	69·4	7·4	69·2	7·5
β-naphthyl	NC_5H_{10}	,,	175 to 176	$C_{18}H_{24}O_2NCl$	67·2	7·3	67·3	7·5
α-naphthyl	NH_2	,,	decomp. 200	$C_{13}H_{16}O_2NCl$	61·7	6·3	61·7	6·3
,,	NMe_2	methiodide	172 to 173	$C_{16}H_{22}O_2NI$	50·0	5·7	49·4	5·7
,,	NEt_2	HCl	127 to 130	$C_{17}H_{24}O_2NCl$	65·1	7·8	65·1	7·8
,,	NC_5H_{10}	,, (*a*)	183 to 186	$C_{18}H_{24}O_2NCl$	67·7	7·0	67·3	7·5
,,	,,	,, (*b*)	185 to 186		66·8	7·5		
,,	NPr^{α}_2	,,	155 to 156	$C_{19}H_{28}O_2NCl$	67·5	8·4	67·6	8·3
,,	NPr^{β}_2	,,	173	$C_{19}H_{28}O_2NCl$	67·6	8·3	67·6	8·3
,,	NBu^{α}_2	,,	95 to 98	$C_{21}H_{32}O_2NCl$	68·4	8·7	69·0	8·8

1. Found: N, 9·9. Required N, 10·0 per cent.

EXPERIMENTAL

(Analyses by Weiler and Strauss. Melting-points uncorrected.)

The aryloxypropylene epoxides were prepared by the method of Boyd and Marle.[8] The crude oily product was warmed on the water-bath with 50 per cent. aqueous potash in order to convert any chlorohydrin present into the epoxide and the latter was usually isolated by fractional distillation *in vacuo*, and converted into the alkamine without further purification. Three of the epoxides used proved to be crystalline solids, viz., *p*-nitrophenoxypropylene epoxide, crystallised from ether, m.p. 66° to 68° C. (not analysed); *p*-phenylphenoxypropylene epoxide, crystallised from light petroleum, m.p. 80° to 83° C. Found: C, 79·7; H, 6·3, $C_{15}H_{15}O_2$ requires C, 79·7; H, 6·2 per cent.; and β-naphthoxypropylene epoxide, crystallised from light petroleum, m.p. 62° to 64° C. Found: C, 78·0; H, 6·1. $C_{13}H_{12}O_2$ requires C, 78·0; H, 6·0 per cent.

The aryloxypropanolamines were prepared by heating equimolar amounts of epoxide and secondary amine for a short time on the water-bath. The reaction is exothermic so that completion of the reaction was readily ascertained by observation of the temperature; no solvent was necessary unless the amine was very volatile; e.g., dimethylamine was used in ethanol in a pressure bottle. The product was dissolved in acetone and acidified with concentrated hydrochloric acid. The alkamine hydrochloride usually crystallised, or could be induced to do so by the addition of ether. The hydrochlorides were recrystallised at least twice from ethanol-ether mixtures. Their melting-points and analyses are given in Table II.

The two primary amines listed in Table II, viz., phenoxy- and α-naphthoxy-propanolamine, were prepared from the corresponding phthalimides by Ing and Manske's method.[5] The phthalimides were prepared by heating equimolar amounts of epoxide and phthalimide with a trace of potassium phthalimide at 180° C. 3-Phenoxy-2-hydroxypropylphthalimide crystallised from ethanol or benzene-light petroleum, m.pt. 116° to 117° C. Found: C, 68·7; H, 5·2. $C_{17}H_{15}O_4N$ requires C, 68·7; H, 5·1 per cent. 3-α-Naphthoxy-2-hydroxypropylphthalimide crystallised from ethanol, m.pt. 152° to 153° C.

Alternative synthesis of 3-phenoxy-2-hydroxypropylpiperidine. 3-Chloro-1-phthalimido-acetone (Gabriel and Ohle[6]), dissolved in acetone, was treated with excess of sodium iodide in acetone. 3-Iodo-1-phthalimido-acetone crystallised almost at once; it was recrystallised from benzene, m.pt. 180° to 183° C., yield 63 per cent. Found: C, 40·6; H, 2·5. $C_{11}H_8O_3NI$ requires C, 40·1; H, 2·4 per cent. 3-Phenoxy-1-phthalimido-acetone was prepared by treating the iodo-compound with a benzene suspension of sodium phenate (prepared from phenol and powdered sodium in benzene) for 12 hr. at room temperature. The reaction mixture was carefully acidified and steam-distilled to remove excess of phenol and benzene. The non-volatile residue was extracted with boiling xylene; the extract, after treatment with charcoal, deposited 3-phenoxy-1-phthalimido-acetone; m.pt. 163° to 164·5° C., after recrystallisation from ethanol.

Found: C, 69·4; H, 4·6. $C_{17}H_{13}O_4N$ requires C, 69·2; H, 4·4 per cent. The same product was obtained by oxidising 3-phenoxy-2-hydroxypropylphthalimide (prepared from phenoxypropylene epoxide) with chromium trioxide in acetic acid.

3-Phenoxy-1-phthalimido-acetone, suspended in ethanol, was reduced over Raney nickel with hydrogen at room temperature and pressure (reaction time, 24 hours). The ready solubility of the product in ethanol made its isolation easy; it was crystallised from benzene light petroleum, m.pt. 112° to 114° C. Found: C, 69·5; H, 5·1. $C_{17}H_{15}O_4N$ requires C, 68·7; H, 5·1 per cent. Clearly the product was not so pure as the specimen prepared from phenoxypropylene epoxide and phthalimide, but removal of the phthalyl group with hydrazine gave 3-phenoxy-2-hydroxypropylamine hydrochloride identical with that produced through the epoxide, i.e., melting to an opaque liquid at 135° to 136° C. and to a clear liquid at 228° C. The free base, liberated from the hydrochloride, was heated on the water-bath with pentamethylene dibromide for 1 hour; alcoholic potassium hydroxide (1 mol.) was now added and heating continued; finally excess of amine was fixed by warming the mixture in aqueous alkali with toluene sulphonyl chloride. The mixture was acidified, extracted with ether, then basified with ammonia and the free base converted into its hydrochloride, which, after crystallisation from ethanol-ether, proved to be identical with 3-phenoxy-2-hydroxypropylpiperidine hydrochloride prepared from phenoxypropylene epoxide and piperidine, m.pt. 185° to 186° C., mixed m.pt. unchanged.

SUMMARY

Sixteen aryloxypropanolamines of the general formula

$$ArOCH_2CHOH{\cdot}CH_2NR_2$$

were prepared and tested for local anæsthetic activity by the guinea-pig weal method. All but one were local anæsthetics, varying in activity from about a half to twice that of procaine.

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