216. *Di*-N-*substituted* 2-*Halogenoethylamines. Part IV.*[1] NN-*Bis*-2′-*aryloxyethyl Derivatives: Syntheses, Reactivity, and Pharmacology.*

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The synthesis of compounds $(Ar{\cdot}O{\cdot}CH_2{\cdot}CH_2)_2N{\cdot}CH_2{\cdot}CH_2X,HX$ with X = Cl, Br, or I, and Ar = Ph, *o*-tolyl, or *p*-tolyl, is described. The mode of decomposition in acetone–water (2 : 1) at 30° of these compounds is reported and their pharmacological properties are briefly discussed. Evidence is provided that piperazinium salts formed by dimerisation of the halogenoamines are inactive against adrenaline and noradrenaline.

The present investigation concerned the influence of structure on reactivity, especially as to ethyleniminium ion formation, and on pharmacological properties in a series of adrenaline antagonists. We prepared the salts $(ArO{\cdot}CH_2{\cdot}CH_2)_2N{\cdot}CH_2{\cdot}CH_2X,HX$ where Ar = phenyl or *o*- or *p*-tolyl and X = halogen (except F). A *p*-methyl group decreases the pharmacological activity, but in the *ortho*-position enhances it (Gump and Nikawitz,[2] Graham [3]). Some of the intermediates, obtained by Gump and Nikawitz as oils, have now been obtained crystalline and characterised. Interaction of the appropriate 2-aryloxyethyl chloride or bromide with an excess of ethanolamine gave an *N*-monosubstituted derivative, which on further treatment with the same chloro-compound gave the required di-*N*-substituted hydroxy-amine, from which the corresponding halogeno-compounds were obtained by the method of Chapman and James.[4]

Experimental

Preparation of Materials.—2-[*Di*-(2-*aryloxyethyl*)*amino*]*ethanols.* Heating 2-chloroethyl-phenyl ether (1 mole) with 2-aminoethanol (6 moles) at the b. p. for 6 hr., followed by acidification, removal of unchanged 2-chloroethyl phenyl ether with ether, basification, and removal of dissolved ether with a current of air gave a wax. Pure 2-2′-phenoxyethylaminoethanol, m. p. 33·5—35° (cf. Gump and Nikawitz,[2] who obtained an oil), was obtained as white needles (83%) by adding 10% aqueous sodium hydroxide to a saturated aqueous solution of the crude product; this base gave a *picrate* (from ethanol), m. p. 114—115° (mixed m. p. with picric acid 92—112°) (Found: C, 47·2; H, 4·3; N, 14·1. $C_{16}H_{18}N_4O_9$ requires C, 46·8; H, 4·4; N, 13·7%), and a *hydrochloride* (from chloroform), m. p. 135—136° (Found: Cl, 16·2. $C_{10}H_{15}NO_2,HCl$ requires Cl, 16·3%).

Similarly were prepared the N-2′-o-*tolyloxyethyl analogue* (87%) [from light petroleum (b. p. 40—60°)], m. p. 62·5—63·5° (cf. ref. 2) (Found: C, 68·2; H, 8·9; N, 7·0. $C_{11}H_{17}NO_2$ requires C, 67·7; H, 8·8; N, 7·2%) [*picrate* (from ethanol), m. p. 118—119° (mixed m. p. with picric acid 94—116°) (Found: C, 48·5; H, 4·7; N, 13·2. $C_{17}H_{20}N_4O_9$ requires C, 48·1; H, 4·8; N, 13·2%)], and the -tolyl compound (77%) [from chloroform–light petroleum (b. p. 40—60°)], m. p. 52—52·5° [*picrate* (from ethanol), m. p. 115·5—116·5° (Found: C, 48·1; H, 4·7; N, 12·9%); *hydrochloride* (from chloroform), m. p. 156—157° (Found: Cl, 15·4. $C_{11}H_{17}NO_2,HCl$ requires Cl, 15·3%)].

Heating 2-2′-phenoxyethylaminoethanol (0·19 mole) suspended in 1 : 19 ethanol–water (100 ml.) with 2-chloroethyl phenyl ether (0·095 mole) at the b. p. for 80 hr., followed by working up as for the monophenoxyethyl compound, gave an oily mixture of mono- and bis-2′-phenoxyethyl compounds. The crystalline sulphate of the bis-compound separated after the oil had dissolved in dilute sulphuric acid. Liberation of the base followed by crystallisation from light petroleum (b. p. 40—60°) gave needles of 2-[di-(2-phenoxyethyl)amino]ethanol (85%), m. p. 35·5—36° (Found: C, 72·0; H, 7·8; N, 4·5. Calc. for $C_{18}H_{23}NO_3$: C, 71·8; H, 7·7; N, 4·7%). Gump and Nikawitz [2] reported this compound as an oil.

[1] Part III, Chapman and Allen, *J.*, 1960, 1482.
[2] Gump and Nikawitz, *J. Amer. Chem. Soc.*, 1950, **72**, 3846.
[3] Graham, *Brit. J. Pharmacol.*, in the press.
[4] Chapman and James, *J.*, 1953, 1865.

2-[Di-(2-*o*-tolyloxyethyl)- (as an oil and as sulphate, 92%) and 2-[di-(2-*p*-tolyloxyethyl)-amino]ethanol [*hydrochloride* (85%) (from chloroform or dilute hydrochloric acid), m. p. 84·5—85° (Found: Cl, 8·95. $C_{20}H_{27}NO_3$,HCl,$2H_2O$ requires Cl, 8·9%)] were similarly prepared by using the corresponding tolyloxyethyl bromides.

Halogeno-compounds. The following were prepared as described in Part I,[4] and except where otherwise stated were recrystallised from dry ethanol:

2-[Di-(2-phenoxyethyl)amino]ethyl chloride hydrochloride (from ethanol–ether; 97%), m. p. 128—129° (lit.,[2] 131°) (Found: Cl, 19·9. Calc. for $C_{18}H_{22}ClNO_2$,HCl: Cl, 19·9%); the *o*-tolyl analogue (from ethanol–ether; 60%), m. p. 141—142·5° (Found: Cl, 18·4. Calc. for $C_{20}H_{26}ClNO_2$,HCl: Cl, 18·6%); and the *p*-tolyl analogue (from ethyl acetate; 58%), m. p. 154—155° (lit.,[2] 148—151°) (Found: C, 52·4; H, 6·9; N, 3·7; Cl, 18·6. Calc. for $C_{20}H_{26}ClNO_2$,HCl: C, 52·5; H, 6·9; N, 3·6; Cl, 18·6%).

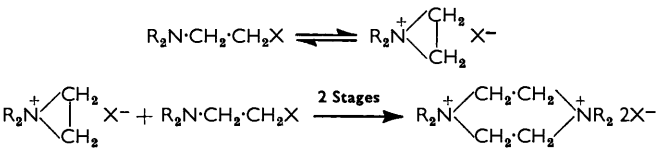
The corresponding *bromide hydrobromides*: *phenoxy* (89%), m. p. 115·5—116·5° (Found: C, 48·8; H, 5·6; H, 3·4; Br, 36·3. $C_{18}H_{22}BrNO_2$,HBr requires C, 48·6; H, 5·2; N, 3·2; Br, 35·9%); *o-tolyloxy* (62%), m. p. 164·5—165·5° (Found: C, 50·9; H, 5·4; N, 3·2; Br, 33·6. $C_{20}H_{26}BrNO_2$,HBr requires C, 50·7; H, 5·7; N, 3·0; Br, 33·8%); and p-*tolyloxy* (79%), m. p. 153·5—154·5° (Found: C, 51·1; H, 5·8; N, 3·0; Br, 33·8%).

The corresponding *iodide hydriodides*: *phenoxy* (70%), m. p. 152—152·5° (Found: C, 40·3; H, 4·5; N, 2·8; I, 47·2. $C_{18}H_{22}INO_2$,HI requires C, 40·1; H, 4·3; N, 2·6; I, 47·1%); o-*tolyloxy* (42%), m. p. 191—192: (Found: C, 42·6; H, 5·1; N, 2·7; I, 44·6. $C_{20}H_{26}INO_2$,HI requires C, 42·4; H, 4·8; N, 2·5; I, 44·7%); and p-*tolyloxy* (80%), m. p. 119·5—120·5° (Found: C, 42·5; H, 4·9; N, 2·2; I, 44·5%).

Procedure.—This was as described in Part II.[5] In reactivity experiments with the di-*p*-tolyloxy-chloride hydrochloride, diphenoxy-iodide hydriodide, and di-*p*-tolyloxy-iodide hydriodide, crystalline salts were precipitated and were isolated. These are very probably *piperazinium salts* formed by dimerisation of the halogenoamines in the usual way but they were not fully characterised. The three products had respectively m. p. 230—231° (Found: Cl, 10·5. $C_{40}H_{52}Cl_2N_2O_4$ requires Cl, 10·2%), m. p. 240—241° (Found: C, 52·1; H, 5·34. $C_{36}H_{44}I_2N_2O_4$ requires C, 52·6; H, 5·4), and m. p. 244° (decomp.) (Found: C, 55·0; H, 6·0; N, 3·3; I, 29·0. $C_{40}H_{52}I_2N_2O_4$ requires C, 54·7; H, 5·9; N, 3·2; I, 28·9%).

Discussion

Fig. 1 shows curves typical of the decomposition of the chloro-compounds of this group, and Fig. 2 curves typical of the decomposition of the bromo- and iodo-compounds. These curves show the usual general pattern. It seems likely that with some of the compounds of this group piperazinium salt formation according to the following scheme plays a significant rôle in the decomposition (cf. above):



The ethyleneiminium ion is also hydrolysed, as can be seen from the development of titratable acidity in the system. However, the concentration of halide produced at any given time will now, if no other reactions occur, be equal to the sum of the free ethyleneiminium-ion concentration, the hydrogen-ion concentration, and twice the piperazinium salt concentration. The curves in Figs. 1 and 2 allow us, therefore, to set an upper limit to the concentration of piperazinium salt at any given time.

Although it has not been possible so far to synthesise these piperazinium salts directly, and so to study their pharmacological properties, pharmacological testing [3] of suitable

[5] Chapman and James, *J.*, 1954, 2103.

aged solutions of the halogenoethylamines, which almost certainly contain these piperazinium salts, has shown that, in agreement with previous observations, the piperazinium salts have no detectable anti-adrenaline activity.

Application of Belleau's [6] theory to *N*-alkyl-*N*-aryloxyethyl-2-halogenoethylamines leads to the conclusion that *o*- and possibly *p*-methyl groups in the aryloxy-residue should enhance activity. Similar conclusions for bisaryloxyethyl compounds seem reasonable. The results assembled in the Table confirm such conclusions for these compounds, save for the *p*-tolyloxy-derivative among the chloro-compounds, and the *o*-tolyloxy-derivative

FIG. 1. FIG. 2.

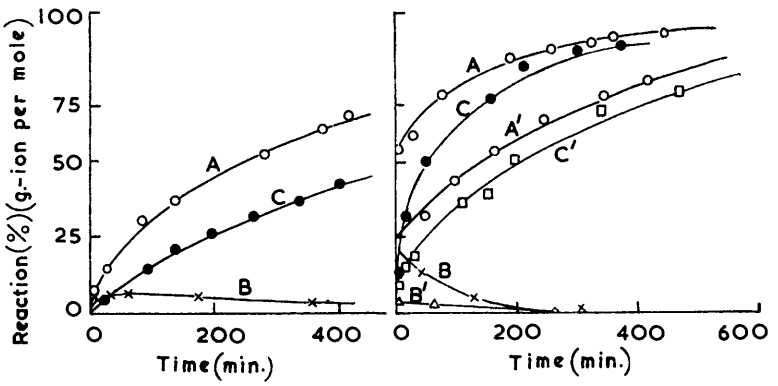


FIG. 1. *Decomposition of* 2-[*di*-(2-*phenoxyethyl*)*amino*]*ethyl chloride at* 30° *in aqueous acetone.* (A) *Chloride ion liberated.* (B) *Ethyleneiminium ion formed.* (C) *Hydrogen ion formed.*

FIG. 2. *Decomposition of* 2-[*di*-(2-o-*tolyloxy*)*amino*]*ethyl bromide and iodide at* 30° *in aqueous acetone.* A, B, C, *refer to the bromide, and* A′, B′, C′ *to the iodide; otherwise as for* Fig. 1

among the iodo-compounds, but clearly the observations are marginal and may well be complicated, as has previously been shown,[1] by differing efficiencies of utilisation of ethyleneiminium ions *in vivo*. Finally we note that there is only a rough qualitative correlation between maximum concentration of ethyleniminium ion *in vitro* and anti-adrenaline and -noradrenaline activity *in vivo* (see Table).

Reactions and properties of salts $(Ar{\cdot}O{\cdot}CH_2{\cdot}CH_2)_2{\cdot}N{\cdot}CH_2{\cdot}CH_2X,HX$.

Compound Ar	X	Proportion of X liberated * (%) after ~360 min.	Max. proportion of ethyleniminium ion formed * (%)	Anti-adrenaline activity † (micromoles/kg.)	Anti-noradrenaline activity † (micromoles/kg.)
Ph	Cl	59	6	4·6	7·6
Ph	Br	93	33	2·2	4·5
Ph	I	70	7	3·0	5·6
o-Tolyl	Cl	48	4	3·0	3·6
,,	Br	91	21	1·0	1·5
,,	I	74	3	3·9	6·8
p-Tolyl	Cl	56	6	7·3	12·4
,,	Br	93	27	1·7	2·8
,,	I	—	—	1·2	2·0

* G.-ion/mole. † $E.D._{50}$ in spinal rats.

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[6] Belleau, *Canad. J. Biochem. Physiol.*, 1958, **36**, 731.