923. *Di*-N-*Substituted* 2-*Halogenoethylamines. Part VII.*[1] NN-*Dialkyl*-2-1′- *or* -2′-*naphthyl Derivatives, and Some Miscellaneous Related Compounds: Synthesis, Reactivity, and Pharmacology.*

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A series of compounds Ar·CRBr·CH_2·NR′R″,HBr has been prepared with Ar = 1- or 2-naphthyl, R = H, R′ = R″ = alkyl, and with Ar = Ph or 1-naphthyl, R = Me, Et, or Pr^i, and R′ = R″ = Me; the corresponding tertiary alcohols have been prepared by the action of an alkylmagnesium halide on an aryl dimethylaminomethyl ketone. The hydrobromides of *NN*-dimethyl-2-bromo-4-phenylbutylamine, of *NN*-dimethyl-2-bromo-4-phenylbut-3-enylamine, and of the corresponding piperidino-compounds have also been prepared. From the product of reaction of phosphorus tribromide with *NN*-dimethyl-2-hydroxy-2,2-diphenylethylamine only dimethylamine hydrobromide was isolated. The action of phosphorus tribromide on (±)-*cis*- or (±)-*trans*-*NN*-dimethyl-2-hydroxycyclohexylamine gave one and the same substance, which is believed to be a mixture of about 37% of the corresponding (±)-*trans*-bromo-compound, and about 63% of the (±)-*cis*-bromo-compound. (±)-*cis*- and (±)-*trans*-*NN*-Dimethyl-2-hydroxy-2-phenylcyclohexylamine have been prepared and characterised, but with phosphorus tribromide they yielded only uncrystallisable products.

The solvolysis in 1 : 1 aqueous acetone at 31·0° of some of the bromoamines has been studied. Compounds containing a naphthyl group or a tertiary arylalkyl bromide group differ from *NN*-dimethyl-β-bromophenethylamine in yielding no ethyleniminium ion, despite a rapid initial release of bromide ion. These observations are interpreted in terms of a reaction scheme involving a carbonium ion derived from the ethyleniminium ion, and the influence of its structure on its stability and reactivity towards nucleophiles.

The pharmacological properties of some of the compounds are briefly discussed.

In Part VI [1] we described the preparation, and chemical and pharmacological properties, of compounds of type (I) with Ar = phenyl or substituted phenyl, R = H, R′ = alkyl or H, and R″ = alkyl. The present paper deals first with the preparation by methods

Ar·CRBr·CH_2·NR′R″,HBr (I)

similar to those described in Part VI, of compounds of type (I) specified in the Summary above, and the hydrobromides of *NN*-dimethyl-2-bromo-4-phenyl-but-3-enylamine and -butylamine and of the corresponding piperidino-compounds.

NN-Dimethyl-2-hydroxy-2,2-diphenylethylamine, on treatment with phosphorus tribromide, gave dimethylamine hydrobromide as the only isolable product, possibly because a first-formed tertiary bromo-compound underwent spontaneous elimination.

The action of phosphorus tribromide on (±)-*cis*- or (±)-*trans*-*NN*-dimethyl-2-hydroxycyclohexylamine gave the same substance in each case, probably a mixture of the corresponding geometrically isomeric bromo-compounds. In this respect the reaction apparently differs from those of phosphorus chlorides with simple alcohols which are reputed to give the chloride more or less stereospecifically, but with inversion of configuration.[2] (±)-*cis*- and (±)-*trans*-*NN*-Dimethyl-2-hydroxy-2-phenylcyclohexylamine were also prepared, but their reactions with phosphorus tribromide gave no crystallisable products. The pure geometrically isomeric bromo-compounds would be of great interest in connection with the mechanism of solvolysis of this class of compounds and with their

[1] Part VI, Chapman and Triggle, *J.*, 1963, 1385.
[2] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell & Sons, London, 1st edn., 1953, p. 392.

pharmacological properties, the *cis*-iomers in each case being expected to be much less reactive chemically and less active pharmacologically, possibly even inert in both respects.

The usual synthesis of 1,1-diphenylethylene oxide [3] gives poor yields, but we have obtained it in >60% overall yield by the action of hot aqueous-ethanolic sodium hydroxide on *NNN*-trimethyl-2-hydroxy-2,2-diphenylethylammonium iodide, itself readily obtained from ω-dimethylaminoacetophenone by the action of phenylmagnesium bromide, followed by quaternisation with methyl iodide of the amino-alcohol so obtained.

Experimental

Materials.—NN-*Disubstituted* 2-*bromo*-2-1′- *or* -2′-*naphthylethylamine hydrobromides.* 1- and 2-Acetylnaphthalene were prepared by Baddeley's method [4] (yield 94 and 66%, respectively) and were converted into the corresponding ω-bromo-compounds by the method given in *Org. Synth.*, 1939, **19**, 24. 1-Bromoacetylnaphthalene (67%) had b. p. 160—170°/1 mm. (decomp.) and the 2-isomer (93%) had m. p. 81—83° (from aqueous methanol) (lit.,[5] 82—84°). From these ω-bromo-compounds *N*-substituted ω-aminoacetonaphthone hydrochlorides were prepared; they crystallised from ethanol and were reduced to the corresponding alcohols with aluminium isopropoxide in propan-2-ol, and then were converted into the bromo-compounds as described in Part VI.[1] Details are given in Tables 1 and 2.

Table 1.

NN-Disubstituted ω-aminoacetonaphthone hydrochlorides, $Ar{\cdot}CO{\cdot}CH_2Y,HCl$.

Y	Ar	M. p.*	Yield (%)	Found (%) Cl^-	Required (%) Cl^-
NMe_2	1-$C_{10}H_7$	186—188°	87	14·4	14·2
NEt_2	1-$C_{10}H_7$	226—228	88	12·9	12·8
Piperidino	1-$C_{10}H_7$	232—234	96	12·5	12·2
NMe_2	2-$C_{10}H_7$	212—213	88	14·3	14·2
NEt_2	2-$C_{10}H_7$	184—186	92	12·9	12·8
Piperidino †	2-$C_{10}H_7$	—	96	—	—

* With decomp. † Not purified.

Table 2.

NN-Disubstituted 2-hydroxy- and 2-bromo-2-1′- or -2′-naphthylethylamines.

					$Ar{\cdot}CHX{\cdot}CH_2X$							
					Found (%)				Required (%)			
Ar	X	Y	M. p. or b. p./mm.	Yield (%)	C	H	N	Hal	C	H	N	Hal
1-$C_{10}H_7$	OH	NMe_2	124—136°/0·001	75	78·0	8·1	6·3	—	78·1	7·9	6·5	—
,,	OH	NMe_2,MeI †	234—235° *	—	50·6	5·3	—	35·7	50·4	5·6	—	35·5
,,	OH	NEt_2	160°/0·01	67	79·2	8·7	6·0	—	79·0	8·7	5·7	—
,,	OH	NC_5H_{10} ‡	84—85°	65	80·0	8·6	5·4	—	80·0	8·3	5·5	—
2-$C_{10}H_7$	OH	NMe_2	148—150°/0·1	66	78·3	8·2	6·6	—	78·1	7·9	6·5	—
,,	OH	NMe_2,MeI †	260—262° *	—	50·5	5·5	—	35·4	50·4	5·6	—	35·5
,,	OH	NEt_2	180°/0·01	68	79·1	8·5	5·7	—	79·0	8·7	5·8	—
,,	OH	NC_5H_{10} ‡	99—100°	73	80·0	8·1	5·6	—	80·0	8·3	5·5	—
1-$C_{10}H_7$ ††	Br	NMe_2,HBr §	195—197°	55	46·8	4·4	3·6	44·6	46·8	4·8	3·9	44·5
2-$C_{10}H_7$ ‡‡	Br	NMe_2,HBr **	155—157°	65	47·0	4·6	3·8	44·7	46·8	4·8	3·9	44·5
,,	Br	NC_5H_{10},HBr †	193—194°	76	51·3	5·0	3·0	40·2	51·1	5·3	3·6	40·1

* With decomp. Recrystallisation solvents: † EtOH, ‡ 70% Aq. EtOH, § MeOH, ** MeOH–Pr^iOH. †† $E.D._{50}$ on rat blood pressure against adrenaline 0·02, and against noradrenaline 0·02 micromole/kg.; ‡‡ 0·002 and 0·06 micromole/kg., respectively (the *NN*-diethylamino-bromo-compounds and the isomeric piperidino-bromo-compound could not be obtained crystalline). NC_5H_{10} = Piperidino.

NN-*Dimethyl*-2-*bromo*-4-*phenylbutylamine Hydrobromide.*—Interaction of epichlorhydrin and benzylmagnesium chloride by Fourneau and Tiffeneau's method [6] gave 1-chloro-4-phenylbutan-2-ol (79%), b. p. 140—142°/18 mm. (lit.,[6] 156°/22 mm.). The chloro-compound (0·2 mole)

[3] Klages and Kessler, *Ber.*, 1906, **39**, 1753.
[4] Baddeley, *J.*, 1949, S99.
[5] Rabcewicz and Zubkowski, *Rocniki Chem.*, 1929, **9**, 538; cf. *Chem. Zentr.*, 1929, **100**, 275.
[6] Fourneau and Tiffeneau, *Bull. Soc. chim. France*, 1907, **1**, 1231.

and dimethylamine (0·5 mole) in 90% aqueous ethanol (250 ml.) were set aside at room temperature for 7 days, and then water (500 ml.) was added and the solution was acidified with hydrochloric acid. Unchanged chloro-compound was extracted with ether, and the aqueous layer was made strongly alkaline with 40% aqueous sodium hydroxide (200 ml.) and shaken with ether (2 × 200 ml.). The ethereal solution was dried (Na_2SO_4), the ether was removed, and the residual oil was distilled. This gave *NN*-dimethyl-2-hydroxy-4-phenylbutylamine (88%), b. p. 140—142°/18 mm. (lit.,[7] 145—147°/15 mm.) [methiodide (from propan-2-ol), m. p. 170—171° (lit.,[7] 170°)].

Similar reactions gave *NN-diethyl-2-hydroxy-4-phenylbutylamine* (79%), b. p. 100—105°/0·2 mm. (Found: C, 76·2; H, 10·0; N, 6·4. $C_{14}H_{23}NO$ requires C, 76·0; H, 10·4; N, 6·3%), and 1-(2-*hydroxy-4-phenylbutyl*)*piperidine* (85%), b. p. 123—125°/0·25 mm. (Found: C, 77·3; H, 10·1; N, 6·4. $C_{15}H_{23}NO$ requires C, 77·3; H, 9·9; N, 6·0%) [*picrate* (from benzene–ethanol) m. p. 185—187° (decomp.) (Found: C, 54·8; H, 5·9. $C_{21}H_{26}N_4O_8$ requires C, 54·5; H, 5·7%)].

Interaction of the appropriate amino-alcohol and phosphorus tribromide in the usual way [1] and crystallisation of the product from propan-2-ol gave NN-*dimethyl-2-bromo-4-phenylbutylamine hydrobromide* (77%), m. p. 162—162·5° (Found: C, 42·9; H, 5·2; Br, 47·7. $C_{12}H_{19}Br_2N$ requires C, 42·7; H, 5·6; Br, 47·5%) [inactive against adrenaline or noradrenaline (rat blood pressure)], and 1-(2-*bromo-4-phenylbutyl*)*piperidine hydrobromide* (88%), m. p. 146—148° (Found: C, 48·0; H, 6·0; Br, 42·3. $C_{15}H_{23}Br_2N$ requires C, 47·8; H, 6·1; Br, 42·4%).

NN-*Dimethyl-2-bromo-4-phenylbut-3-enylamine Hydrobromide.*—1,3,4-Tribromo-4-phenylbut-2-one was prepared by Southwick and Dimond's method [8] and was converted into 1-iodo-4-phenylbut-3-ene-2-one, m. p. 53—57° (lit.,[9] 56·5—58·5°) by Southwick, Pursglove, and Numerof's method.[9] The iodo-compound (0·2 mole) in dry ether (500 ml.) was added gradually to dimethylamine (0·42 mole) in dry ether (500 ml.), and the mixture was kept at room temperature overnight. The precipitated amine hydriodide was filtered off and the ether was removed from the filtrate to give the crude dialkylaminophenylbutenone as a dark oil. This oil (~0·1 mole) was reduced with lithium aluminium hydride as described in Part VI,[1] p. 1392. This gave NN-*dimethyl-2-hydroxy-4-phenylbut-3-enylamine* (49%), b. p. 60°/0·2 mm. (Found: C, 75·8; H, 8·5. $C_{12}H_{17}NO$ requires C, 75·4; H, 8·9%).

A similar reaction gave 1-(2-*hydroxy-4-phenylbut-3-enyl*)*piperidine* (57%), b. p. 100—110°/0·1 mm. (Found: C, 78·3; H, 8·7. $C_{15}H_{21}NO$ requires C, 77·9; H, 9·1%) [*picrate* (from benzene–ethanol) m. p. 149—150° (decomp.) (Found: C, 54·1; H, 5·6; N, 12·0. $C_{21}H_{24}N_4O_8,\frac{1}{2}H_2O$ requires C, 53·7; H, 5·4; N, 11·9%).

These unsaturated amino-alcohols were converted into the corresponding bromo-compounds as described above: NN-*Dimethyl-2-bromo-4-phenylbut-3-enylamine hydrobromide* (49%, from methanol) had m. p. 171—172° (Found: C, 43·2; H, 4·8; Br, 47·6. $C_{12}H_{17}Br_2N$ requires C, 43·0; H, 5·1; Br, 47·7%), and 1-(2-*bromo-4-phenylbut-3-enyl*)*piperidine hydrobromide* (67%; from propan-2-ol) had m. p. 201—203° (Found: C, 47·8; H, 5·8; Br, 42·7. $C_{15}H_{21}Br_2N$ requires C, 48·0; H, 5·6; Br, 42·7%) and $E.D._{50}$ (rat blood pressure) against adrenaline and noradrenaline < 100 micromoles/kg.

NN-*Dimethyl-2-alkyl-2-bromo-2-phenyl-* or *-1′-naphthyl-ethylamine Hydrobromides.*—ω-Dimethylaminoacetophenone (0·20 mole) in dry ether (250 ml.) was added to the appropriate alkylmagnesium bromide or iodide (0·25 mole) in dry ether at such a rate that the ether boiled gently, and the mixture was then stirred at room temperature for a further 2 hr. An excess of aqueous ammonium chloride was added, the ethereal layer was separated and dried (Na_2SO_4), the ether was removed, and the residual oil was distilled under reduced pressure. Thus were prepared: *NN*-dimethyl-β-hydroxy-β-methyl- (85%), b. p. 118—120°/20 mm. (lit.,[10] 132°/32 mm.), -β-*ethyl-* (75%), b. p. 125—130°/18 mm. (Found: C, 74·2; H, 9·5. $C_{12}H_{19}NO$ requires C, 74·5; H, 9·9%) [*picrate* (from ethanol–propan-2-ol), m. p. 141—142° (Found: C, 50·2; H, 4·8. $C_{18}H_{22}N_4O_8,\frac{1}{2}H_2O$ requires C, 50·1; H, 5·3%)], and -β-*isopropyl-phenethylamine* (66%), b. p. 120—124°/13 mm. (Found: C, 75·0; H, 10·0. $C_{13}H_{21}NO$ requires C, 75·4; H, 10·1%).

[7] von Braun, *Ber.*, 1923, **56**, 2182.
[8] Southwick and Dimond, *J. Amer. Chem. Soc.*, 1954, **76**, 5669.
[9] Southwick, Pursglove, and Numerof, *J. Amer. Chem. Soc.*, 1950, **72**, 1604.
[10] Fourneau, *Compt. rend.*, 1904, **138**, 767.

1-Dimethylaminoacetonaphthone (0·3 mole) was added gradually with stirring to methylmagnesium iodide (0·4 mole) in dry ether, and the mixture was stirred at room temperature for a further 3 hr. Aqueous ammonium chloride was then added, the ethereal layer was separated and dried (Na_2SO_4), and dry hydrogen chloride was passed into the solution until no more gum was precipitated. The gum crystallised from methanol–propan-2-ol, to give NN-*dimethyl*-2-*hydroxy*-2-1′-*naphthylpropylamine hydrochloride* (34%), m. p. 231—233° (decomp.) (Found: C, 68·1; H, 7·5; Cl, 13·5. $C_{15}H_{20}ClNO$ requires C, 67·8; H, 7·5; Cl, 13·4%). Isopropylmagnesium iodide did not react in the above way.

Interaction of the above amino-alcohols with phosphorus tribromide in the usual way [1] and crystallisation of the products from propan-2-ol gave the *hydrobromides* of: NN-*dimethyl*-β-*bromo*-β-*methyl*- (64%), m. p. 173—174° (Found: C, 41·1; H, 5·0; Br, 49·3. $C_{11}H_{17}Br_2N$ requires C, 40·9; H, 5·3; Br, 49·5%) [inactive against adrenaline and noradrenaline (rat blood pressure)], -β-*ethyl*- (44%), m. p. 183—184° (Found: C, 42·8; H, 5·7; Br, 47·5. $C_{12}H_{19}Br_2N$ requires C, 42·7; H, 5·6; Br, 47·5%), and -β-*isopropyl*-*phenethylamine* (68%), m. p. 152—154° (Found: C, 45·1; H, 6·0; Br, 45·3. $C_{13}H_{21}Br_2N$ requires C, 44·4; H, 6·0; Br, 45·6%), and NN-*dimethyl*-2-*bromo*-2-1′-*naphthylpropylamine* (29%), m. p. 174—176° (Found: C, 48·5; H, 4·7. $C_{15}H_{19}Br_2N$ requires C, 48·3; H, 5·1%).

NN-*Dimethyl*-2-*hydroxy*-2,2-*diphenylethylamine Hydrochloride*.—ω-Dimethylaminoacetophenone hydrochloride (0·3 mole) was added during 3 hr. to stirred ethereal phenylmagnesium bromide at 10°, and the mixture was then stirred for 3 hr. at room temperature, and an excess of dilute hydrochloric acid was added. The product was kept overnight at 0° and the above *hydrochloride* (80%) was filtered off. After recrystallisation from methanol it had m. p. 228—230° (decomp.) (Found: C, 69·5; H, 7·0. $C_{16}H_{20}ClNO$ requires C, 69·2; H, 7·2%). The *methiodide*, m. p. 248° (decomp.) (Found: C, 52·9; H, 5·8. $C_{17}H_{22}INO$ requires C, 53·3; H, 5·8%), was prepared in the usual way, and also by the action of an excess of methyl iodide on 2-hydroxy-2,2-diphenylethylamine. On being treated with a 33% excess of sodium hydroxide in 60% aqueous methanol it gave in quantitative yield 1,1-diphenylethylene oxide, m. p. 53° (lit.,[3] 56°), undepressed on admixture with an authentic sample.

The only product isolated on treatment of the amino-alcohol with phosphorus tribromide in the usual way was dimethylamine hydrobromide, m. p. 131—133° (Found: C, 19·2; H, 6·1. Calc. for C_2H_8BrN: C, 19·0; H, 6·3%).

NN-*Dimethyl*-2-*bromocyclohexylamine*.—Cyclohexene oxide (0·25 mole; b. p. 130°; lit.,[11] 131—132°) and dimethylamine (1·0 mole) in benzene (500 ml.) were set aside at room temperature for 14 days. Fractional distillation then gave (±)-*trans*-*NN*-dimethyl-2-hydroxycyclohexylamine (95%), b. p. 90°/20 mm. [methiodide, m. p. 210—212° (lit.,[12,13] 214°, 217—217·5°); picrate, m. p. 150—151° (lit.,[14] 149—150°)].

Crude 2-bromocyclohexanone (~1·0 mole; obtained by the action of bromine on cyclohexanone in ether at 0°) in dry ether (250 ml.) was added to a stirred solution of dimethylamine (3·0 moles) in dry ether (750 ml.) during 5 hr. The precipitated dimethylamine hydrobromide was then filtered off and the filtrate was shaken with an excess of 5N-hydrochloric acid. The acidic solution was run into ice-cold 10% aqueous sodium hydroxide, and the oil which was liberated was extracted with ether (3 × 200 ml.), the ethereal solution was dried (Na_2SO_4), and *NN*-dimethylaminocyclohexan-2-one (18·2%) was obtained by fractional distillation. It had b. p. 90—93°/18 mm. and gave a picrate, m. p. 113—114° (lit.,[14] 113—114°). Reduction of the amino-ketone (0·1 mole) in dry ethanol (100 ml.) with hydrogen and Raney nickel (3 g.) at 35°/25 atm. gave *cis*-(±)-*NN*-dimethyl-2-hydroxycyclohexylamine (98%), b. p. 100—101°/18 mm. (lit.,[14] 98°/20 mm.) [picrate, m. p. 159—160° (lit.,[14] 162—163°)].

The action of phosphorus tribromide in the usual way on either the *cis*- or the *trans*-amino-alcohol gave the same substance (44 and 39%, respectively), m. p. 167—169° (Found: C, 33·8; H, 7·1. Calc. for $C_8H_{17}Br_2N$: C, 33·4; H, 6·0%). This was probably a mixture of *cis*- and *trans*-(±)-*NN*-dimethyl-2-bromocyclohexylamine hydrobromide (see p. 4841).

cis- *and* trans-(±)-NN-*Dimethyl*-2-*hydroxy*-2-*phenylcyclohexylamine*.—Crude 1,2-epoxy-1-phenylcyclohexane [~0·1 mole, prepared from 1-phenylcyclohexene,[15] b. p. 126—130°/18 mm.

[11] Bedos, *Bull. Soc. chim. France*, 1926, **39**, 299.
[12] Read and Wilson, *J.*, 1935, 1269.
[13] King and Holmes, *J.*, 1947, 164.
[14] Mousseron, Julliers, and Jolchine, *Bull. Soc. chim. France*, 1952, **19**, 757.
[15] Eliel, McCoy, and Price, *J. Org. Chem.*, 1957, **22**, 1533.

(lit.,[16] 128°/16 mm.) by Curtin and Schmukler's method [16]] was kept with an excess of dimethylamine in ethanol (250 ml.) at room temperature for 7 days. Water (500 ml.) was then added and the solution was acidified with 2N-hydrochloric acid. Insoluble material was extracted with ether, the aqueous layer was made alkaline with 10% aqueous sodium hydroxide and shaken with ether (2 × 200 ml.). The ethereal solution was dried (Na_2SO_4), the ether was removed, and the oil was distilled, to give (±)-trans-NN-*dimethyl*-2-*hydroxy*-2-*phenylcyclohexylamine* (5%), b. p. 100—110°/0·1 mm. [*methiodide*, m. p. 193—195° (decomp.) (Found: C, 50·2; H, 6·8. $C_{15}H_{24}INO$ requires C, 49·9; H, 6·7%)].

(±)-*cis*-2-Hydroxy-2-phenylcyclohexylamine (0·05 mole; m. p. 88—92°; prepared by Curtin and Schmukler's method [16]—they give m. p. 92—93°) was dissolved in 85% formic acid (15 ml.) at 20° and 40% aqueous formaldehyde (7 ml.) was added. The solution was heated at 95° until no more gas was evolved, then at the b. p. for 30 min., cooled, made alkaline with 10% aqueous sodium hydroxide, and shaken with ether (3 × 100 ml.). The ethereal solution was dried (Na_2SO_4), the ether was removed, and the oil was distilled, to give (±)-cis-NN-*dimethyl*-2-*hydroxy*-2-*phenylcyclohexylamine* (73%), b. p. 100—102°/0·1 mm. [*methiodide*, m. p. 212—213° (Found: C, 50·0; H, 6·9%)].

The action of phosphorus tribromide in the usual way on the last two amino-alcohols gave products which could not be crystallised. On the other hand, *m*- and *p*-sympathol and (±)-adrenaline gave only the corresponding crystalline hydrobromides on being treated similarly.

Reactivity Measurements

Procedure.—This was described in Part VI.[1] The results are summarised in Table 3.

Table 3.

Solvolysis of *NN*-disubstituted 2-aryl-2-bromoethylamines, Ar·CRBr·CH_2·NMe_2, in 1 : 1 acetone–water at 31·0°.*

		Br^- liberated (g.-ion/mole, %)		E^+	H^+
Ar	R	5 min.	24 hr.	(Max., %)	(%, after 5 min.)
1-$C_{10}H_7$	H	24·7	26·3	0	6·0
2-$C_{10}H_7$	H	42·3	46·0	0	10·0
Ph	Me	36·5	37·8	0	—
Ph	Et	40·8	42·2	0	—
Ph	Pr^i	65·0	69·6	0	—
1-$C_{10}H_7$	Me	30·1	30·3	0	—
Ph	H	99·9	99·9	92·3	—

E^+ = ethyleniminium ion.

* The results shown in Figs. 2—4, and Table 11 in Part VI [1] also relate to 31·0°. This point was omitted in Part VI.

Discussion

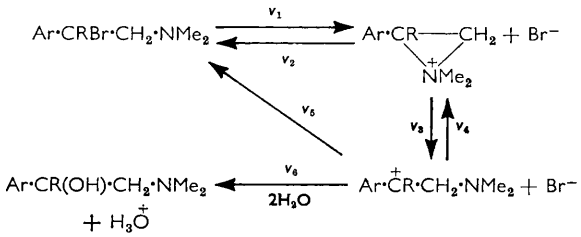
The pharmacological properties of a few of the compounds described have been examined by Graham and James [17] [cf. table 2, last three entries, and p. 4838]. In compounds of the type Ar·CRBr·CH_2·NMe_2,HBr with R = H, replacing phenyl by 1-naphthyl as the aryl group increases activity against adrenaline or noradrenaline (rat blood-pressure test) by a factor of about 2 or 5, respectively, and by 2-naphthyl by a factor of about 20 or 2, respectively. When Ar is Ph·$[CH_2]_2$· or Ph·CH:CH· the compounds are virtually inactive and similarly when Ar = Ph and R = Me. Further discussion of these observations is deferred to a later paper in this series.

The chemical behaviour in initially neutral 1 : 1 acetone–water of the first six of the compounds listed in Table 3 stands in marked contrast with that of *NN*-dimethyl-β-bromophenethylamine which very rapidly liberates 99·9% of its combined bromine as bromide ion, with concurrent formation of an approximately equivalent amount of ethyleniminium ion. The results in Table 3 show features common to the compounds now studied, *viz.*,

[16] Curtin and Schmukler, *J. Amer. Chem. Soc.*, 1955, **77**, 1105.
[17] Graham and James, *J. Med. Pharm. Chem.*, 1961, **3**, 489.

liberation of 25—65% of combined bromine as bromide ion after 5 min. (the pattern is unaltered after 24 hr.) without concurrent formation of a detectable amount of ethyleniminium ion. Hydrogen-ion concentrations formed could not be measured in all cases, but where they were measured there was no detectable increase after 5 min.

The observations may be interpreted in terms of the following reaction scheme (cf. Part VI, p. 1398):



There is an initial rapid release of bromide ion and formation of ethyleniminium ion, the latter being very rapidly converted into the corresponding carbonium ion which may then undergo each of two reactions: (*a*) with water to form the amino-alcohol (v_6), and (*b*) with bromide ion to regenerate the substituted 2-bromoethylamine (v_5). In the early stages of the reaction it is likely, since [Br^-] is low, that $v_6 > v_5$. Further liberation of bromide ion, however, causes an increase in v_5 according to the mass law, until $v_5 > v_6$ and there is a state of apparent equilibrium. The equilibrium can be only apparent because v_6 must be finite, which results in a further very slow liberation of bromide ion (Table 3). Early in the reaction some carbonium ion may be removed by piperazinium salt formation; this would account for the observed discrepancies between bromide and hydrogen-ion concentrations.

It is expected that a carbonium ion which is more effectively stabilised by charge delocalisation will be less reactive towards a given nucleophilic reagent and, furthermore, will be more selective in its reactions, *i.e.*, its rates of reaction with a series of reagents of differing nucleophilic power will span a wider range than the corresponding rates for a less stable and more reactive carbonium ion.[18] The almost quantitative release of bromide ion from *NN*-dimethyl-β-bromophenethylamine (Table 3) implies that the reactivity of the carbonium ion in this case is so great that it reacts with water rather than with bromide ion in 1 : 1 acetone–water, in which the water is present in a 750-fold excess over bromide ion, even though the nucleophilicity of bromide ion (3·89) is much greater than that of water (0·0) on the scale proposed by Swain and Scott.[19]

The alkyl substituents in compounds of the type Ar·CRBr·CH_2·NMe_2 stabilise the corresponding carbonium ions by inductive and hyperconjugative electron-release: the presence of a formal positive charge in the molecule implies the greater importance of the hyperconjugative mechanism. The stability of the derived carbonium ions should lie in the order: Me > Et > Pr^i. The order of extent of release of bromide ion found (Me < Et < Pr^i) accords with this prediction, since increasing the stability of the carbonium ion will increase the ratio v_5/v_6.

We note also that *NN*-dimethyl-2-bromo-2-1′- or -2′-naphthylethylamine shows the same type of behaviour. A similar explanation can be put forward, the effect being due principally to the powerful conjugative effect of the naphthyl nucleus which will stabilise the carbonium ion to a greater extent than the phenyl residue does. The 2-naphthyl compound liberates more bromide ion than does the 1-naphthyl compound. This accords with the views of Ketelaar and Oosterhaut [20] that the naphthalene nucleus is conjugated to a greater extent with 1-substituents than with 2-substituents. *NN*-Dimethyl-2-bromo-2-methyl-2-1′-naphthylethylamine liberates more bromide ion than does the corresponding

[18] Swain, Scott, and Lohmann, *J. Amer. Chem. Soc.*, 1953, **75**, 136.
[19] Swain and Scott, *J. Amer. Chem. Soc.*, 1954, **76**, 141.
[20] Ketelaar and Oosterhaut, *Rec. Trav. chim.*, 1946, **65**, 448.

secondary bromide after 5 min. (or 24 hr.), although according to the views set out above it is expected that the additional stabilisation of the corresponding carbonium ion by the 2-methyl group would diminish the extent of release of bromide ion. Examination of a model of the derived tertiary carbonium ion, however, reveals the possibility of steric interaction between the 1-substituent and the *peri*-hydrogen atom in the naphthalene nucleus, which may reduce the stability of this ion, by preventing the naphthalene ring from becoming coplanar with the rest of the molecule.

The substance of m. p. 167—169° obtained by the action of phosphorus tribromide on (±)-*cis*- or (±)-*trans*-NN-dimethyl-2-hydroxycyclohexylamine, on being dissolved in 1 : 1 acetone–water and treated with one equivalent of sodium hydroxide, instantly liberated 37% of its covalently bound bromine as bromide ion and then a state of apparent equilibrium was attained. The most likely interpretation of this is that the substance of m. p. 167—169° is a mixture of the (±)-*cis*- and (±)-*trans*-bromo-amines containing about 37% of the latter, because it may reasonably be supposed that for stereochemical reasons the *cis*-isomer would be inert or nearly so, whereas the *trans*-isomer might be expected to liberate bromide ion and form the corresponding ethyleniminium ion rapidly and completely. Analogies for this argument are to be found in the reactions of geometrically isomeric 1-halogeno-2-hydroxycyclohexanes to form cyclohexene oxide.

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