265. *Di-N-substituted 2-Halogenoethylamines. Part VI.*[1] *NN-Dialkyl-(or N-Alkyl)-2-alkyl(or aryl or arylalkyl) Derivatives: Synthesis, Reactivity, and Pharmacology.*

By N. B. Chapman and D. J. Triggle.

The preparation is described of a series of compounds Ar·CHX·CH_2·NRR′, HX with X = Cl, Br, or, rarely, I, Ar = phenyl or substituted phenyl, R = alkyl or hydrogen, and R′ = alkyl; and of a second series CH_3·CHX·CH_2·NR_2,HX, with X = Cl or Br, and R = alkyl. Where necessary the corresponding alcohols have been unambiguously synthesised by reduction of the related ketone of definite structure, but usually interaction of an amine and an epoxide has been used to obtain the alcohols. These have been converted into the corresponding halogeno-compounds by standard methods.

In some cases the products of solvolysis of the halogeno-amines in 1 : 1 aqueous acetone have been characterised; and in suitable cases rate coefficients and Arrhenius parameters for the solvolysis in 1 : 1 aqueous acetone of the related ethyleniminium ions have been determined, and the proportions of three possible products calculated.

The anti-adrenaline and anti-noradrenaline activities of many of the compounds are reported: this series includes some of the most potent known substances of this kind. Their pharmacological activity, however, differs in important respects from that of the "Dibenamine" group of compounds, particularly as to their briefer action. In this series also some secondary alkylamino-compounds with significant activity have been discovered. Structure–action relationships are discussed and the relevance of the results to Belleau's theory of anti-adrenaline activity is considered.

The relation of the structure of the substituted 2-halogenoethylamine molecule to its rate of cyclisation is discussed in terms of an internal S_N2 mechanism (involving neighbouring-group participation). Also the orientation and rate of solvolysis of the ethyleniminium ions formed in this process are discussed by citing analogies with the corresponding reaction of epoxides, mainly in terms of the steric and polar influences of the various dialkylamino-groups present in the compounds studied.

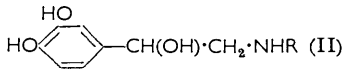
Earlier [1-3] papers in this series have dealt with the synthesis, reactivity, and pharmacology of *NN*-disubstituted 2-halogenoethylamines possessing anti-adrenaline and anti-noradrenaline activity, of type (I), where Ar = 1- or 2-naphthyl, R = Me or Et, X = Cl, Br, or I, and where Ar = *o*-, *m*-, or *p*-Cl·C_6H_4, R = Et, X = Cl or Br, among others. Also

Ar·CH_2·NR·CH_2·CH_2X,HX (I)

compounds of the formula $(ArO·CH_2·CH_2)_2N·CH_2·CH_2X$,HX, with X = Cl, Br, or I, have been studied. The common structural features of these compounds are the N·CH_2·CH_2X group, and the attachment of one or two arylalkyl groups to the nitrogen atom. We now turn our attention to compounds of the type Ar·CHX·CH_2·NRR′,HX with X = Cl, Br, or, rarely, I, Ar = phenyl or substituted phenyl, R = alkyl or hydrogen, and R′ = alkyl; and also of the type CH_3·CHX·CH_2·NR_2,HX, with X = Cl or Br, and R = alkyl. It is noteworthy that the last two groups of compounds contain a secondary or tertiary alkylamino-group and a secondary alkyl halide group, unlike those previously studied. The general formula includes structures approximating quite closely, especially if molecular geometry is mainly considered, to those of adrenaline (II; R = Me) and

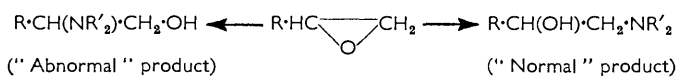
[1] Part V, Chapman and Tompsett, *J.*, 1961, 1291.
[2] Chapman and James, *J.*, 1954, 2103.
[3] Chapman and Allen, *J.*, 1960, 1482; 1961, 1076.

noradrenaline (II; R = H). Moreover, many of the free bases, as well as their hydrohalides, are readily soluble in water, unlike those previously studied. The pharmacological properties of a few of these compounds have previously been described by Hunt [4a] and by



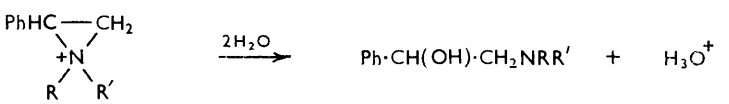
Ferguson and Wescoe,[4b] and a little preparative work is described in a patent.[5] A preliminary account of the present work has been given.[6] A full account of the pharmacology of a selection of the compounds now to be reported has been given by Graham and James.[7]

The synthesis of the intermediate *N*-mono- and *NN*-di-alkyl-β-hydroxyphenethylamines required for the preparation by methods previously described [1–3] of the corresponding 2-halogenoethylamines presents points of interest. The reaction of 1,2-epoxyethylbenzene with amines may give rise to two isomeric amino-alcohols; the amine may attack either of the two carbon atoms of the epoxide ring to give an amino-primary-alcohol or an amino-secondary-alcohol. These two modes of fission are often referred to as " abnormal " and " normal " ring-opening, respectively.



N-Mono- or *NN*-di-alkyl(or -arylalkyl)-β-hydroxyphenethylamines were synthesised from 1,2-epoxyethylbenzene; also unambiguously from ω-bromoacetophenone and the corresponding amine, followed by reduction of the amino-ketone, see p. 1387. The products were identical, although our method of analysis would not have shown the presence of small amounts of " abnormal " products (*ca.* 5%) present in the crude products from 1,2-epoxyethylbenzene. Recent quantitative work by Chapman, Isaacs, and Parker [8] lends strong support to our conclusion that the reaction between 1,2-epoxyethylbenzene and amines gives predominantly the amino-secondary-alcohol: the same authors also showed that amino-secondary-alcohol was obtained from the reaction between 1,2-epoxy-3-phenylpropane and an amine. Accordingly we did not carry out unambiguous syntheses of the amino-alcohols derived from this epoxide. The syntheses of some *NN*-dialkyl-2-hydroxy-1-phenylethylamines were carried out unambiguously starting from ethyl α-chloro-α-phenylacetate, and the products were shown to be different from those obtained in the reaction between 1,2-epoxyethylbenzene and amines. 4-Substituted phenethylamine derivatives were always prepared through the corresponding ω-bromo-(or chloro)acetophenone.

Similarly, substituted ethyleniminium ions may give rise on hydrolysis to two isomeric amino-alcohols, and the process may be represented by a scheme similar to that given above for the ring-opening of an epoxide. The amino-alcohols were isolated after the hydrolysis by extraction with ether, and then were treated with methyl iodide, and the crude methiodide which was precipitated from the ethereal solution was compared with an authentic sample of the methiodide of known constitution. It was shown that the *NN*-dialkyl-2-phenylethyleniminium ions yield the amino-secondary-alcohol on hydrolysis in initially neutral solution.



[4] (*a*) Hunt, *J. Pharmacol.*, 1949, **95**, 177; (*b*) Ferguson and Wescoe, *ibid.*, 1950, **100**, 100.
[5] Cheney, U.S.P. 2,548,652/1951.
[6] Chapman, in " Adrenergic Mechanisms," J. & A. Churchill, London, 1960, p. 270.
[7] Graham and James, *J. Med. Pharm. Chem.*, 1961, **3**, 489.
[8] Chapman, Isaacs, and Parker, *J.*, 1959, 1925.

Experimental

Materials

NN-*Disubstituted 2-Hydroxy-n-propylamines.*—1,2-Epoxypropane (0·4 mole) and the amine (0·5 mole) were heated at the b. p. for 12 hr. and the product was then fractionally distilled. Yields, m. p. or b. p., and analytical results for the *products* and their *methiodides* are given in Table 1.

N-*Mono- and* NN-*Disubstituted-2-aryl-2-hydroxyethylamines.*—*Method A.* 1,2-Epoxyethylbenzene (48 g., 0·4 mole) and the amine (1·0 mole), dissolved in dry benzene (200 ml.), were kept for 14 days at room temperature. Fractional distillation gave the required compound.

Method B. 1,2-Epoxyethylbenzene (24 g., 0·2 mole) and the amine (0·3 mole) were heated under reflux for 4—12 hr. and the product was then fractionally distilled.

Method C. 1,2-Epoxyethylbenzene (24 g., 0·2 mole) and the amine (2·0 moles, as 33% aqueous solution) were set aside for 7 days at room temperature with intermittent shaking; the product was then fractionally distilled. For details of individual compounds, see Table 3.

Method D: Reduction of N-*mono- and* NN-*di-substituted* 4-*substituted* ω-*aminoacetophenones.* (*a*) Preparation of substituted ω-aminoacetophenones. The following is a typical example. A solution of phenacyl bromide [9] (20 g., 0·1 mole) in sodium-dried benzene (100 ml.) was added dropwise to a stirred and cooled solution of the amine (0·2 mole; 0·6 mole in the case of dimethylamine) in sodium-dried ether (200 ml.) at 10°. The mixture was kept at room temperature overnight and the theoretical weight of amine hydrobromide was then filtered off. The substituted ω-aminoacetophenone was isolated by fractional distillation of the filtrate under reduced pressure or by formation of the crystalline hydrochloride. Yields, m. p. or b. p., and analytical results for those products which were purified are given in Table 2. The crude hydrochlorides of the morpholino-, n-butylamino-, cyclohexylamino-, benzylamino-, *N*-methylanilino-compounds, and in the case of the *N*-mono- or di-allyl compounds, the free bases, were obtained in yields usually greater than 95%, and were used for further work without purification.

(*b*) Reduction of substituted ω-aminoacetophenones. The substituted ω-aminoacetophenone (as free base or hydrochloride; 0·25 mole) was dissolved in dry propan-2-ol (1 l.) containing aluminium isopropoxide (80 g., 0·4 mole) and heated under reflux with only partial condensation of vapour until acetone was no longer detected in the distillate (3—9 hr.). The excess of propan-2-ol was distilled off under reduced pressure, and the residue was dissolved in 10% hydrochloric acid and poured into a large excess of ice-cold 15% aqueous sodium hydroxide. The product was extracted with ether (3 × 150 ml.), dried (Na_2SO_4), recovered, and distilled or crystallised. Yields, m. p. or b. p., and analytical results are given in Table 3.

ω-*NN*-Dialkylamino-4-methoxyacetophenones were best prepared from ω-chloro-4-methoxyacetophenone [10] and were reduced as described above.

N-*Ethyl*-N-*methyl*-β-*hydroxyphenethylamine.*—*N*-Methyl-β-hydroxyphenethylamine (30 g., 0·2 mole), ethyl iodide (45 g., 0·33 mole), and sodium carbonate (70 g., 0·7 mole) in water (500 ml.) were heated under reflux for 8 hr. The mixture was then cooled and shaken with ether (2 × 300 ml.), and the ethereal extract was dried (Na_2SO_4). After removal of ether the residue was distilled, to give a colourless oil (97%), b. p. 140°/16 mm.

N-*Alkyl*-N-2′-*phenoxyethyl*-β-*hydroxyphenethylamines* (for details see Table 4).—(*a*) N-*Alkyl*-2-*phenoxyethylamines.* The solution obtained by keeping 2-phenoxyethyl bromide (0·5 mole) and a primary aliphatic amine (2·0 moles) in 90% aqueous ethanol (500 ml.) at room temperature for 14 days was diluted with water (1 l.) and acidified with hydrochloric acid. Unchanged 2-phenoxyethyl bromide was extracted with ether, the aqueous layer was made alkaline with sodium hydroxide, and the *product* was extracted with ether, dried (Na_2SO_4), and, after removal of ether, fractionally distilled under reduced pressure.

(*b*) N-*Alkyl*-N-*phenacyl*-2-*phenoxyethylamines.* These were prepared as described above and the crude products were reduced as described on p. 1386.

NN-*Dialkyl*-2-*hydroxy*-1-*phenylethylamines.*—(*a*) *Ethyl* α-NN-*dialkylamino*-α-*phenylacetates.* Ethyl α-chloro-α-phenylacetate (0·25 mole) and the amine (0·5 mole) were kept in dry benzene (250 ml.) at room temperature for 14 days. The theoretical weight of amine hydrochloride was then filtered off and the product was isolated by fractional distillation of the filtrate.

[9] *Org. Synth.*, 1939, **19**, 24.
[10] Wilds and Johnson, *J. Amer. Chem. Soc.*, 1945, **67**, 267.

TABLE 1.

NN-Disubstituted 2-hydroxy- and 2-bromo-n-propylamines, $CH_3 \cdot CHX \cdot CH_2Y$.

Y	X	M. p. or b. p./mm.	Yield (%)	Found (%) C	H	N	Hal	Formula	Required (%) C	H	N	Hal
$N(CH_2Ph)_2$	OH	132—142°/1	77	—	—	—	—	$C_{17}H_{21}NO$	—	—	—	—
$N(CH_2Ph)_2$,MeI *	OH	186—187°	—	54·8	5·6	3·3	32·1	$C_{18}H_{24}INO$	54·4	6·1	3·5	32·0
$N(CH_2Ph)_2$,HBr †	Br	142·5—143·5°	56	51·2	5·0	3·8	39·9	$C_{17}H_{21}Br_2N$	51·0	5·3	3·5	40·0
Piperidino	OH	88—92°/20	63	—	—	—	—	$C_8H_{17}NO$	—	—	—	—
Piperidino,MeI *	OH	142—143°	—	38·2	6·9	—	44·4	$C_9H_{20}INO$	37·9	7·1	—	44·5
Piperidino,HBr †	Br	195—196° ‡	65	33·8	5·5	4·8	55·9	$C_9H_{17}Br_2N$	33·5	6·0	4·9	55·7
Morpholino	OH	98—102°/20	66	—	—	—	—	$C_7H_{15}NO_2$	—	—	—	—
Morpholino,MeI *	OH	117—118·5°	—	33·8	5·9	—	44·3	$C_8H_{18}INO_2$	33·5	6·3	—	44·2
Morpholino,HBr	Br	152° ‡	67	29·6	5·2	—	55·4	$C_7H_{15}Br_2N$	29·1	5·2	—	55·3
$N(C_6H_{11})_2$ §	OH	122—124°	73	—	—	—	—	$C_{15}H_{29}NO$	—	—	—	—
$N(C_6H_{11})_2$,MeI	OH	236—238°	—	50·7	8·2	—	33·0	$C_{16}H_{32}INO$	50·4	8·5	—	33·3
$N(C_6H_{11})_2$,HBr	Br	324—326° ‡	56	47·7	7·7	—	41·7	$C_{15}H_{29}Br_2N$	47·0	7·6	—	41·7
$N(CH_2 \cdot CH{:}CH_2)_2$	OH	82—84°/15	90	69·9	10·6	—	—	$C_9H_{17}NO$	69·6	11·0	—	—
$N(CH_2 \cdot CH{:}CH_2)_2$,HBr †	Br	112—113°	77	36·3	5·6	—	53·6	$C_9H_{17}Br_2N$	36·1	5·7	—	53·4

* Recryst. from ethanol. † Recryst. from propan-2-ol. ‡ With decomp. § Cyclohexyl compound, recryst. from methanol.

TABLE 2.

N-Mono- or *NN*-di-substituted 4-substituted ω-aminoacetophenones, $4\text{-}X \cdot C_6H_4 \cdot CO \cdot CH_2Y$.

X	Y	M. p. or b. p./mm.	Yield (%)	Found Hal (%)	Formula	Required Hal (%)	Notes & ref.
H	NMe_2	130—132°/20	74	—	—	—	1, *a*
H	NEt_2	85°/0·2	61	—	—	—	1, *b*
H	NPr^i_2,HCl	219—220°	66	14·1	$C_{14}H_{22}ClNO$	13·9	2, 3
H	Piperidino	134—136°/1	75	—	—	—	—
H	Piperidino,MeI	175—176°/5	—	36·5	$C_{14}H_{20}INO$	36·8	1
H	$NPh \cdot CH_2Ph$	107—108°	40	—	$C_{21}H_{19}NO$	—	2, 6
Br	NMe_2,HCl	200—201°	87	12·5	$C_{10}H_{13}BrClNO$	12·7	3, 4, *c*
Br	NEt_2,HCl	170—171°	70	11·6	$C_{12}H_{17}BrClNO$	11·6	4, *c*
Br	Piperidino,HCl	232—233°	68	11·1	$C_{13}H_{17}BrClNO$	11·1	3, 4, *d*
Me	NMe_2HCl	176—178°	88	16·8	$C_{11}H_{16}ClNO$	16·6	3, 5
Me	NEt_2,HCl	222—224°	86	14·6	$C_{13}H_{20}ClNO$	14·7	3, 5
Me	Piperidino,HCl	194—195°	95	14·2	$C_{14}H_{20}ClNO$	14·0	3, 5
F	NMe_2, NEt_2, piperidino	Hydrochlorides not purified	85—96	—	—	—	—

(1) Darkens in air. (2) Recryst. from ethanol. (3) M. p. with decomp. (4) From ethanol–propan-2-ol. (5) From propan-2-ol. (6) Found: C, 83·7; H, 6·4; N, 4·2. Required: C, 83·4; H, 6·3; N, 4·6%.

(*a*) von Braun and Weissbach, *Ber.*, 1929, **62**, 2425. (*b*) Marvel and du Vigneaud, *J. Amer. Chem. Soc.*, 1924, **46**, 2098. (*c*) Mathieson and Newbury, *J.*, 1949, 1133. (*d*) Speer and Hill, *J. Org. Chem.*, 1937, **2**, 138.

TABLE 3.

N-Mono- or *NN*-di-substituted 4′-substituted β-hydroxyphenethylamines, $4\text{-}X \cdot C_6H_4 \cdot CH(OH) \cdot CH_2Y$.

X	Y	Method	M. p. or b. p./mm.	Yield (%)	Found (%) C	H	N	I	Formula	Required (%) C	H	N	I	Notes & ref.
H	NMe_2	A, D	136—140°/18	91	—	—	—	—	—	—	—	—	—	*a*
H	NMe_2,MeI	—	221—223° *	—	—	—	—	—	—	—	—	—	—	1, *b*
H	NMeEt	A	138—142°/16	83	73·5	9·9	—	—	$C_{11}H_{17}NO$	73·7	9·6	—	—	2
H	NMeEt,MeI	—	142—144°	—	45·6	6·7	—	39·2	$C_{12}H_{20}INO$	44·9	6·3	—	39·5	3
H	NEt_2	B, D	141—142°/15	88	—	—	—	—	—	—	—	—	—	*c*

TABLE 3. (*Continued.*)

X	Y	Method	M. p. or b. p./mm.	Yield (%)	Found (%) C	H	N	I	Formula	Required (%) C	H	N	I	Notes & ref.
H	NEt_2,MeI	—	149—151°	—	46·6	6·5	3·8	37·9	$C_{13}H_{22}INO$	46·6	6·6	4·2	37·9	3
H	NPr^n_2	B	164—168°/18	73	—	—	—	—	—	—	—	—	—	*c*
H	NPr^n_2,MeI	—	123·5—125°	—	49·6	7·4	4·0	34·9	$C_{15}H_{26}INO$	49·6	7·2	3·9	34·9	3
H	NBu^n_2	B	180—182°/14	66	—	—	—	—	—	—	—	—	—	*c*
H	$N(C_5H_{11}\text{-}n)_2$	B	208°/20	63	—	—	—	—	—	—	—	—	—	*c*
H	$N(C_6H_{13}\text{-}n)_2$	B	110—120°/0·01	68	78·8	11·7	—	—	$C_{20}H_{35}NO$	78·6	11·6	—	—	—
H	Pyrollidino	B	57—58°	78	75·6	8·9	—	—	$C_{12}H_{17}NO$	75·4	9·0	—	—	3
H	Piperidino	B, D	68—70°	85	—	—	—	—	—	—	—	—	—	4, *d*
H	Piperidino,MeI	—	136—137°	—	—	—	—	—	—	—	—	—	—	3, *d*
H	Morpholino	B	81—82°	74	—	—	—	—	—	—	—	—	—	4, *e*
H	$N(CH_2Ph)_2$	B	210—215°/3	74	—	—	—	—	—	—	—	—	—	*f*
H	$NMe{\cdot}CH_2Ph$	B	200—210°/18	76	80·0	7·4	—	—	$C_{16}H_{19}NO$	79·6	7·9	—	—	—
H	NMePh	B	160°/1	50	—	—	—	—	—	—	—	—	—	—
H	NMePh,MeI	—	154·5°	—	51·9	5·4	—	34·8	$C_{16}H_{20}INO$	52·0	5·5	—	34·4	3
H	$N(CH_2{\cdot}CH{:}CH_2)_2$	B	85—90°/0·1	92	—	—	—	—	$C_{14}H_{19}NO$	77·4	8·8	—	—	—
H	NHMe	C	148—150°/20	58	—	—	—	—	—	—	—	—	—	—
H	NHEt	C	148—152°/18	31	72·7	9·2	—	—	$C_{10}H_{15}NO$	72·7	9·2	—	—	—
H	$NHPr^n$	B	166—176°/20	75	73·7	9·0	—	—	$C_{11}H_{17}NO$	73·7	9·6	—	—	—
H	$NHBu^n$	B	170—180°/20	77	74·5	10·0	—	—	$C_{12}H_{19}NO$	74·6	9·9	—	—	—
H	$NH{\cdot}CH_2{\cdot}CH{:}CH_2$	B	152—158°/15	65	—	—	—	—	$C_{11}H_{15}NO$	—	—	—	—	5
H	$NH{\cdot}C_6H_{11}$	B	138—142°/1	67	77·0	9·4	—	—	$C_{14}H_{21}NO$	76·7	9·7	—	—	*f*
H	NHPh	B	160—162°/0·8	67	78·6	7·2	6·6	—	$C_{14}H_{15}NO$	78·8	7·1	6·6	—	—
H	$NH{\cdot}CH_2Ph$	B	101—103°	75	—	—	—	—	—	—	—	—	—	4, *g*
F	NMe_2	D	120°/16	86	65·3	7·6	—	—	$C_{10}H_{14}FNO$	65·6	7·7	—	—	—
F	NMe_2,MeI	—	193—195°	—	40·8	5·1	—	39·2	$C_{11}H_{17}FINO$	40·6	5·3	—	39·0	6
F	NEt_2	D	75—85°/0·2	79	68·4	8·6	—	—	$C_{12}H_{18}FNO$	68·2	8·6	—	—	—
F	NEt_2,MeI	—	125—127°	—	44·3	5·8	—	36·0	$C_{13}H_{21}FINO$	44·2	6·0	—	35·9	6
F	Piperidino	D	79—80°	75	69·9	8·5	6·0	—	$C_{12}H_{18}FNO$	69·9	8·1	6·3	—	4
Br	NMe_2	D	102—110°/0·15	72	—	—	—	—	—	—	—	—	—	—
Br	NMe_2,MeI	—	201·5—203·5°	—	34·4	4·4	3·5	32·9	$C_{11}H_{17}BrINO$	34·2	4·4	3·6	32·9	—
Br	NEt_2	D	124—126°/0·2	63	—	—	—	—	—	—	—	—	—	—
Br	NEt_2,MeI	—	137—139°	—	—	5·2	3·3	30·7	$C_{13}H_{21}BrINO$	37·7	5·1	3·4	30·7	6
Br	Piperidino	D	79—80°	55	55·1	6·3	4·9	—	$C_{13}H_{18}BrNO$	54·9	6·4	4·9	—	4, 7
Me	NMe_2	D	150—150°/20	82	73·6	9·8	7·5	—	$C_{11}H_{17}NO$	73·7	9·6	7·8	—	—
Me	NMe_2,MeI	—	238—240° *	—	45·1	6·0	4·2	39·6	$C_{12}H_{20}INO$	44·9	6·3	4·4	39·5	—
Me	NEt_2	D	154—158°/18	76	75·4	10·0	6·6	—	$C_{13}H_{21}NO$	75·3	10·2	6·8	—	—
Me	NEt_2,MeI	—	160°	—	48·3	6·8	3·9	36·5	$C_{14}H_{24}INO$	48·1	6·9	4·0	36·3	3
Me	Piperidino	D	71—74°	77	76·3	10·1	6·1	—	$C_{14}H_{21}NO$	76·7	9·7	6·4	—	4
Et	NMe_2	D	95°/0·5	76	74·7	11·0	—	—	$C_{12}H_{19}NO$	74·6	10·9	—	—	—
Et	NMe_2,MeI	D	205—207°	—	—	—	—	37·6	$C_{13}H_{22}INO$	—	—	—	37·9	6
Pr^i	NMe_2	D	105—115°/0·3	69	74·6	11·0	—	—	$C_{13}H_{21}NO$	75·3	10·2	—	—	—
OMe	NMe_2	—	160—168°/16	86	67·9	8·6	—	—	$C_{11}H_{17}NO_2$	67·7	8·8	—	—	—
OMe	NMe_2,MeI	—	126—127°	—	43·0	5·6	—	—	$C_{12}H_{20}INO_2$	42·7	6·0	—	—	6
OMe	NEt_2	—	110—115°/1	78	70·0	9·3	—	—	$C_{13}H_{21}NO_2$	69·9	9·5	—	—	—
OMe	Piperidino	—	140°/2	45	71·5	8·0	—	—	$C_{14}H_{21}NO_2$	71·5	9·0	—	—	—

* With decomp.

(1) Recryst. from methanol. (2) See p. 1387 for prep. (3) Recryst. from propan-2-ol. (4) Recryst. from 70% aq. ethanol. (5) Of doubtful purity. (6) Recryst. from ethanol. (7) Hydrochloride (from ethanol), m. p. 243—245° (Found: Cl, 11·1; $C_{13}H_{19}BrClNO$ requires Cl, 11·1%).

(*a*) Tiffeneau, *Compt. rend.*, 1908, **146**, 697. (*b*) Campbell and Read, *J.*, 1930, 2682. (*c*) Emerson, *J. Amer. Chem. Soc.*, 1946, **67**, 517. (*d*) Rabe and Braasch, *Annalen*, 1909, **365**, 377. (*e*) Rubin and Day, *J. Org. Chem.*, 1940, **5**, 54. (*f*) Ref. 5. (*g*) Brown and Lutz, *J. Org. Chem.*, 1952, **17**, 1187.

TABLE 4.

N-Alkyl-*N*-2′-phenoxyethyl-β-bromo- or -β-hydroxyphenethylamines, $Ph{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}NRR'$.

R	R′	B. p. or m. p./mm.	Yield (%)	Hydrobromide,* m. p.	Found (%) C	Found (%) H	Found (%) Br	Formula	Required (%) C	Required (%) H	Required (%) Br
H	Me	110—115°/18	89	190—192°	46·8	5·7	34·5	$C_9H_{14}BrNO$	46·6	6·1	34·4
H	Et	126—128°/18	86	175—177	48·9	6·3	32·7	$C_{10}H_{16}BrNO$	48·8	6·6	32·5
H	Pr^n	132—134°/18	78	161—162	51·0	6·5	30·9	$C_{11}H_{18}BrNO$	50·7	7·0	30·7
H	Pr^i	124—128°/18	79	169—171	50·9	6·8	30·6	$C_{11}H_{18}BrNO$	50·7	7·0	30·7
$CH_2{\cdot}CHPh{\cdot}OH$	Me †	154—156°/0·01	76	—	75·8	7·8	—	$C_{17}H_{21}NO_2$	75·3	7·8	—
$CH_2{\cdot}CHPhBr$	Me ‡	—	67	146—147	49·1	5·3	38·4	$C_{17}H_{21}Br_2NO$	49·2	5·1	38·5
$CH_2{\cdot}CHPh{\cdot}OH$	Et †	145—150°/0·003	69	—	76·2	8·2	—	$C_{18}H_{23}NO_2$	75·8	8·1	—
$CH_2{\cdot}CHPhBr$	Et ‡	—	57	162—164 §	50·1	5·2	37·2	$C_{18}H_{23}Br_2NO$	50·4	5·4	37·2
$CH_2{\cdot}CHPh{\cdot}OH$	Pr^n	165—170°/0·001	75	—	76·5	8·1	—	$C_{19}H_{25}NO_2$	76·2	8·4	—
$CH_2{\cdot}CHPh{\cdot}OH$	Pr^i	160°/0·001	73	—	76·9	8·8	—	$C_{19}H_{25}NO_2$	76·2	8·4	—
$CH_2{\cdot}CHPhBr$	Pr^i ‡	—	75	165—167	51·4	5·9	36·0	$C_{19}H_{25}Br_2NO$	51·5	5·7	36·1

* Recryst. from propan-2-ol. † Hydrochloride (from propan-2-ol), m. p. 120—121° (Me) and 132—133° (Et). ‡ Hydrobromide. § Sinters at 114°.

TABLE 5.

NN-Dialkyl-2-bromo-1-phenylethylamine (*NN*-dialkyl-α-bromomethylbenzylamine) hydrobromides and related compounds, $Ph{\cdot}CHRR'$.

R	R′	B. p. or m. p./mm.	Yield (%)	Found (%) C	Found (%) H	Found (%) N	Found (%) Hal	Formula	Required (%) C	Required (%) H	Required (%) N	Required (%) Hal
CO_2Et	NMe_2	100—105°/0·7 ‡	83	—	—	—	—	—	—	—	—	—
CO_2Et	NMe_3I *	167—168° †	—	44·5	5·7	3·8	36·3	$C_{13}H_{20}INO_2$	44·7	5·8	4·0	36·3
CO_2Et	NEt_2	86—88°/0·2 ‡	85	71·5	8·9	5·7	—	$C_{14}H_{21}NO_2$	71·5	9·0	6·0	—
CO_2Et	Piperidino	132—136°/1	64	72·9	8·5	5·5	—	$C_{15}H_{21}NO_2$	72·8	8·5	5·7	—
$CH_2{\cdot}OH$	NMe_2	138°/16	65	—	—	—	—	—	—	—	—	—
$CH_2{\cdot}OH$	NEt_2	84—86°/0·6 ‡	84	74·5	10·0	7·1	—	$C_{12}H_{19}NO$	74·6	9·9	7·3	—
$CH_2{\cdot}OH$	Piperidino	108°/0·4	68	76·0	9·1	6·7	—	$C_{13}H_{19}NO$	76·1	9·3	6·8	—
$CH_2{\cdot}OH$	$N(CH_2{\cdot}CH{:}CH_2)_2$	110°/0·8	88	77·9	8·3	—	—	$C_{14}H_{19}NO$	77·4	8·8	—	—
CH_2Br,HBr	NMe_2 *	172—174° †	58	38·7	5·0	4·3	51·6	$C_{10}H_{16}Br_2N$	38·8	4·9	4·5	51·7
CH_2Br,HBr	Piperidino *	134—136°	63	44·9	5·1	3·5	46·9	$C_{13}H_{20}Br_2N$	44·7	5·5	4·0	46·8

* Recryst. from propan-2-ol. † With decomp. ‡ See ref. *a* of Table 3.

TABLE 6.

NN-Dialkyl-2-bromo-3-phenylpropylamine hydrobromides and related compounds, $Ph{\cdot}CH_2{\cdot}CHX{\cdot}CH_2Y$.

Y	X	Method	M. p. or b. p./mm.	Yield (%)	Found (%) C	Found (%) H	Found (%) N	Found (%) Hal	Formula	Required (%) C	Required (%) H	Required (%) N	Required (%) Hal
NMe_2 *	OH	A	140—142°/18	86	—	—	—	—		—	—	—	—
NEt_2	OH	B	155—162°/18	68	75·5	10·0	6·6	—	$C_{13}H_{21}NO$	75·3	10·2	6·8	—
NEt_2,MeI †	OH	—	126—128°	—	48·4	6·6	3·8	36·2	$C_{14}H_{24}INO$	48·1	6·9	4·0	36·3
Piperidino	OH	B	132°/0·7, 44—45°	76	76·4	9·4	6·0	—	$C_{14}H_{21}NO$	76·7	9·6	6·4	—
NMe_2,HBr †	Br	—	145—146°	69	41·2	5·1	4·4	49·6	$C_{11}H_{17}Br_2N$	40·9	5·3	4·3	49·5
NEt_2,HBr †	Br	—	133·5—134·5°	62	44·7	5·8	3·9	45·5	$C_{13}H_{21}Br_2N$	44·4	6·0	4·0	45·5
Piperidino, HBr †	Br	—	147—149°	66	46·1	6·2	3·4	43·6	$C_{14}H_{21}Br_2N$	46·3	5·8	3·9	44·0

* Levy and Sfiras, *Compt. rend.*, 1930, **191**, 261. † Recryst. from propan-2-ol.

TABLE 7.

N-Mono- and *NN*-di-substituted 2-chloro(or bromo)-2-(4-substituted phenyl)ethylamine hydrohalides, p-X·C_6H_4·CHY·CH_2Z,HY.

No.	Z	Y	X	M. p.*	Yield (%)	Found (%) C	H	N	Hal	Formula	Required (%) C	H	N	Hal	E.D.$_{50}$ § (10^{-6} mole/kg.) A	NA
1	NMe_2	Cl	H	205—207° † [1]	54	—	—	—	—	—	—	—	—	—	0·046	0·1
2	Piperidino	Cl	H	172—172·5 † [2]	50	60·0	7·3	5·2	27·8	$C_{13}H_{19}Cl_2N$	60·0	7·4	5·4	27·2	—	—
3	Morpholino	Cl	H	189 ‡ [2]	67	55·2	6·5	4·8	27·1	$C_{12}H_{17}Cl_2NO$	55·0	6·5	5·3	27·1	—	—
4	$N(CH_2Ph)_2$	Cl	H	151 ‡ [3]	52	70·9	6·2	3·5	19·1	$C_{22}H_{23}Cl_2N$	71·0	6·2	3·8	19·1	1·5	1
5	NHC_6H_{11}	Cl	H	149—151 [3]	75	61·5	7·3	5·0	25·9	$C_{14}H_{21}Cl_2N$	61·3	7·7	5·1	25·9	—	—
6	NMe_2	Br	H	173—174 ‡ [4]	75	38·6	5·1	4·3	51·8	$C_{10}H_{15}Br_2N$	38·8	4·9	4·5	51·7	0·035	0·056
7	NMeEt	Br	H	127—128 [3]	67	41·1	5·2	4·0	48·9	$C_{11}H_{17}Br_2N$	40·9	5·3	4·3	49·5	2·8	3
8	NEt_2	Br	H	110·5—111·5 [3]	67	42·9	5·6	4·2	47·5	$C_{12}H_{19}Br_2N$	42·8	5·7	4·2	47·4	5	1·8
9	NPr^n_2	Br	H	121·5—122·5 [3]	71	46·1	6·3	3·8	43·8	$C_{14}H_{23}Br_2N$	46·1	6·4	3·8	43·8	1	1·3
10	NPr^i_2	Br	H	117—119 [3]	59	46·2	6·2	3·9	43·7	$C_{14}H_{23}Br_2N$	46·1	6·4	3·8	43·8	30	22
11	NBu^n_2	Br	H	141—141·5 [3]	63	49·0	6·8	3·5	40·8	$C_{16}H_{27}Br_2N$	48·9	6·9	3·6	40·7	4·4	4·5
12	$N(CH_2{\cdot}CH{:}CH_2)_2$	Br	H	122—123 [3]	83	46·7	5·3	3·6	44·2	$C_{14}H_{19}Br_2N$	46·6	5·3	3·9	44·3	0·03	0·03
13	Piperidino	Br	H	156 ‡ [2]	35	44·5	5·8	4·3	46·7	$C_{13}H_{19}Br_2N$	44·7	5·5	4·0	45·8	15	14
14	Morpholino	Br	H	159—160 [2]	47	41·2	4·9	4·3	45·5	$C_{12}H_{17}Br_2NO$	41·1	4·9	4·0	45·5	4	4·5
15	1-Pyrrolidinyl	Br	H	162—163 [3]	79	43·5	5·0	—	49·0	$C_{12}H_{17}Br_2N$	43·0	5·1	—	47·7	0·05	0·08
16	$N(CH_2Ph)_2$	Br	H	139—140 ‡ [3]	33	57·4	4·8	2·8	34·7	$C_{22}H_{23}Br_2N$	57·3	5·0	3·0	34·7	2·4	1·7
17	NMe·CH_2Ph	Br	H	146—147 ‡ [3]	58	50·0	5·1	3·3	42·5	$C_{16}H_{19}Br_2N$	49·9	5·0	3·6	41·5	0·22	0·39
18	NHMe	Br	H	142—143 [3]	53	36·7	4·2	4·6	54·4	$C_9H_{13}Br_2N$	36·6	4·4	4·8	54·2	0·6	0·5
19	NHEt	Br	H	149—149·5 [3]	59	38·9	4·7	4·2	51·7	$C_{10}H_{15}Br_2N$	38·9	4·9	4·5	51·7	100	80
20	$NHPr^n$	Br	H	149 [3]	68	41·1	5·1	4·2	49·4	$C_{11}H_{17}Br_2N$	40·9	5·3	4·3	49·5	Very weak	
21	$NHBu^n$	Br	H	141—141·5 [2]	63	42·9	5·8	4·2	47·4	$C_{12}H_{19}Br_2N$	42·8	5·7	4·2	47·4	Very weak	
22	NH·C_6H_{11}	Br	H	152—153 ‡ [5]	67	46·5	5·7	3·8	43·9	$C_{14}H_{21}Br_2N$	46·3	5·8	3·9	44·0	—	—
23	NH·CH_2Ph	Br	H	158 ‡ [2]	56	48·7	4·6	3·6	42·9	$C_{15}H_{17}Br_2N$	48·5	4·6	3·7	43·1	3	2·8
24	NH·CH_2·$CH{:}CH_2$	Br	H	129—130 [5]	79	41·2	5·0	4·4	49·6	$C_{11}H_{15}Br_2N$	41·2	4·7	4·4	49·8	—	—
25	NMe_2	Br	F	175—176 ‡ [4]	66	36·1	4·0	4·4	49·1	$C_{10}H_{14}Br_2FN$	36·7	4·3	4·3	48·9	—	—
26	NEt_2	Br	F	104—106 [3]	69	40·8	5·0	3·6	45·0	$C_{12}H_{18}Br_2FN$	40·6	5·1	3·9	45·0	—	—
27	Piperidino	Br	F	135—137 [5]	76	42·6	4·6	—	43·3	$C_{13}H_{18}Br_2FN$	42·5	4·9	—	43·5	—	—
28	NMe_2	Br	Br	168—169 [5]	78	31·1	3·7	3·5	61·9	$C_{10}H_{14}Br_3N$	31·0	3·6	3·6	61·8	0·0006	0·0002
29	NEt_2	Br	Br	135·5—136·5 [6]	74	34·7	4·5	3·5	57·6	$C_{12}H_{18}Br_3N$	34·6	4·4	3·4	57·6	—	—
30	Piperidino	Br	Br	167—167·5 [2]	78	36·5	4·3	3·5	56·0	$C_{13}H_{18}Br_3N$	36·5	4·2	3·3	56·0	—	—
31	NMe_2	Br	Me	147—149 ‡ [1]	65	41·0	5·0	4·4	49·1	$C_{11}H_{17}Br_2N$	40·9	5·3	4·3	49·5	0·0003	0·0007
32	Piperidino	Br	Me	150—152 [3]	73	46·5	5·5	3·5	44·2	$C_{14}H_{21}Br_2N$	46·3	5·8	3·9	44·0	—	—
33	NMe_2	Br	Et	167—168 ‡ [3]	66	43·0	5·4	—	47·6	$C_{12}H_{19}Br_2N$	42·8	5·7	—	47·4	—	—
34	NMe_2	Br	Pr^i	135—137 ‡ [3]	64	44·8	6·0	—	45·4	$C_{13}H_{21}Br_2N$	44·5	6·0	—	45·5	—	—
35	NMe_2	Br	Bu^t	156—158 ‡ [3]	43	46·3	6·1	—	44·0	$C_{14}H_{23}Br_2N$	46·1	6·4	—	43·8	—	—
36	NEt_2	Br	OMe	211—212 ‡ [3]	55	42·8	5·4	—	43·3	$C_{13}H_{21}Br_2NO$	42·5	5·8	—	43·5	—	—
37	Piperidino	Br	OMe	150—151 ‡ [3]	48	44·8	5·5	—	42·0	$C_{14}H_{21}Br_2NO$	44·4	5·6	—	42·2	—	—

* Superscript numerals refer to solvents for recrystn.: (1) methanol–ethanol; (2) ethanol; (3) propan-2-ol; (4) methanol; (5) ethanol–propan-2-ol; (6) propan-2-ol–ether. † See ref. 4. ‡ With decomp. § E.D.$_{50}$ on rat blood pressure (see ref. 7) against (A) adrenaline and (NA) noradrenaline; values for "Dibenamine" 7·7 and 10, respectively, and for phenoxybenzamine 0·28 and 0·55, respectively.

(*b*) *Reduction with lithium aluminium hydride.* To a suspension of lithium aluminium hydride (5·6 g., 0·15 mole) in dry ether (250 ml.), the ethyl α-*NN*-dialkylamino-α-phenylacetate (0·15 mole) in dry ether (100 ml.) was added dropwise during 4 hr., and the mixture was then refluxed. Water (10 ml.) was added to the cooled mixture, the product was filtered through " Supercel," and the ethereal layer was separated and dried (Na_2SO_4). The ether was then removed and the residual oil was distilled. See Table 5 for details of *products*.

NN-*Dialkyl-2-hydroxy-3-phenylpropylamines.*—*Method A.* A solution of 1,2-epoxy-3-phenylpropane (0·2 mole) and the amine (0·5 mole) in benzene (150 ml.) was kept at room temperature for 14 days. Fractional distillation of the product gave the required compound.

Method B. 1,2-Epoxy-3-phenylpropane (0·2 mole) and the amine (0·3 mole) were heated under reflux for 12 hr., and the product was fractionally distilled. For details of *products* see Table 6.

Preparation of Halogeno-compounds.—NN-*Disubstituted 2-bromo-n-propylamine hydrobromides.* To phosphorus tribromide (30·0 g., 0·11 mole), dissolved in dry chloroform (100 ml.), at 0° was added dropwise with stirring the *NN*-disubstituted 2-hydroxy-n-propylamine (0·1 mole) in dry chloroform (100 ml.) during 50 min. The mixture was then heated under reflux until no more hydrogen bromide was evolved (12—16 hr.). The chloroform was removed under reduced pressure, dry ethanol was added to the residue, and the solution so formed was filtered through " Supercel." Addition of dry ether precipitated the required hydrobromide which was then recrystallised. Details are given in Table 1.

N-*Mono- and* NN-*di-substituted 2-chloro(or bromo)-2-(4-substituted phenyl)ethylamine hydrohalides.* These were prepared as described above except that for chloro-compounds phosphorus pentachloride was used in place of the tribromide. For details of the *products* see Table 7.

NN-*Disubstituted* β-*iodophenethylamine hydriodides.* These were prepared from phosphorus tri-iodide (50 g., 0·11 mole) and the amino-alcohol (0·1 mole) in a manner similar to that outlined for the preparation of *NN*-disubstituted β-bromophenethylamine hydrobromides. Thus were obtained NN-*dimethyl-*, (from methanol; 50%)-, m. p. 138—140° (decomp.) (Found: C, 30·2; H, 3·4; N, 3·3; I, 63·4. $C_{10}H_{15}I_2N$ requires C, 29·8; H, 3·8; N, 3·5; I, 63·0%), and NN-*dibenzyl-*β-*iodophenylethylamine hydriodide* (from propan-2-ol; 40%), m. p. 147·5—149° (Found: C, 47·8; H, 4·0; N, 2·4; I, 45·8. $C_{22}H_{23}I_2N$ requires C, 47·6; H, 4·2; N, 2·5; I, 45·7%).

Kinetics

Procedure.—This was described in Part II. Because of the rapidity with which the halogenoethylamines liberated halide ion, it was not possible to check the efficiency of the ether-extraction for removal of unchanged halogenoethylamine but, in view of the ready solubility in ether of the corresponding hydroxy-amines, it seems very likely that the solubility of the halogenoamines in ether would be sufficient to ensure complete extraction. The reactions proved much simpler than those previously studied since the halogeno-amine is converted virtually instantaneously on liberation from its salt into the corresponding ethyleniminium salt. It has thus been possible to measure first-order rate coefficients for the solvolysis of the ethyleniminium ion with fair accuracy.

Identification of Products.—The 2-halogenoethylamine hydrohalide was dissolved in 1 : 1 acetone–water, and the combined hydrogen halide was neutralised exactly with 0·5N-sodium hydroxide. The solution was set aside at room temperature until the concentration of ethyleniminium ion had fallen to zero. Sodium hydroxide was then added and the slightly turbid solution was shaken several times with 50 ml. portions of ether. The ethereal solution was dried (Na_2SO_4) and concentrated to 20 ml., and an excess of methyl iodide was added; after 12 hr. the amine methiodide was filtered off, washed with ether, and dried. M. p. and mixed m. p. determination proved that the compounds isolated were the methiodides of *NN*-dialkyl-β-hydroxy-2-arylethylamines.

Results.—The rate-coefficients and Arrhenius parameters obtained for the solvolysis of the ethyleniminium ions are summarised in Table 8. Except where otherwise stated, the ethyleniminium ions were obtained from β-bromophenethylamines.

The validity of the assumption that the solvolyses of the ethyleniminium ions are unimolecular is discussed below (p. 1398). A good proportion of the reaction was always followed, usually 50—90%, and all the runs were done in duplicate, the values of k_1 generally agreeing

TABLE 8.

Measured rate coefficients and Arrhenius parameters for the solvolysis of ethyleniminium ions, in 1 : 1 acetone–water (or distilled water).

$C_6H_5{\cdot}HC(X){-}CH_2$

X	10^3k_1 (min.$^{-1}$)	10^3k_1 (min.$^{-1}$)	10^3k_1 (min.$^{-1}$)	E (kcal./mole)	log A
	23·0°	31·0°	41·0°		
NMe_2^+	7·9	14·5	75·0	13·7	8·1
		13·8 *			
		7·6 †			
$NMeEt^+$	4·7	10·4	31·3	17·8	10·9
NEt_2^+	4·2	9·0	36·7	16·9	10·2
		3·2 †			
$NPr^n_2{}^+$	18·6	35·1	3·0 ‡	14·2	8·8
$NPr^i_2{}^+$	24·1	64·8	6·2 ‡	22·1	14·3
$NBu^n_2{}^+$	12·5	37·1	0·17‡	24·3	16·1
Piperidinium	2·4	5·2	15·5	17·7	10·4
		5·1 *			
		2·6 †			
Pyrrolidinium	6·7	16·1	59·6	19·5	12·3
$N(CH_2{\cdot}CH{:}CH_2)_2^+$	—	Very fast	—	—	—
$NMe{\cdot}CH_2Ph^+$	—	Very fast	—	—	—

* Ethyleniminium ion derived from isomeric 2-bromo-1-phenylethylamine. † Solvolysis in distilled water. ‡ At 0°.

to better than 2%. Table 8 does not include all the compounds studied; many of the compounds were not amenable to accurate kinetic studies but the relevant results are discussed qualitatively below.

Values of E and log A were evaluated from the rate coefficients in the usual way and plots of log k against $1/T$ were always good straight lines. Values of k_1 are accurate to $\pm 5\%$, of E to ± 800 cal./mole, and of log A to $\pm 0{\cdot}8$ unit.

Some runs were carried out in alkaline solution. The reaction did not pursue either first- or second-order kinetics in these cases. The significance of these results is discussed briefly below (p. 1399).

DISCUSSION

Pharmacological Results.—Consideration of the E.D.$_{50}$ values given in Table 7 and of the more detailed pharmacological results reported by Graham and James [7] shows that the most active of these compounds (*e.g.*, nos. 28 and 31) are some 10,000—20,000 times more potent than " Dibenamine " as antagonists of adrenaline or noradrenaline. These are among the most active anti-adrenaline agents known.

The antagonism is rapid in onset, of relatively short duration except for the *NN*-dibenzyl derivatives, and is of the " non-competitive " kind. Maximal activity is associated with a *para*-substituted phenyl group as the aryl portion and a dimethylamino-group. Indeed the closer the aryl structure of the antagonist to that of adrenaline the greater the potency. Significant activity (*e.g.*, compounds 18 and 23) is observed with certain compounds containing secondary amino-groups, a phenomenon not previously observed among adrenaline antagonists of the halogenoethylamine series.

All the *NN*-dialkyl-2-aryl-2-bromoethylamines whose pharmacological properties have been studied are extremely rapidly converted into the corresponding ethyleniminium bromides in initially neutral aqueous acetone at 30° (see p. 1397) and it seems very likely that a similarly rapid transformation will occur *in vivo*. In view of this and the very rapid transport of ionic species through the animal circulatory system, complicating side reactions such as piperazinium salt formation will be unimportant and an approximately quantitative release of ethyleniminium ion at the receptor is likely. Moreover, *NN*-dimethyl-β-hydroxyphenethylamine and the corresponding *NNN*-trimethylammonium compound

are inactive (Graham and James [7]), so that in assessing structure–action relationships it is the structure of the ethyleniminium that is to be considered. The action of these compounds is not reduced by administration of large amounts of adrenaline or sodium thiosulphate after the antagonism is established. If the action of the 2-halogenoethylamines was readily reversible then both adrenaline and sodium thiosulphate should abolish their activity, the former by displacement of the ethyleniminium ion and the latter by reacting irreversibly with the ethyleniminium ion.

There is a 150-fold drop in activity on passing from the *NN*-dimethyl to the *NN*-diethyl compound which cannot be explained in terms of differing reactivities of the respective ethyleniminium ions (p. 1393); this difference in activities must be related to undetermined biological factors. Increasing length and branching of the *N*-alkyl groups of the *C*-phenylethyleniminium ion decreases the anti-adrenaline activity; there is an

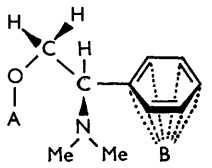


FIG. 1. Alkylation of adrenaline receptors by a *NN*-dimethyl-β-halogenophenylethylamine.

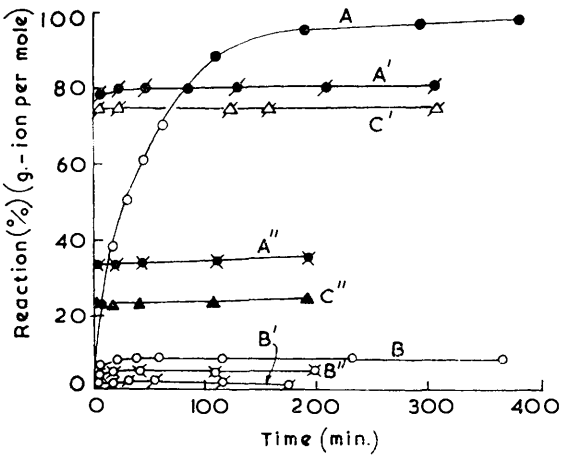


FIG. 2. Decomposition of *NN*-dibenzyl-β-halogenophenethylamines. A and B refer to the chloro-, A′, B′, and C′ to the bromo-, and A″, B″, and C″ to the iodo- compound. A, B, C refer to halide, ethyleniminium, and hydrogen ion, respectively.

850-fold drop in activity on passing from NMe_2 to NPr^i_2. This is probably to be associated with the attachment of the ethyleniminium ion to the adrenaline receptor. The shape of the receptor must be such as to enable the *NN*-dimethyl-2-phenylethyleniminium ion to become closely attached; lengthening and branching of the alkyl chain reduces the efficiency of this attachment, and hence of the anti-adrenaline activity.

Belleau [11] has put forward a theory of action of 2-halogenoethylamines of the "Dibenamine" type, which requires that there shall be approximately three aliphatic carbon–carbon bond lengths between a ring carbon of the ethyleniminium ion and of the aromatic nucleus. Obviously an *NN*-dialkyl-2-phenylethyleniminium ion will not fit the adrenaline receptor in the manner envisaged by Belleau, who admits this, but claims that alkylation of the receptor (Fig. 1) will favour a more complete interaction of the benzene ring with the receptor and that this in turn will favour an equilibrium in the direction of attachment rather than of desorption.*

It will be shown however (p. 1398) that the rings of ethyleniminium ions of this type open in neutral aqueous solution in the opposite direction to that proposed by Belleau and,

* It is doubtful whether the oxygen atom attached to A in Fig. 1 should logically be included. The figure s taken from Belleau's paper [11] as printed. Absence of the oxygen atom would strengthen the above arguments. This point will be pursued in a later Part of the present series.

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

if it is assumed that the mechanism of ring opening is the same *in vivo* as *in vitro*, then Belleau's theory is inapplicable to this class of compound. However, when the ethyleniminium ion is close to the receptor it may be effectively exposed to a high concentration of nucleophilic species so that an S_N2 ring-opening occurs, in which case Belleau's views may be acceptable. It is possible that the *NN*-dimethyl-2-phenylethyleniminium ion reacts by a bimolecular mechanism in alkaline media (p. 1399).

The *N*-mono- and *NN*-di-benzyl-β-halogenophenethylamines might, on the above grounds, be expected to be only feebly active, but in fact they are quite active. In fact, the ethyleniminium ions derived from them fit the adrenaline receptor in the manner postulated for compounds of the "Dibenamine" class (Belleau, ref. 11). Indeed these compounds are probably best thought of as belonging to the "Dibenamine" group rather than to the main group under discussion. The kinetic results for these compounds (Fig. 2) show that the release of halide ion is incomplete in aqueous solutions and that the extent of release of halide ion is in the order Cl > Br > I. They give a low and fairly persistent level of ethyleniminium ion in the order Cl > I > Br, which is not the order of the adrenaline-blocking activities, which indicates that other biological factors here play a role in the latter action.

Belleau's views as to the mode of attachment of ethyleniminium ions of the "Dibenamine" type at the adrenaline receptor imply the existence of two major sites of binding in the ethyleniminium ion—the positively charged nitrogen atom and the aromatic ring. Both sites appear to be necessary in the adsorption process, but greater importance is attached to the adsorption of the aromatic ring at the receptor site. With *NN*-dialkyl-2-phenylethyleniminium ions (and related compounds) we believe that the same two major binding sites are involved, but that their relative importance is reversed: the binding of the quaternary ammonium-group is now of greater significance than that of the aromatic ring, although the latter is still necessary for activity. The specificity of the binding process involving the quaternary nitrogen atom is noteworthy. There is an approximately 20-fold drop in activity on passing from the *NN*-dimethyl compound to the *N*-monomethyl compound and a 160-fold drop in activity on passing from this to the *N*-monoethyl compound; the *N*-mono-n-propyl and the *N*-mono-n-butyl compounds are almost inactive. The essential character of the *NN*-dimethylamino-group for maximum anti-adrenaline activity in this class of compounds is clear. This evidence suggests that it is the size of the cationic head which is important in determining activity. This view is similar to that put forward by Ing and his co-workers concerning the acetylcholine-like compounds.

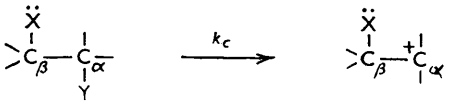
There is an interesting difference in activity between the piperidino- and the morpholino-compounds which may be reasonably ascribed to the possibility of hydrogen bonding between the oxygen atom of the morpholine ring and the receptor. The high activity of *NN*-diallyl-β-bromophenethylamine is surprising in view of the great instability of the derived ethyleniminium ion, which is completely hydrolysed within 10 minutes at 31·0° in 1 : 1 aqueous acetone (cf. p. 1393), and this is not in accordance with the above views on the size of the quaternary ammonium group.

The duration of blockade produced by these compounds is far less that that for "Dibenamine." If it is assumed that an ester is formed by alkylation of the adrenaline receptor, then the hydrolysis of the ester which is necessary to regenerate the receptor may well be anchimerically assisted by the *NN*-dialkylamino-group (cf. Belleau [11]). The greater nucleophilic driving force of the *NN*-dimethylamino-group than of the *NN*-dibenzylamino-group should be reflected in faster hydrolysis of the ester formed from the *NN*-dimethyl-β-bromophenethylamine, and consequently shorter duration of blockade.

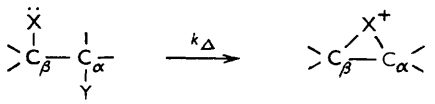
Reactivity.—In our previous studies [1-3] it was not possible to measure rate coefficients for any of the reactions involved because of the complexity of the reacting system. Many of the compounds described in the present paper show much simpler behaviour, so that rate coefficients for the solvolysis of first-formed ethyleniminium ions have been measured.

Freundlich [12] showed that in neutral or weakly alkaline aqueous solution, suitable 2-halogenoethylamines underwent a first-order displacement of halide ion to yield a cyclic ion, although side reactions (formation of piperazinium and other quaternary salts) led to complications in the determination of rate coefficients. The observed first order release of halide ion is consistent with an S_N1 or an internal S_N2 process (cf. Chapman and James [2]). Evidence is presented below that the S_N2 process is, in fact, operating.

Winstein, Grunwald, and their co-workers [13] have discussed the effect of structure on the rates of reactions involving neighbouring groups. They point out that in the nucleophilic displacement reactions of compounds containing a neighbouring group, $-\ddot{X}$, the rate-determining step may be either carbonium-ion formation:



or an internal nucleophilic displacement by the neighbouring group:



It has been found that in the series of compounds $Ph{\cdot}CHBr{\cdot}CH_2{\cdot}NRR'$ (R, R' = alkyl) the rate of displacement of bromide ion is far too rapid to measure. These very high rates of displacement are good evidence that the reaction proceeds by an internal bimolecular nucleophilic displacement; bromide ion is liberated from these compounds many thousands of times faster than from analogous compounds which do not contain a β-*NN*-dialkylamino-group. Winstein *et al.*[13] defined a quantity, L, termed the driving force due to participation of the neighbouring group in the rate determining step, by the relation $L = \boldsymbol{R}T \ln k_\Delta/k_c$. It is possible to obtain approximate values of L and k_Δ/k_c for various substituted 2-halogenoethylamines and these values are given in Table 9.

TABLE 9.

Compound	L	$\log_{10} k_\Delta/k_c$
$Br{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2$	9·6	7·0
$CH_3{\cdot}CHBr{\cdot}CH_2{\cdot}NMe_2$	7·3	3·4
$Ph{\cdot}CHBr{\cdot}CH_2{\cdot}NMe_2$	5·0	3·7
$Ph{\cdot}CMeBr{\cdot}CH_2{\cdot}NMe_2$	2·7	2·0
$Ph_2CBr{\cdot}CH_2{\cdot}NMe_2$	0·47	0·35

These values, though approximate, show that save for the last compound the internal S_N2 mechanism is energetically favoured. It will be observed that 2-alkyl and 2-aryl groups lower the driving force due to a neighbouring group, although the overall rate of reaction may increase.

Further confirmation that the 2-halogenoethylamines of the type described react through an intermediate ethyleniminium ion comes from a study of the following two pairs of isomeric 2-bromoethylamines which give rise each to a single amino-alcohol on solvolysis:

$Ph{\cdot}CHBr{\cdot}CH_2{\cdot}NMe_2$ and $Ph{\cdot}CH(NMe_2){\cdot}CH_2Br$ → $Ph{\cdot}CH(OH){\cdot}CH_2{\cdot}NMe_2$

$Ph{\cdot}CHBr{\cdot}CH_2{\cdot}NC_5H_{10}$ and $Ph{\cdot}CH(NC_5H_{10}){\cdot}CH_2Br$ → $Ph{\cdot}CH(OH){\cdot}CH_2{\cdot}NC_5H_{10}$

[$C_5H_{10}N{\cdot}$ = piperidino.]

[12] Freundlich and his co-workers, *Z. phys. Chem.*, 1911, **76**, 79; 1914, **87**, 69; 1933, **166**, 161.
[13] Winstein, Grunwald, and their co-workers, *J. Amer. Chem. Soc.*, 1948, **70**, 828; 1953, **75**, 147.

Several factors will influence the value of k_1, the initial rate coefficient for the release of halide ion. It has been established that the extent of release of halide ion from 2-halogenoethylamines is usually in the order I $\simeq$ Br > Cl, whilst the initial rate of release of halide ion is usually in the order I > Br > Cl. The order for bromide and iodide in the former case may be related to the greater nucleophilic power of the iodide ion which will cause the reverse reaction between ethyleniminium ion and halide ion to assume greater significance. The *NN*-dibenzyl-β-halogenophenethylamines present an example of this; the rates of release of halide ion fall in the order I $\simeq$ Br > Cl (Fig. 2), and the final extent of release of halide ion is in the order Cl > Br > I. α-Alkyl and α-aryl groups increase k_1:

Compound	$Cl{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$	$CH_3{\cdot}CHCl{\cdot}CH_2{\cdot}NH_2$	$Ph{\cdot}CHCl{\cdot}CH_2{\cdot}NH_2$
Rel. rate	1	10	400

In compounds containing α-aryl groups the powerful mechanism of conjugative electron displacement is available to assist the separation of the displaced group and α-aryl groups will therefore facilitate both uni- and bi-molecular nucleophilic displacement, particularly

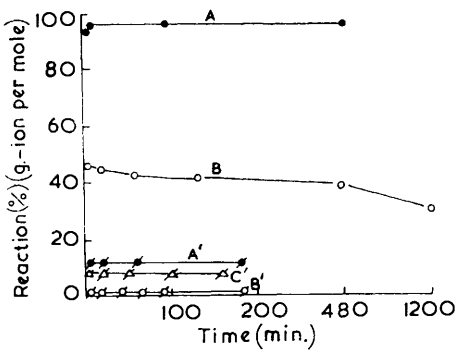


FIG. 3. Decomposition of *NN*-dimethyl-2-bromo-n-propylethylamine (A and B) and of *NN*-dimethyl-2-bromo-3-phenylpropylamine (A′, B′, and C′). A, B, and C as for Fig. 4.

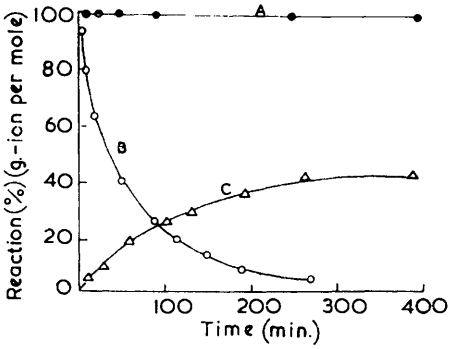


FIG. 4. Decomposition of *NN*-β-bromodimethylphenethylamine. (A) Halide ion liberated. (B) Ethyleniminium ion formed. (C) Hydrogen ion formed.

the former. Increased basicity of the nitrogen atom may well be reflected by an increase in k_1; since for a given nucleophilic atom, the nucleophilicity is roughly correlated with the basicity. In agreement with this, *NN*-dimethyl-2-halogenoethylamines cyclise more rapidly than unsubstituted compounds, *e.g.*:

$$CH_3{\cdot}CHBr{\cdot}CH_2{\cdot}NMe_2 > CH_3{\cdot}CHBr{\cdot}CH_2{\cdot}NH_2$$

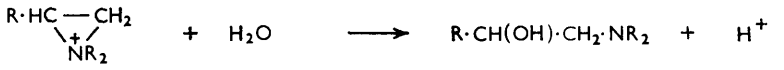
and

$$Ph{\cdot}CHBr{\cdot}CH_2{\cdot}NMe_2 > Ph{\cdot}CHBr{\cdot}CH_2{\cdot}NH_2$$

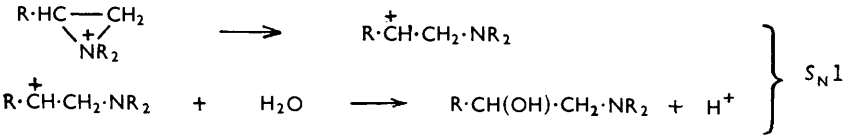
The cyclisation of *NN*-dimethyl-2-bromo-n-propylamine (Fig. 3), *NN*-dimethyl-β-bromophenethylamine (Fig. 4), and *NN*-dimethyl-2-bromo-3-phenylpropylamine (Fig. 3) present interesting features for comparison. The accelerating effect of the 2-phenyl group on the rate and extent of cyclisation is immediately evident, but the 3-phenyl group has considerably less effect on the extent of cyclisation (12·9%). Nothing can be said concerning its effect on the rate of cyclisation. It is interesting that a 2-methyl group has a much greater effect on the extent of cyclisation (97·5%) than a 2-benzyl (3-phenyl) group. The reason is not obvious.

Little quantitative work has been done on the ring-opening reactions of ethyleniminium ions, but they are comparable to the ring-opening reactions of epoxides about which more is known. The solvolyses of the ethyleniminium ions in initially neutral solution

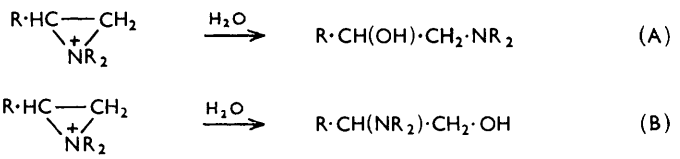
were studied quantitatively but some qualitative work was carried out with alkaline media. The rates of solvolysis in neutral media were given by $v = k_1[E^+]$. There are thus two possible mechanisms; an S_N2 reaction between the ethyleniminium ion and water:*



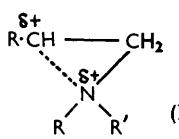
or an S_N1 reaction involving prior formation of a carbonium ion:



The former mechanism can be discarded on several grounds. In the decomposition of the ethyleniminium ions several products are formed including amino-secondary-alcohols, piperazinium salts, and quaternary salts formed by reaction between the ethyleniminium ion and amino-alcohol. If these second-order processes were occurring simultaneously with the observed first-order solvolyses, then good first-order rate coefficients for the solvolyses over 70—80% of the reaction would not be observed. The complex nature of the products formed (Table 10), together with the first-order rate coefficients, implies, therefore, a common rate-determining step for all these processes, namely, the opening of the ethyleniminium ion ring by an S_N1 mechanism. This is confirmed by the nature of the amino-alcohols formed in the solvolyses, which have been isolated and characterised to show that attack has taken place on the secondary carbon atom (route A) rather than on the primary carbon atom (route B):



This is characteristic of an S_N1 mechanism.



(III)

The transition state for the S_N1 mechanism is shown in (III), the stretching and polarisation of the carbon–nitrogen bond being the energetically significant step. Electron-releasing *N*-alkyl substituents will reduce the electron transfer involved in this process but will increase the strength of the carbon–nitrogen bond. The electron-releasing (inductive) powers of alkyl groups lie in the order: Me < Et < $Pr^n \approx$ higher alkyl groups; Me < Et < Pr^i < Bu^t.

In the series NMe_2^+, $NMeEt^+$, NEt_2^+ we find a decrease in the rate of solvolysis accompanied by an increase in the energy of activation, which implies a dominant role for the increase in bond strength. The increase in activation energy is partially compensated by an increase in the log *A* term, *i.e.*, an increase in the entropy of activation. On the basis of the known inductive effects of the alkyl groups one expects little difference between the rates of solvolysis of the *NN*-diethyl-2-phenylethyleniminium and of the higher *NN*-di-n-alkyl-2-phenylethyleniminium ions. However, the *NN*-di-n-propyl-2-phenylethyleniminium ion is solvolysed approximately four times faster than the *NN*-diethyl compound; and this increased rate appears to be due to a decreased activation energy and an increased log *A* term. The *NN*-di-isopropyl-2-phenylethyleniminium ion is solvolysed more rapidly still, although on the basis of inductive electron release it is expected to be more stable than the other *NN*-dialkyl-2-phenylethyleniminium ions; it is interesting, however, that this rapid rate of solvolysis is accompanied by a high activation energy (~22 kcal./

* We assume the orientation of ring opening to be as shown at this stage.

TABLE 10.

Reactions of 2-halogenoethylamines, $Ph{\cdot}CHX{\cdot}CH_2Y$ in 1 : 1 acetone–water. §

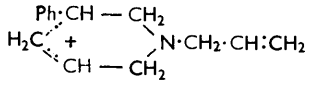
Y	X	Piperazinium salt (%) *	Amino-alcohol (%) ‡	Quat. salt from amino-alcohol (%) *
NMe_2	Cl	4·0	34·0	52·0
NMe_2	Br	1·8	53·5	42·8
NMeEt	Br	6·0	36·5	51·4
NEt_2	Br	7·4	17·5	65·9
NPr^n_2	Br	18·6	14·0	48·8
NPr^i_2	Br	34·9	8·5	21·6
NBu^n_2	Br	24·6	17·0	33·8
$N(CH_2{\cdot}CH{:}CH_2)_2$	Br	5·5	86·5	3·0
Piperidino	Br	8·6	39·5	43·0
$N(CH_2Ph)_2$ †	Cl	—	—	—
$N(CH_2Ph)_2$ †	Br	—	78·2	—
$N(CH_2Ph)_2$ †	I	—	27·5	—
$Ph{\cdot}CH(NMe_2){\cdot}CH_2Br$		7·5	37·5	42·3
$Ph{\cdot}CH(NC_5H_{10}){\cdot}CH_2Br$		6·0	15·0	70·0

* Calc. from kinetic results. † In 3 : 1 acetone–water. ‡ Based on H^+ values.
§ At 31·0°. Values are thought to be accurate to ±5%.

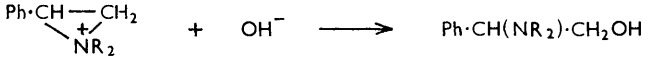
mole) which may indicate some inductive stabilisation of the ethyleniminium ion ring, but is more than offset by the high log A term. It is suggested that the rate of solvolysis of the ethyleniminium ions is determined by the balance between the inductive stabilisation of the ion by the N-alkyl groups, which will increase with chain length and branching, and the labilisation of the ion by non-bonded compressions exerted by the N-alkyl groups, which will increase with increasing chain branching and will be relieved in the transition state. The value of the solvolysis rate obtained for the *NN*-di-n-butyl-2-phenylethyleniminium ion arises from a higher activation energy (~24 kcal./mole) accompanied by a higher log A term. It is difficult to explain the high activation energy obtained here since it would not be expected to be significantly different from that for the reaction of the di-n-propyl compound.

The differences in the rates of solvolysis of the ethyleniminium ions derived from 2-bromo-1-ethyl-2-phenyl-pyrrolidine and -piperidine are interesting. The faster solvolysis of the former appears to be largely due to differences in the log A term and this may possibly be related to differences in the conformation of the respective rings.

The very rapid solvolysis of the *NN*-diallyl-2-phenylethyleniminium ion is unexpected; the rate of solvolysis is about fifty times that of the *NN*-di-n-propyl compound and it is difficult to account for this in terms of a sterically accelerated solvolysis. Examination of the transition state, however, shows the possibility of the formation of a stabilised six-membered ring which would result in a lower energy of activation for the solvolysis.



The addition of hydroxide ion accelerates the rate of decomposition of the *NN*-dimethyl-2-phenylethyleniminium ion; this may be due to the incursion of an S_N2 process:



The rates of solvolysis of the ethyleniminium ions which were studied with distilled water as solvent were found to be less than the corresponding rates in 1 : 1 acetone–water. Since the transition state involves a dispersal of positive charge these results accord with the Hughes–Ingold theory of solvent action,[14] since a change from a less to a more polar solvent will hinder charge dispersal.

[14] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons, London, 1953, 1st edn., p. 345.

The nature of the products formed in the reactions of *NN*-dialkyl-β-halogenophenethylamines has been mentioned previously and a list of approximate percentages of products has been given (Table 10). There appears to be an approximate correlation between the reactivity (k_1) of the ethyleniminium ion and the amount of piperazinium salt formed. The amounts of piperazinium salt formed lie in the order: $NPr^i > NBu^n_2 > NPr^n_2 >$ piperidino $> NEt_2 > NMeEt > NMe_2$; the rates of S_N1 ring opening at 31·0° lie in the order: $NPr^i_2 > NBu^n_2 > NPr^n_2 > NMe_2 > NMeEt > NEt_2 >$ piperidino. The reverse order holds good roughly for the amounts of amino-alcohol, and quaternary salt formed by reaction of the ethyleniminium ion with the amino-alcohol. There are, however, certain exceptions to this; an outstanding example is the *NN*-diallyl-2-phenylethyleniminium ion which is solvolysed extremely rapidly and gives 86·5% of the amino-alcohol and relatively little quaternary salt. It will be recalled that the rates of the S_N1 ring opening of these ethyleniminium ions could be explained on the basis of two opposing effects exerted by the *N*-alkyl group (p. 1399). Electron-releasing substituents will stabilise the carbonium ions formed from the ethyleniminium ions; the electron-attracting ($-I$) effects of *NN*-dialkylamino-groups will lie in the order: $NMe_2 > NMeEt > NEt_2 > NPr^n_2 > NBu^n_2$; $NMe_2 > NEt_2 > NPr^i_2$. Since carbonium ions carrying *NN*-dialkylamino-groups with the least electron-withdrawing properties will be the most stable, the order of stability of the carbonium ions will be: $NPr^i_2 > NBu^n_2 > NPr^n_2 > NEt_2 > NMeEt > NMe_2$. In view of the increasing " selectivity " of reaction with increasing stability of carbonium ions towards nucleophilic reagents, it is interesting that there is a correlation between the stability of the carbonium ion and the amount of amino-alcohol and piperazinium salt formed (Table 11). It will be observed that as the stability of the

TABLE 11.

Reactivity of carbonium ion, $^+CHPh{\cdot}CH_2X$ (values accurate to ±5%).

Y			Reaction with water (%)	Reaction with 2-bromoethylamine (%)
NPr^i_2		—	8·5	34·8
NBu^n_2	Approx.	—	17·0	24·6
NPr^n_2	order of	—	14·0	18·6
NEt_2	decreasing	—	17·5	7·4
NMeEt	stability	—	36·5	6·0
NMe_2		—	53·5	1·8

carbonium ion decreases, the percentage of reaction with the nucleophilic agent present in the greatest excess increases, and the percentage of reaction with the more powerful nucleophilic entity (present in small amount) decreases.

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