N-*Ethyl*(*or -Methyl or -Phenyl*)-N-2-*halogenoethyl*-1(*or* -2)-*naphthylmethylamines. Part II.* Chemical Reactivity and Pharmacological Activity.*

By N. B. CHAPMAN and J. W. JAMES.

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Graphs are presented showing the behaviour of some of the compounds mentioned in the title in acetone–water (2 : 1) at 30·0°. The bromo- and iodo-compounds of the *N*-ethyl (or *N*-methyl) series lose their halogen almost instantaneously, and there is evidence that a *N*-substituted ethyleneiminium ion is first produced, which is then destroyed more or less rapidly, mainly by hydrolysis. With the chloro-compounds loss of chlorine is incomplete, but the same general features of the reactions are observed. Biological assays, at appropriate times, of solutions prepared as for kinetic experiments give values lying close to the chemically determined curves recording the life-history of the ethyleneiminium ions formed (cf. Graham and Lewis, *Brit. J. Pharmacol.*, 1954, **9**, 68). This provides the first explicit evidence that ethyleneiminium ions are formed and are probably the pharmacologically active species in the antiadrenaline and antihistamine action of these compounds. The mechanism of formation of these ions and their structure are also discussed. Some evidence about the behaviour of dibenamine is also recorded. The fluoro-compounds and the *N*-phenyl compounds decompose very slowly or not at all in aqueous acetone at 30°.

IN Part I* the variation of pharmacological properties with structure of the compounds mentioned in the title was discussed with special reference to mobility of the halogen. The kinetics of the decomposition of some of these compounds in acetone–water (2 : 1) at 30·0° are now presented graphically in Figures 1—5. We did not attempt to determine the details of the kinetics, or to evaluate rate coefficients, because of the complexity of the systems. Our objects were to correlate pharmacological properties with the mobility of the halogen, to provide evidence of the formation of *N*-substituted ethyleneiminium ions when the halogeno-amines were liberated from their salts, and to obtain solutions of these ions of definite but varied concentration for pharmacological assay. We have thus provided cogent evidence that in this range of compounds the substituted ethyleneiminium ion is the pharmacologically active species, a hypothesis advanced by Nickerson and Gump (*J. Pharmacol.*, 1949, **97**, 25). A preliminary account of this work has appeared already (Chapman, James, Graham, and Lewis, *Chem. and Ind.*, 1952, 805). Nickerson and Gump

* Part I, *J.*, 1953, 1865.

(*loc. cit.*) advanced their hypothesis by analogy with the behaviour of the aliphatic bis-2-chloroethylamines (" nitrogen mustards ") which have been thoroughly investigated by Hanby, Hartley, Powell, and Rydon (*J.*, 1947, 519), by Golumbic, Fruton, and Bergmann (*J. Org. Chem.*, 1946, **11**, 518), and by Bartlett, Ross, and Swain (*J. Amer. Chem. Soc.*, 1947, **69**, 2971, 2977).

Experimental

Materials.—The halogeno-amine salts were prepared and purified as in Part I, analytically pure samples being used. " AnalaR " acetone was diluted with distilled water for solvent.

Procedure.—The finely powdered salt (4 mmoles) was dissolved in water (50 c.c.) in a 200 c.c. flask, and acetone was (132 c.c.) added. The quantity of 0·400N-sodium hydroxide solution calculated to neutralise exactly the combined halogen hydracid was added, the time of half-addition being taken as the zero for the reaction. The solution (0·02M) was made up to the mark with water and placed in a thermostat at 30°. Aliquot portions (5 c.c.) were withdrawn at intervals (syringe pipette) and run into water (30 c.c.) covered with ether (20 c.c.), thus arresting the reaction and removing unchanged halogeno-compound. The aqueous layer and washings were titrated as follows: (*a*) chloride ions were determined by the Volhard method, bromide ions by a modified Volhard method (Kolthoff and Stenger, " Volumetric Analysis," New York, 1947, Vol. II, p. 272), and iodide ions by silver titration with dichlorofluorescein as indicator; (*b*) ethyleneiminium ions were determined by the iodine–thiosulphate titration developed by Golumbic *et al.* (*loc. cit.*) save that the reaction mixture was set aside with a five-fold excess of thiosulphate for 30 min. before back-titration, and a control determination was included; and (*c*) hydrogen ions formed were determined by titration of 0·0500N nitric acid (10·0 c.c.) and pure ethanol (30 c.c.) with 0·0500N-sodium hydroxide, in the presence and in the absence of the extracted aliquot portion, phenolphthalein being used as indicator (Simonetta, di Modrone, and Favini, *Gazzetta*, 1950, **80**, 129). In the acid titrations it was shown that the presence of the alcohol corresponding to the halogeno-amines did not affect the titre.

The fluoro-compounds and derivatives of *N*-phenyl-1-naphthylmethylamine were weighed as free bases. Only ethyleneiminium-ion determinations were attempted with the fluoro-compounds.

Isolation of Picrylsulphonates of Ethyleneiminium Ions.—To a solution of *N*-2-bromoethyl-*N*-ethyl-1′-naphthylmethylamine in aqueous acetone, prepared as for kinetic experiments but of greater concentration, was added immediately an excess of acidified aqueous sodium picrylsulphonate (pH 2). The mixture was cooled to 0° and the solid product filtered off and recrystallised from aqueous acetone. N-*Ethyl*-N-1-*naphthylmethylethyleneiminium picrylsulphonate monohydrate* had m. p. 149—150° [Found: C, 49·5; H, 4·0; N, 10·7; S, 6·2; H_2O, 1·8 (loss in wt.). $C_{21}H_{20}O_9N_4S,H_2O$ requires C, 49·1; H, 4·1; N, 10·9; S, 6·2; H_2O, 1·8%]. The picrylsulphonate of the corresponding alcohol had m. p. 193° and, on admixture with the above, m. p. 145—155°. The following picrylsulphonates were similarly prepared. N-*Methyl*-N-1-*naphthylmethylethyleneiminium picrylsulphonate sesquihydrate*, m. p. 154° (Found: C, 46·7; H, 3·8; N, 10·7; S, 5·9. $C_{20}H_{18}O_9N_4S,1·5H_2O$ requires C, 46·4; H, 4·0; N, 10·8; S, 6·2%). N-*Ethyl*-N-2-*naphthylmethylethyleneiminium picrylsulphonate dihydrate*, m. p. 192° (Found: C, 46·9; H, 4·1; N, 10·0; S, 5·9. $C_{21}H_{20}O_9N_4S,2H_2O$ requires C, 46·7; H, 4·4; N, 10·4; S, 5·9%). N-*Methyl*-N-2-*naphthylmethylethyleneiminium picrylsulphonate sesquihydrate*, m. p. 193—194° (Found: C, 47·0; H, 4·0; N, 10·5; S, 6·1%).

Discussion

The reactions of the *N*-2-halogenoethyl-*N*-phenyl-1′-naphthylmethylamines were studied at 30° in acetone–water (4 : 1 or 8 : 1) because of their insolubility in the usual medium. Under these conditions halide ions were liberated very slowly and thiosulphate-consuming products were not formed (see Table). In acetone–water (2 : 1) the *N*-ethyl-(or *N*-methyl)-*N*-2-fluoroethyl-1′-naphthylmethylamines behaved similarly.

Fig. 1 shows behaviour typical of all the chloro-compounds investigated, save the *N*-phenyl compounds. Chloride was liberated at a measurable rate throughout, and ultimately equilibrium was attained, usually at about 80% decomposition. The curves showing the development and decay of a thiosulphate-consuming species, probably an ethyleneiminium ion, all have a maximum of varying magnitude (cf. Table). The hydrogen-ion concentration increased steadily from zero initially, but did not attain a final value

corresponding to complete destruction of the ethyleneiminium ion by water, nor did the amount of hydrogen ion produced at any time correspond exactly to the difference between the amount of halogeno-amine transformed and the amount of ethyleneiminium ion persisting (Fig. 1). Fig. 2 shows the characteristic behaviour of two bromo-compounds: *N*-2-bromoethyl-*N*-ethyl-1'- (curves *A*, *B*, and *C*) and -2'-naphthylmethylamine. The first provides clear evidence of the formation of ethyleneiminium ions from bromo-compounds of this type, since the substituted bromoethylamine lost almost all its bromine virtually instantaneously, only a little hydrogen ion being formed during the same period, and a quantity of a thiosulphate-consuming compound approximately equivalent to the liberated bromide was also produced. Unfortunately it was impossible to standardise thiosulphate against a pure ethyleneiminium salt because the only available salts were insoluble. However, there is evidence that piperazinium salts do not consume thiosulphate (Allen, unpublished work), so that the only transformation of the bromoethylamine which will, in the limit, satisfy these conditions is: $R_2N{\cdot}CH_2{\cdot}CH_2Br \rightleftharpoons R_2\overset{+}{N}<[CH_2]_2 + Br^-$. Moreover, the ethyleneiminium curve "follows" the bromide ion curve in its rapidly ascending phase (Fig. 2), and then shows a characteristic decline in which reaction with water predominates. During the first few minutes, the sum of the amounts of hydrogen ion and ethyleneiminium ion was, within experimental error, equal to the amount of bromide ion liberated, as expected, but in view of the rapidity of these reactions in the early stages no

Reactions and properties of 1-$C_{10}H_7{\cdot}CH_2{\cdot}NR{\cdot}CH_2CH_2X$.‡

Compound R	X	Maximum proportion of X^- liberated, % (usually after ~22 hr.)	Maximum proportion of ethylene-iminium ion formed, %	Antiadrenaline activity * μmoles/kg.	Antihistamins activity † μmoles/kg.
Ph	Cl	(*a*) 0 (*b*) 0·8	0	Inactive	Inactive
Ph	Br	(*a*) 1·6 (*b*) 8	0	,,	,,
Ph	I	(*a*) 0 (*b*) 1·3	0	,,	,,
Et	F	0§	0	,,	,,
Et	Cl	87	34	0·60	0·92
Et	Br	100	86	0·62	0·78
Et	I	100	100	1·22	0·66
Me	F	0§	0	Inactive	Inactive
Me	Cl	96	18	79·3	,,
Me	Br	100	100	1·31	4·79
Me	I	100	47	9·21	2·96

(*a*) After 4 hr., (*b*) after 22 hr. in acetone–water (4 : 1 for X = Cl, Br; 8 : 1 for X = I).

Reactions and properties of 2-$C_{10}H_7{\cdot}CH_2{\cdot}NR{\cdot}CH_2{\cdot}CH_2X$.‡

Et	F	0§	0	Inactive	Inactive
Et	Cl	77	47	31·3	23·8
Et	Br	100	96	14·2	22·8
Et	I	99	79	9·6	17·4
Me	F	0§	0	Inactive	Inactive
Me	Cl	82	15	,,	,,
Me	Br	89	72	18·8	26·5
Me	I	100	53	11·9	35·6

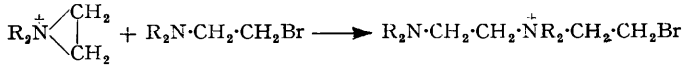
* $E.D._{99}$ Spinal cat. † $E.D._{75}$ Chloralosed cat.
‡ Except where R = Ph and X = F, the compounds were administered as HX salts.
§ Qualitative tests only were done.

exact quantitative significance is ascribed to this. After about 1300 min. the ethyleneiminium ion had disappeared and the hydrogen-ion and bromide-ion concentrations were equivalent, corresponding closely with the simplest type of behaviour, *viz.*:

$$R_2N{\cdot}CH_2{\cdot}CH_2{\cdot}Br \rightleftharpoons \bar{B}r + R_2\overset{+}{N}\!\!<\!\!\begin{matrix}CH_2\\|\\CH_2\end{matrix} \xrightarrow{H_2O} R_2N{\cdot}CH_2{\cdot}CH_2{\cdot}OH + H^+$$

This requires the ethyleneiminium- and hydrogen-ion curves to be symmetrical about the abscissa through their intersection. Departures from this behaviour may be due to

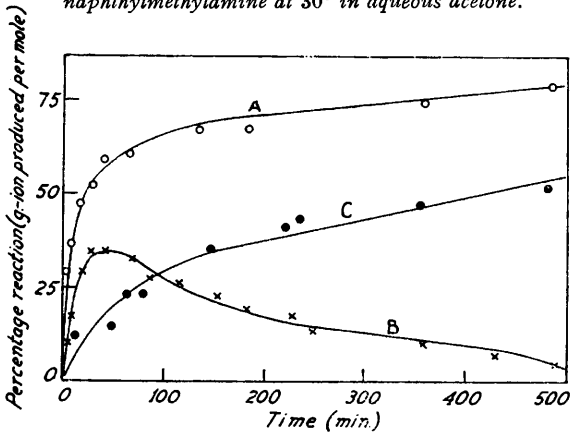
errors in the hydrogen-ion determinations. Curves *A'*, *B'*, and *C'* show the same features, save that the substituted bromoethylamine decomposed more gradually after a rapid initial phase. This may be due to rapid attainment of an initial equilibrium, followed by a slow further decomposition :



We consider the sigmoid character of the hydrogen-ion curve to be fortuitous.

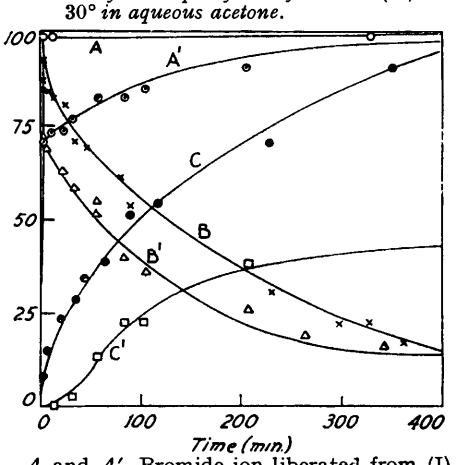
Fig. 3 shows the behaviour of *N*-ethyl-*N*-2-iodoethyl-1'-naphthylmethylamine (*A*, *B*, *C*) and of the corresponding 2'-compound (*A'*, *B'*, and *C'*). The first compound behaved more as the simplest type than the corresponding bromo-compound, whereas the second group of curves shows that among 2'-compounds even the iodo-derivatives behaved in a way characteristic of incomplete initial decomposition, as seen most strikingly with the chloro-

FIG. 1. *Decomposition of* N-2-*chloroethyl*-N-*ethyl*-1'-*naphthylmethylamine at* 30° *in aqueous acetone.*



A, Chloride ion liberated.
B, Ethyleneiminium ion formed.
C, Hydrogen ion formed

FIG. 2. *Decomposition of* N-2-*bromoethyl*-N-*ethyl*-1'- (I) *and* N-2-*bromoethyl*-N-*methyl*-2'-*naphthylmethylamine* (II) *at* 30° *in aqueous acetone.*



A and *A'*, Bromide ion liberated from (I) and (II) respectively.
B and *B'*, Ethyleneiminium ion formed from (I) and (II) respectively.
C and *C'*, Hydrogen ion formed from (I) and (II) respectively.

compounds. The other bromo- and iodo-compounds of the series behaved in a manner governed, apart from minor differences (cf. Table), by the same principles as those set out above.

Fig. 4 shows that at 0°, with a reactive substituted bromoethylamine, the liberation of bromide ion and formation of ethyleneiminium ion pursued closely similar courses, but that raising the temperature caused rapid destruction of the ethyleneiminium ion. Fig. 5 shows the effect of adding the alcohol corresponding to the bromo-compound on the decomposition of the ethyleneiminium ion. It is on the basis of this observation that we believe that the decomposition of the ethyleneiminium ion usually involves not only hydrolysis, but also the reaction :

The various determinations upon which all these curves are based are subject to considerable experimental error, although less than that involved in the biological assays (p. 2108). However, the observations recorded give a good general picture of the trend of events in aqueous-acetone solutions of the halogeno-amines in question.

We attempted to isolate, as picrylsulphonates, the ethyleneiminium ions formed in these reactions. *N*-Ethyl-*N*-1-naphthylmethylethyleneiminium picrylsulphonate was isolated as a crystalline monohydrate and gave satisfactory analyses. The remaining picrylsulphonates are also thought to be hydrated, but the analyses are less satisfactory. However, the mode of preparation and mixed m. p. determinations preclude the alternative formulation of these compounds, *viz.*, as *N*-disubstituted 2-hydroxyethylamine picrylsul-

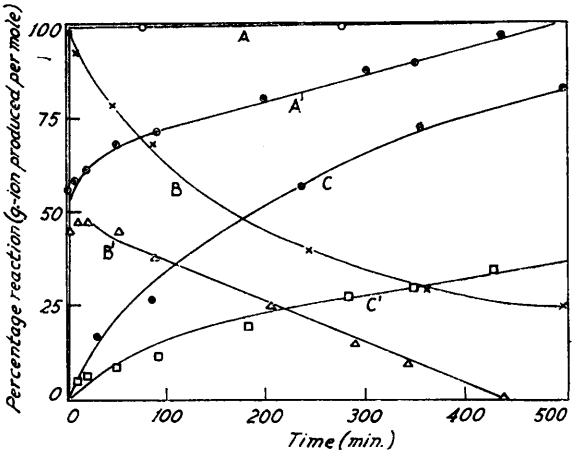


FIG. 3. *Decomposition of* N-*ethyl*-N-2-*iodoethyl*-1′- (III) *and* N-*ethyl*-N-2-*iodoethyl*-2′-*naphthylmethylamine* (IV) *at* 30° *in aqueous acetone.*

A and *A′*, Iodide ion liberated from (III) and (IV) respectively.
B and *B′*, Ethyleneiminium ion formed from (III) and (IV) respectively.
C and *C′*, Hydrogen ion formed from (III) and (IV) respectively.

FIG. 4. FIG. 5.

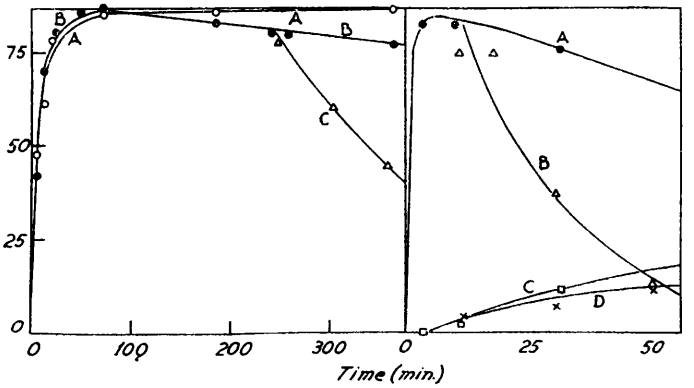


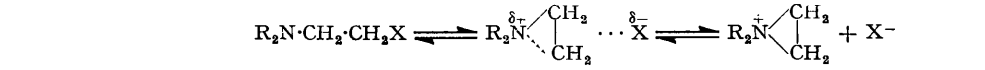
FIG. 4. *Decomposition of* N-2-*bromoethyl*-N-*methyl*-1′-*naphthylmethylamine in aqueous acetone.* *A*, Bromide ion formed and, *B*, ethyleneiminium ion produced, at 0°. *C*, Decomposition of ethyleneiminium ion at 30°.

FIG. 5. *Effect of* N-2-*hydroxyethyl*-N-*methyl*-1′-*naphthylmethylamine* (V) *on decomposition of* N-2-*bromoethyl*-N-*methyl*-1′-*naphthylmethylamine* (*curve B*).
A, Normal decomposition. *D* and *C*, Formation of hydrogen ion with and without added (V) respectively.

phonates, so that we regard this, with slight reserve, as providing confirmation of the formation of ethyleneiminium ions.

The primary decomposition process in reactions of this type has been formulated as conforming to the unimolecular mechanism of aliphatic substitution (Hanby, Hartley, Powell, and Rydon, *loc. cit.*; Ross, *J.*, 1949, 183) but this is improbable. Substituents releasing electrons powerfully to the seat of substitution would be necessary if a primary alkyl bromide were to undergo a rate-determining ionisation: the alkylarylalkylamino-group lacks such electron-releasing powers in saturated systems. Moreover, the observed rates of decomposition of the bromo- and iodo-compounds we have examined are much larger than would be expected for the S_N1 process. It is much more likely that these

reactions pursue an internal bimolecular mechanism wherein the electron-availability at the β-nitrogen atom co-operates in the decomposition, which may be formulated :



(Transition state)

The S_N1 and " internal S_N2 " processes both correspond to first-order kinetics, of course. Approximate values for the basic dissociation constants at 25° of the pharmacologically active members of the series have been determined by measuring the pH of solutions of their salts of known concentration. The values for all the bromo- and iodo-compounds lie between 2×10^{-10} and 3×10^{-11}, but the chloro-compounds have values between 3×10^{-7} and 10^{-8}, so it appears that the strength of the carbon–halogen bond is the major feature in determining rates of cyclisation.

Nickerson and Gump (*loc. cit.*) surveyed the relation between chemical structure and anti-adrenaline activity in a large group of *N*-substituted 2-halogenoethylamines and concluded that the derived ethyleneiminium ion is the pharmacologically active species. The present investigation and the related pharmacological one (Graham and Lewis, *loc. cit.*) provide the first explicit evidence in favour of this conclusion. Points determined by biological assay, using both antiadrenaline and antihistamine activity, at appropriate times, of solutions prepared exactly as for the kinetic experiments, lie close to the chemically determined curves recording the life-histories of the substituted ethyleneiminium ions. This close correspondence has been demonstrated for three *N*-ethyl-*N*-2-halogenoethyl-1′-naphthylmethylamines in which the halogen is chlorine, bromine, or iodine. It seems very probable not only that ethyleneiminium ions are formed when these halogenoethylamines are liberated from their salts, but also that these ions are the pharmacologically active species.

Nickerson also suggested that the influence of structure of the ion on pharmacological activity, with special reference to the *N*-substituents, is due to varying ionic stabilities arising from resonance. The greatest pharmacological activity is undoubtedly associated with *N*-substituents of the type $ArCH_2\cdot$ or $Ar\cdot O\cdot CH_2\cdot CH_2\cdot$, but the possible influence of structure on the stability of the ethyleneiminium ions formed is far from clear, especially if an attempt is made to write down the appropriate canonical forms. Both the ethyleneimine and the ethyleneiminium ring will bear strong structural resemblance to the *cyclo*propane ring. If we accept the structure proposed by Cromwell (*J. Org. Chem.*, 1952, **17**, 414) for the ethyleneimine ring, based on that due to Coulson and Moffitt (*Phil. Mag.*, 1949, **40**, 1) for *cyclo*propane, then the character of the partially delocalised bonds in the three-membered ring leads to a ready understanding of the stabilising influence of substituents on C or N with p or π orbitals. There is, however, no evidence that substituents of this type promote antiadrenaline activity. We think that this aspect of Nickerson and Gump's structural speculations is premature. Even within the limited field we have investigated there are anomalies, as the Table shows, for *N*-2-chloroethyl-*N*-methyl-2′-naphthylmethylamine, administered as its hydrochloride, is inactive against adrenaline, but yields ethyleneiminium ions *in vitro*; nor is there any clear relation between the maximum proportion of ethyleneiminium ion formed and antiadrenaline activity of the halogeno-amine salts. In our compounds the importance of the formation of the substituted ethyleneiminium ion for antiadrenaline and antihistamine activity is established, but the origin of the influence of the structure of the *N*-substituents on pharmacological activity requires further investigation.

Under our conditions dibenamine $[N(CH_2Ph)_2\cdot CH_2\cdot CH_2Cl,HCl]$ lost covalent chlorine extremely slowly and no thiosulphate-consuming species was detectable, but in the presence of an excess of thiosulphate, dibenamine, or a transformation product thereof, reacted slowly with thiosulphate. Harvey and Nickerson (*J. Pharmacol.*, 1953, **109**, 328) have, however, observed different behaviour in 7 : 3 ethanol–water at 27°.

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