250. *Di-N-substituted 2-Halogenoethylamines. Part V.*[1] *Fluorenylamine, Thenylamine, and Thionaphthenylmethylamine Derivatives: their Synthesis, Reactivity, and Pharmacology.*

By N. B. Chapman and A. J. Tompsett.

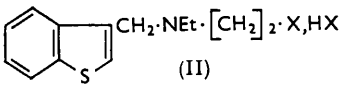
The synthesis of a series of *N*-ethyl-*N*-2′-halogenoethyl-, *N*-ethyl-*N*-2′-halogenopropyl-, and *N*-benzyl-*N*-2′-halogenoethyl-9-fluorenylamines; of some *N*-ethyl-*N*-2′-halogenoethyl-3-thionaphthenylmethylamines; and of some *N*-benzyl-*N*-2′-halogenoethyl-2-thenylamines is described. The decomposition undergone by some of these compounds in aqueous acetone at various temperatures is shown graphically. The anti-adrenaline and anti-noradrenaline activity of two of the fluorenylamine derivatives, which are of extraordinary potency, are strongly correlated with ethyleniminium ion concentration by the method used in Parts II and III, and the pharmacological properties of all the compounds prepared are briefly reported (cf. Graham, ref. 15). Piperazinium salts, probably formed in the decomposition of the compounds, are shown to be inactive against adrenaline and noradrenaline.

The influence of isosteric replacement on the relation between chemical structure and reactivity, and on pharmacological activity is briefly discussed in relation to the properties of the thenylamine and thionaphthenylmethylamine compounds prepared.

Finally the discrepancies in previous reports of the decomposition of dibenamine [$N(CH_2Ph)_2 \cdot CH_2 \cdot CH_2Cl,HCl$] in aqueous solvents have been resolved.

The object of the present paper is to broaden our study of the relation between structure, reactivity, and pharmacological activity in this field by including compounds of the types (I—III) with X = Cl, Br, or I, and R = Et, R′ = H or Me, and R = CH_2Ph, R′ = H. Moreover, as all our previous reactivity studies had been carried out at a temperature of 30°, different from that pertaining *in vivo*, in certain cases reactivity at 19°, 37°, and 45°

(I)



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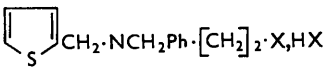


(III)

was studied. Although some of the 9-fluorenylamine derivatives have been previously reported by Kerwin, Herdegen, Heisler, and Ullyot [2] and by Rieveschl,[3] and their pharmacological properties studied by Stone, Komrad, and Loew,[4] most of them are new and have not been investigated pharmacologically. Improvements in existing synthetic processes have also been made and intermediates thoroughly characterised. *N*-2′-Chloroethyl-*N*-ethyl-3-thionaphthenylmethylamine hydrochloride has previously been reported in a patent by Avakian and Martin,[5] but because of the close similarity of compounds of this type to the 1-naphthylmethyl derivatives studied by Chapman and James,[6] it was felt that they were worthy of further investigation. The interest of the thenylamine derivatives lies in their similarity to dibenamine [$N(CH_2Ph)_2 \cdot CH_2 \cdot CH_2Cl,HCl$], the

[1] Part IV, Chapman and Allen, *J.*, 1961, 1076.
[2] Kerwin, Herdegen, Heisler, and Ullyot, *J. Amer. Chem. Soc.*, 1950, **72**, 940.
[3] Rieveschl, U.S.P. 2,573,607—8; cf. *Chem. Abs.*, 1952, **46**, 9607.
[4] Stone, Komrad, and Loew, *Arch. Internat. Pharm.*, 1952, **92**, 7.
[5] Avakian and Martin, U.S.P. 2,553,495; cf. *Chem. Abs.*, 1952, **46**, 537.
[6] Chapman and James, *J.*, 1954, 2103.

behaviour of which in aqueous solvents has been re-investigated in order to resolve the contradictions in the reports of previous workers.[6,7]

Interaction of 9-bromofluorene with *N*-ethyl-2-hydroxyethylamine, *N*-ethyl-2-hydroxypropylamine, or *N*-benzyl-2-hydroxyethylamine gave *NN*-disubstituted hydroxy-amines from which the corresponding halogeno-compounds were prepared by the method of Chapman and James.[6] 3-Thionaphthenylmethyl and 2-thenyl chloride, the essential starting materials in analogous syntheses of compounds of type (II or III), were obtained by chloromethylation of thionaphthen and thiophen respectively.

Experimental

Difficulty was met in analysis of some of these new 2-halogenoalkylamine hydrohalides for nitrogen, and occasionally for iodine because of the unusually high percentages of halogen. In several cases, therefore, carbon, hydrogen, and halogen determinations have been taken as sufficient to identify the compounds and in two cases carbon and hydrogen alone. Picrylsulphonates have been analysed for carbon and hydrogen only.

Preparation of Materials.—*9-Fluorenylamine derivatives.* Bromination of fluorene, m. p. 110—112°, by Wittig and Felletschin's method [8] gave 9-bromofluorene, which on treatment with *N*-ethyl-2-hydroxyethylamine by the method of Kerwin *et al.*[2] afforded *N*-ethyl-*N*-2′-hydroxyethyl-9-fluorenylamine hydrochloride (65%), m. p. 195—197° (from ethanol–ether), (lit.,[2] m. p. 202—204°). The *picrylsulphonate* (from ethanol), m. p. 175—176·5° (Found: C, 50·1; H, 4·0. $C_{23}H_{22}N_4O_{10}S$ requires C, 50·5; H, 4·1%), was obtained from the hydrobromide in aqueous solution by the action of an excess of hot aqueous sodium picrylsulphonate.

Adding a suspension of the powdered hydrochloride of the 9-fluorenylamine derivative (16·2 g., 0·056 mole) in dry chloroform with stirring during 30 min. to an ice-cold suspension of phosphorus pentachloride (12·5 g., 0·06 mole) in dry chloroform, followed by boiling for 3—4 hr. and evaporation to dryness, gave a sticky residue which solidified on trituration with dry ether, to yield *N*-2′-chloroethyl-*N*-ethyl-9-fluorenylamine hydrochloride (83%), m. p. 194·5—195·5° (from ethanol) (lit.,[2] 195—196·5°) (Found: Cl, 23·0. Calc. for $C_{17}H_{18}ClN,HCl$: Cl, 23·0%); Kerwin *et al.*[2] used thionyl chloride instead of phosphorus pentachloride in this preparation. Adding a chloroform solution of the former hydrochloride (14·3 g., 0·05 mole) to a stirred ice-cold mixture of phosphorus tribromide (17·0 g., 0·06 mole) and dry chloroform, followed by heating at the b. p. for 6 hr., removal of chloroform, and crystallisation of the residue from dry ethanol, gave *N*-2′-bromoethyl-*N*-ethyl-9-fluorenylamine hydrobromide (75%), m. p. 197·5—198·5° (Found: C, 51·7; H, 4·8; Br, 40·2; N, 3·9. Calc. for $C_{17}H_{18}BrN,HBr$: C, 51·4; H, 4·8; Br, 40·2; N, 3·6%) [*picrylsulphonate*, m. p. 196—198° (Found: C, 45·3; H, 3·5. $C_{23}H_{21}BrN_4O_9S$ requires C, 45·3; H, 3·6%)]. *N-Ethyl-N-2′-iodoethyl-9-fluorenylamine hydriodide* (72%), m. p. 167—168° (from dry ethanol), was prepared similarly by using phosphorus tri-iodide (Found: C, 41·6; H, 3·7; I, 52·0. $C_{17}H_{18}IN,HI$ requires C, 41·6; H, 3·9; I, 51·7%).

N-Benzyl-*N*-2′-hydroxyethyl-9-fluorenylamine hydrochloride, m. p. 175—178°, was prepared by the method of Kerwin *et al.*[2] using *N*-benzyl-2-hydroxyethylamine, b. p. 118—125°/1 mm., prepared by Rumpf and Quass's method.[9] The base gave a *picrate*, m. p. 157·5—159·5° (from aqueous ethanol) (Found: C, 62·1; H, 4·0; N, 10·7. $C_{28}H_{24}N_4O_8$ requires C, 61·8; H, 4·3; N, 10·3%), and a *picrylsulphonate*, m. p. 194·5—196° (from dry ethanol) (Found: C, 55·0; H, 4·0. $C_{28}H_{24}N_4O_{10}S$ requires C, 55·3; H, 4·0%). *N*-Benzyl-*N*-2′-chloroethyl- [hydrochloride, m. p. 184—186° (lit.,[2] 184—186°)], *N*-benzyl-*N*-2′-bromoethyl- [*hydrobromide*, m. p. 180—182° (from chloroform) (86%) (Found: C, 57·5; H, 4·5; Br, 35·0. $C_{22}H_{20}BrN,HBr$ requires C, 57·6; H, 4·6; Br, 34·8%)], and *N*-benzyl-*N*-2′-iodoethyl-9-fluorenylamine [*hydriodide*, m. p. 172—173·5° (from much dry ethanol) (60%) (Found: C, 47·6; H, 3·8. $C_{22}H_{20}IN,HI$ requires C, 47·8; H, 3·8%)], were prepared from the corresponding alcohols in the usual way.

N-Ethyl-*N*-2′-hydroxypropyl-9-fluorenylamine hydrochloride (72%), m. p. 187·5—189°, was prepared by the method of Kerwin *et al.*[2] using *N*-ethyl-2-hydroxypropylamine (prepared

[7] Harvey and Nickerson, *J. Pharmacol.*, 1953, **109**, 328.
[8] Wittig and Felletschin, *Annalen*, 1944, **555**, 138.
[9] Rumpf and Quass, *Bull. Soc. chim. France*, 1943, **10**, 347.

by Krasouskii's method [10]), b. p. 69—70°/16 mm., and from it were prepared by the usual methods *N*-2′-chloropropyl- [hydrochloride (64%), m. p. 156·5—157·5° (from ethanol–ether) (cf. Kerwin *et al.*[2])] and *N*-2′-bromopropyl-*N*-ethyl-9-fluorenylamine [*hydrobromide* (78%), m. p. 147·5—148·5° (from ethanol–ether) (Found: C, 52·3; H, 5·6; Br, 38·2. $C_{18}H_{20}BrN,HBr$ requires C, 52·6; H, 5·5; Br, 38·9%)].

3-*Thionaphthenylamine Derivatives.*—3-Chloromethylthionaphthen, m. p. 37·5—39° [from light petroleum (b. p. 60—80°)], b. p. 100—105°/0·2 mm., was prepared (40% yield) by Avakian and Martin's method [5] (Found: C, 60·3; H, 4·2. Calc. for C_9H_7ClS: C, 59·2; H, 3·9%; suggesting contamination with thionaphthen). Interaction of the chloromethyl compound (37·2 g., 0·2 mole) and *N*-ethyl-2-hydroxyethylamine (37·2 g., 0·42 mole) in benzene at the b. p. for 6 hr., followed by addition of an excess of dry ether, storage at 0° overnight, and removal of *N*-ethyl-2-hydroxyethylamine hydrochloride, gave a filtrate, which on saturation with dry hydrogen chloride at 0° gave *N*-ethyl-*N*-2′-hydroxyethyl-3-thionaphthenylmethylamine hydrochloride, m. p. 127·7—129° (from ethanol–ether) (79%) (lit.,[5] 129—130°), pure enough for further synthetic work [*picrylsulphonate*, m. p. 159—160° (from aqueous acetone) (Found: C, 43·6; H, 4·0. $C_{19}H_{20}N_4O_{10}S_2$ requires C, 43·2; H, 3·8%); *picrate*, m. p. 128—129° (from aqueous ethanol) (Found: C, 49·1; H, 4·2; S, 6·6. $C_{19}H_{20}N_4O_8S$ requires C, 49·1; H, 4·3; S, 6·9%)]. The *N*-2′-hydroxyethyl compound was then converted by the usual methods into *N*-2′-chloroethyl- [hydrochloride (100%), m. p. 148—150° (from ethanol) (lit.,[5] 147—148°) (Found: C, 53·6; H, 5·9. Calc. for $C_{13}H_{16}ClNS,HCl$: C, 53·8; H, 5·9%)], *N*-2′-bromoethyl- [*hydrobromide*, m. p. 179—180° (from ethanol–ether) (79%) (Found: C, 41·6; H, 4·5; Br, 42·9. $C_{13}H_{16}BrNS,HBr$ requires C, 41·2; H, 4·5; Br, 42·2%)], and *N*-2′-iodoethyl-*N*-ethyl-3-thionaphthenylmethylamine [*hydriodide* (47%), m. p. 182·5—183·5 (decomp.) (from ethanol) (Found: C, 33·3; H, 3·4. $C_{13}H_{16}INS,HI$ requires C, 33·0; H, 3·6%)].

2-*Thenylamine Derivatives.*—Chloromethylation of redistilled thiophen, b. p. 82—84°, by Wiberg and McShane's method [11] gave 2-chloromethylthiophen (40%), b. p. 64—66°/12·5 mm., which on treatment with benzylamine by the method of Campbell *et al.*[12] gave *N*-benzyl-2-thenylamine, b. p. 120—122°/0·2 mm., and N-*benzyldi*-2-*thenylamine*, m. p. 79—80° (from ethanol) (Found: C, 67·6; H, 5·9. $C_{17}H_{17}NS_2$ requires C, 68·2; H, 5·7%). The method of Campbell *et al.*[12] was used to convert the *N*-benzyl-2-thenylamine into *N*-benzyl-*N*-2′-hydroxyethyl-2-thenylamine, b. p. 135—143°/0·05 mm. [hydrochloride, m. p. 147—149° (from ethanol–ether) (lit.,[12] 146—147°)]. The usual procedures then gave *N*-benzyl-*N*-2′-chloroethyl- [hydrochloride (77%), m. p. 177—178° (from ethanol) (lit.,[12] 177—178°)], *N*-benzyl-*N*-2′-bromoethyl- [*hydrobromide* (82%), m. p. 164·5—165·5° (from ethanol) (Found: C, 43·2; H, 4·4; Br, 39·9. $C_{14}H_{16}BrNS,HBr$ requires C, 43·0; H, 4·4; Br, 40·8%); *picrylsulphonate*, m. p. 145—146° (from chloroform) (Found: C, 39·4; H, 3·5. $C_{20}H_{19}BrN_4O_9S_2$ requires C, 39·8; H, 3·2%)], and *N*-benzyl-*N*-2′-iodoethyl-2-thenylamine [*hydriodide* (58%), m. p. 162—163° (from much ethanol) (Found: C, 35·1; H, 3·7; I, 52·8. $C_{14}H_{16}INS,HI$ requires C, 34·7; H, 3·5; I, 52·3%)].

Dibenamine and its Analogues. Dibenamine (from L. Light and Co. Ltd.) was recrystallised from ethanol to m. p. 192—194°. The corresponding alcohol, prepared by the method of Gump and Nikawitz,[13] had m. p. 42—43°, b. p. 135—145°/2·5 mm., and gave a *picrylsulphonate*, m. p. 147—148·5° (Found: C, 50·0; H, 4·0. $C_{22}H_{22}N_4O_{10}S$ requires C, 49·5; H, 4·1%), and was converted into the bromo-compound (63%), m. p. 177—179° (lit.,[13] 177—179°), by the action of phosphorus tribromide (Gump and Nikawitz [13] used hydrobromic acid), and into the iodo-compound (80%), m. p. 175—176·5° (lit.,[13] 178—179°), by the action of phosphorus tri-iodide (cf. Geissman *et al.*[14]) (Found: C, 40·4; H, 3·7; I, 52·7. Calc. for $C_{16}H_{19}IN,HI$: C, 40·1; H, 4·0; I, 53·0%).

Procedure.—This was as described in Part II.[6] The efficiency of the ether-extraction in removing unchanged halogenoalkylamine has been checked by appropriate halogen determinations. Hydroxyalkylamine has been shown not to interfere with the acidity titrations, and one of the less stable ethyleniminium ions has been shown to be unhydrolysed during the thiosulphate–iodine procedure for determination of ethyleniminium ion.

[10] Krasouskii, *J. Chem. Ukraine*, 1924, **1**, 398; cf. *Chem. Abs.*, 1926, **20**, 2820.
[11] Wiberg and McShane, *Org. Synth.*, 1949, **29**, 31.
[12] Campbell, Ackerman, and Campbell, *J. Amer. Chem. Soc.*, 1949, **71**, 2905; cf. U.S.P. 2,640,828, and *Chem. Abs.*, 1954, **49**, 4001.
[13] Gump and Nikawitz, *J. Amer. Chem. Soc.*, 1950, **72**, 1309.
[14] Geissman, Hochmann, and Fukuto, *J. Amer. Chem. Soc.*, 1952, **74**, 3313.

FIG. 1.

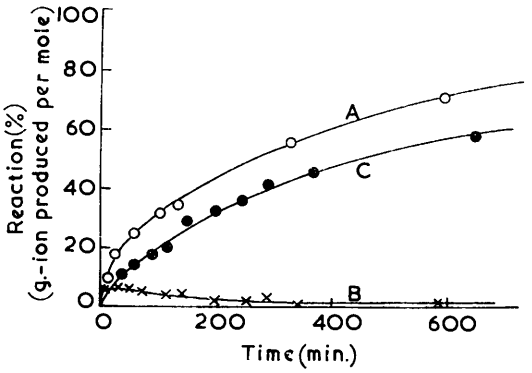


FIG. 2.

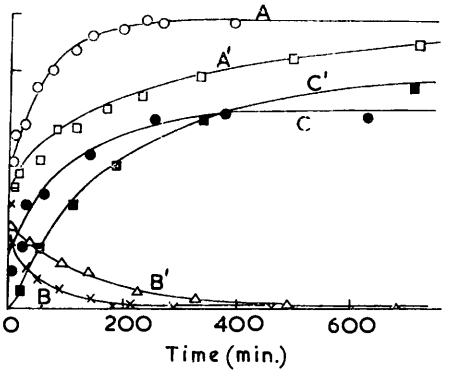
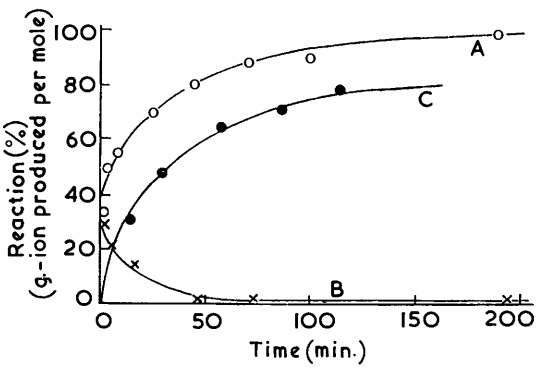


FIG. 1. *Decomposition of* N-2′-*chloroethyl*-N-*ethyl*-9-*fluorenylamine at* 30° *in aqueous acetone.*
A, *Chloride ion liberated.* B, *Ethyleniminium ion formed.* C, *Hydrogen ion formed.*

FIG. 2. *Decomposition of* N-2′-*bromoethyl*-N-*ethyl*-9-*fluorenylamine at* 30° *and at* 19° *in aqueous acetone.*
A,A′, *Bromide ion formed*; B,B′, *Ethyleniminium ion formed*; C,C′, *Hydrogen ion formed*; *at* 30° *and* 19° *respectively.*

FIG. 3.



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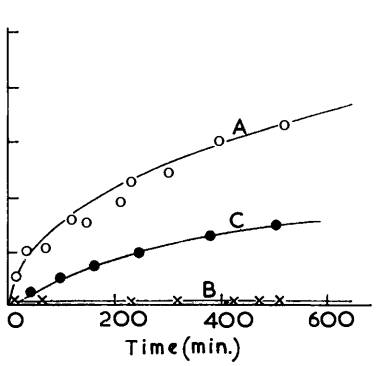


FIG. 3. *Decomposition of* N-2′-*bromoethyl*-N-*ethyl*-9-*fluorenylamine at* 37° *in aqueous acetone.*
FIG. 4. *Decomposition of* N-*benzyl*-N-2′-*bromoethyl*-9-*fluorenylamine at* 30° *in aqueous acetone.*
For Figs. 3 *and* 4: A, *bromide ion liberated.* B, *Ethyleniminium ion formed.* C, *Hydrogen ion formed.*

FIG. 5. N-2′-*Chloroethyl*-N-*ethyl*-9-*fluorenylamine.*

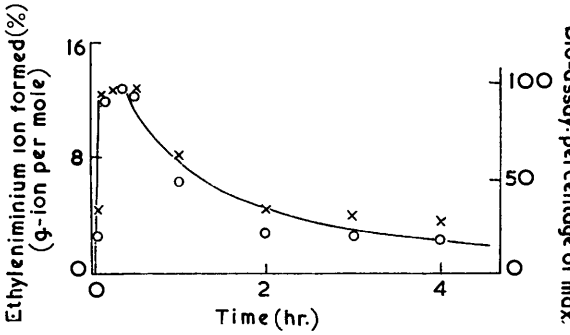
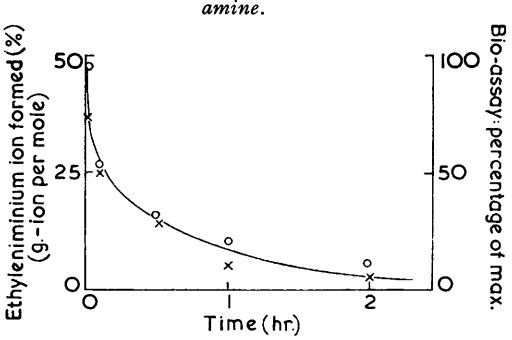


FIG. 6. N-2′-*Bromoethyl*-N-*ethyl*-9-*fluorenylamine.*



For Figs. 5 *and* 6: *The curve shows the concentration of ethyleniminium ion in in g.-ion per mole. Points represent bio-assays* (○) *against noradrenaline,* (×) *against adrenaline. Both refer to aqueous acetone solutions at* 30°.

Discussion

It will be seen from Table 1 that the bromo- and iodo-compounds derived from *N*-ethyl-9-fluorenylamine are, on a molar basis, anti-adrenaline and anti-noradrenaline agents of extraordinary potency,[15] being some 10—20 times more active than the well-known substances Phenoxybenzamine (Dibenyline) and SY28. It seemed to us of particular interest therefore to study the reactivity of these compounds and some closely related ones, and in one or two cases, to try to relate the variation with time of the chemically determined ethyleniminium-ion concentrations with variation with time of the bio-assays of the ion based on anti-adrenaline and anti-noradrenaline activity. The results are displayed in Figs. 1—6.

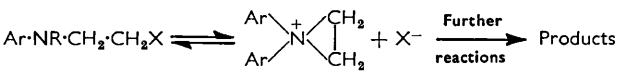
Comparison of Figs. 2 and 3 shows that for *N*-2′-bromoethyl-*N*-ethyl-9-fluorenylamine, the concentration of the related ethyleniminium ion at any time is little affected by increasing the temperature from 30°, at which most of our measurements have been made, to 37° which is approximately physiological. The overall rate of reaction of the halogeno-

Table 1. *Reactions and properties of* Ar·NR·CH_2·CH_2X,HX.

Compound			Propn. of X^- formed * (%) at 30° (after 360 min.)	Max. propn. of ethylen-iminium ion formed * (%) at 30°	Anti-adrenaline activity † (micromole/kg.)	Anti-nor-adrenaline activity † (micromole/kg.)
Ar	X	R				
9-Fluorenyl	Cl	Et	56	6·5	0·32	0·45
,,	Br	Et	100	36	0·06	0·10
,,	I	Et	88	14	0·03	0·04
,,	Cl	CH_2Ph	12·5	1	7·4	7·5
,,	Br	CH_2Ph	56	4	1·9	2·4
3-Thionaphthenyl-methyl	Cl	Et	58	22	1·4	1·9
,, ,,	Br	Et	93·5	72	1·6	2·6
,, ,,	I	Et	82	56	1·3	2·4
2-Thenyl	Cl	CH_2Ph	9	1·5	29·8	33·1
,,	Br	CH_2Ph	71·5	10	2·4	19·7
,,	I	CH_2Ph	35	4	1·2	2·2
9-Fluorenyl §	Cl	Et	78	4	2·6	4·3
,, §	Br	Et	99·5	31	0·06	0·06
Benzyl	Cl	CH_2Ph	12	2	10 ‡	—
,,	Br	CH_2Ph	78	16	5 ‡	—
,,	I	CH_2Ph	38	4·5	—	—
SY28 [a]			100	86	0·75	0·98
Dibenyline [b]	—	—	—	—	0·40	0·49

* G.-ion/mole. † E.D. 50 in spinal rats. ‡ Ref. 13. § Side chain is CHMe·CH_2X,HX.
[a] 1-$C_{10}H_7$·CH_2·NEt·CH_2·CH_2Cl,HCl. [b] PhO·CH_2·CHMe·N(CH_2Ph)·CH_2·CH_2Cl,HCl.

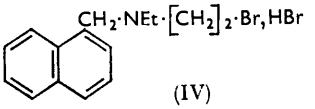
amine increases noticeably on so increasing the temperature, as would be expected, and the limited effect on the ethyleniminium-ion concentration must be due to a balance of increased rate of formation and of decomposition. Figs. 5 and 6 show that with these very active fluorenylamine derivatives, there is the same proportionality between ethyleniminium-ion concentration and anti-adrenaline activity as has been observed with other groups of compounds.[15] The general pattern of the decomposition as exemplified in Figs. 1—4 conforms with previous observations in this field, and is interpreted in terms of the scheme:



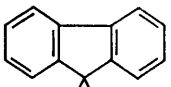
It is clear that hydrolysis is the predominant mode of further reaction of the ethyleniminium ion, but it is probable that significant amounts of halogeno-amine are consumed by reaction with the ion to yield piperazinium salts. Pharmacological testing of appropriately aged

[15] Graham, (*a*) *Brit. J. Pharmacol.*, 1957, **12**, 489; (*b*) *J. Med. Pharm. Chem.*, 1960, **2**, 911.

solutions has again shown that these salts are inactive against adrenaline and noradrenaline (cf. Part III [16]). In the fluorenylamine group, replacement of an *N*-ethyl radical by a *N*-benzyl radical depresses reactivity and anti-adrenaline activity (Table 1).



(IV)



(V) H NEt·[CH₂]₂·Br,HBr

The change of structure from (IV) to (V) is associated with increased anti-adrenaline activity, but diminished reactivity. It is unfortunate that the related ethyleniminium

FIG. 7.

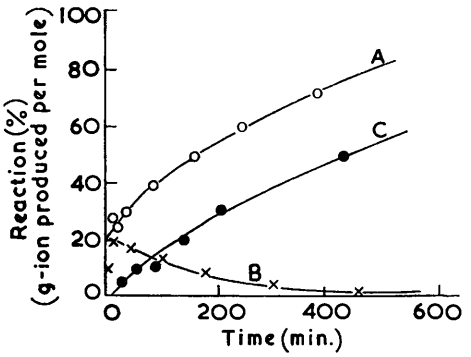


FIG. 8.

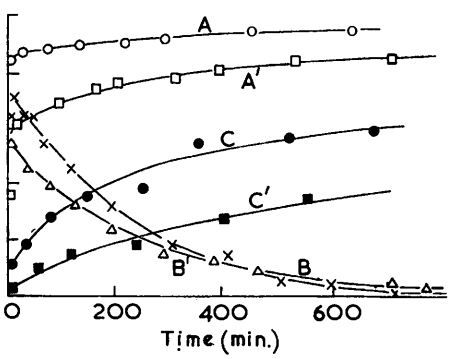


FIG. 7. *Decomposition of* N-2′-*chloroethyl*-N-*ethyl*-3-*thionaphthenylmethylamine at* 37° *in aqueous acetone.*

FIG. 8. *Decomposition of* N-2′-*bromoethyl*-N-*ethyl*-3-*thionaphthenylmethylamine and the corresponding iodo-compound at* 30° *in aqueous acetone.* A′, *Iodide ion liberated.* B′, *Ethyleniminium ion formed.* C′, *Hydrogen ion formed.*

FIG. 9.

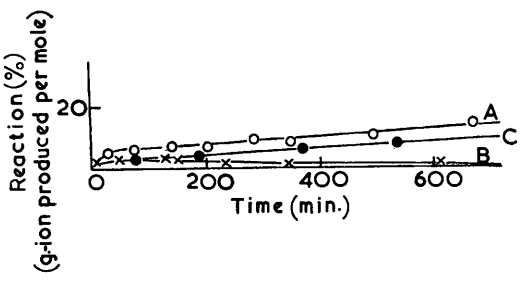


FIG. 10.

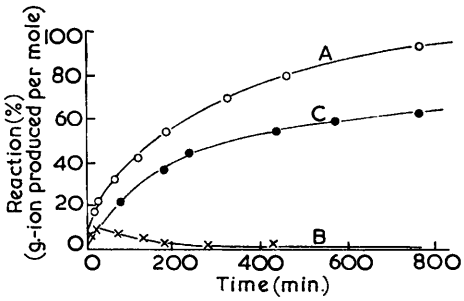


FIG. 9. *Decomposition of* N-*benzyl*-N-2′-*chloroethyl*-2-*thenylamine at* 30° *in aqueous acetone.*

FIG. 10. *Decomposition of* N-*benzyl*-N-2′-*bromoethyl*-2-*thenylamine at* 30° *in aqueous acetone.*

For Figs. 7 *and* 9: A, *Chloride ion liberated.* B, *Ethyleniminium ion formed.* C, *Hydrogen ion formed.*
For Figs. 8 *and* 10: A, *Bromide ion liberated.* B, *Ethyleniminium ion formed.* C, *Hydrogen ion formed.*

picrylsulphonates have either not been prepared, despite much effort, or are too insoluble for pharmacological study, so that the intrinsic pharmacological properties of the ions are unknown. Nevertheless, given that compound (IV) yields its ethyleniminium ion more rapidly and extensively than does (V), it appears very probable that the 9-fluorenyl group is associated with remarkably high intrinsic anti-adrenaline properties. Belleau [17] has

[16] Chapman and Allen, *J.*, 1960, 1482.
[17] Belleau, *Canad. J. Biochem. Physiol.*, 1958, **36**, 731.

explained this in terms of the relative basicities of the naphthalene and fluorene nuclei, but possibly the flatness, area, and compactness of the fluorene nucleus are also relevant.

The results assembled in Table 1 and in Figs. 7—10 relate to the effect of isosteric replacement of two aromatic carbon atoms by a sulphur atom on the phenomena under investigation. Considering the thionaphthenylmethyl derivatives in relation to the 1-naphthylmethyl derivatives previously reported (Part II [6]) some divergencies of pattern emerge. With 1-naphthylmethyl derivatives the maximum proportion of ethyleniminium ion produced is in the order I > Br > Cl, whereas with thionaphthenylmethyl derivatives the order is Br > I > Cl. As to anti-adrenaline activities these show the orders Cl ≈ Br > I for 1-naphthylmethyl compounds and Cl ≈ Br ≈ I for thionaphthenylmethyl compounds. The outstanding feature of both of these groups of compounds is the almost equal anti-adrenaline activity of the chloro-, bromo-, and iodo-compounds, whereas with fluorenyl-, chlorobenzyl-, dibenzyl-, and benzyl-thenyl derivatives the chloro-compounds are significantly less active. We can offer no explanation of this at present.

On isosteric replacement in dibenamine and its bromo- and iodo-analogues, the pattern of reactivity is in this case largely unaltered and, after allowance for the fact that the pharmacological results are not exactly comparable, so is that of anti-adrenaline activity.

Chapman and James [6] previously reported that dibenamine in aqueous acetone (1 : 2) at 30° gave negligible amounts of ethyleniminium ion. Careful re-investigation of this compound and related compounds has revealed small but measurable amounts of ethyleniminium ion in these solutions. Harvey and Nickerson,[7] working with aqueous ethanol solutions, also found by an indirect method small amounts of ethyleniminium ion. We have re-investigated this system, using a different and more direct technique than that of Harvey and Nickerson [7] and confirm their observations qualitatively, but find quantitative differences both as to chloride and ethyleniminium-ion concentrations. The differences as to ethyleniminium-ion concentration are small in absolute magnitude, but in our view significant and beyond the limits of experimental error in this work. The relevant results are assembled in Table 2. It is clear from these results that aqueous ethanol is a more

TABLE 2. *Decomposition of dibenamine (free base) at 27° and 37°.*

Propn. of Cl^- liberated * at 27° after 800 min.		Max. propn. of ethyleniminium ion produced * at 27°	
70% Aq. EtOH	2 : 1 Acetone–water	70% Aq. EtOH	2 : 1 Acetone–water
60%	20%	4%	2%
68% †	—	5% ‡	—
		10% §	—
At 37° after 400 min.		At 37°	
65%	27%	2%	2%
90%	—	5% ‡	—
		8% §	—

* G.-ion/mole. † After 400 min. ‡ Determined by thiosulphate consumption. § Determined by Harvey and Nickerson's method.[7]

favourable solvent for the decomposition of halogenoethylamines by an internal S_N2 process than is aqueous acetone. Harvey and Nickerson [7] used an excess of sodium hydrogen carbonate for the liberation of the free base from the hydrochloride, whereas we have used one equivalent of sodium hydroxide. We have shown that this leads to significant differences in the chloride ion figures.

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