383. N-*Ethyl(or -Methyl or -Phenyl)*-N-2-*halogenoethyl*-1′(*or* -2′)-*naphthylmethylamines. Part I. Structure and Pharmacological Activity.*

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A series of *N*-alkyl(or aryl)-*N*-2-halogenoethyl-1′(or 2′)-naphthylmethylamines, 1- or 2-$C_{10}H_7 \cdot CH_2 \cdot NR \cdot CH_2 \cdot CH_2X$, has been prepared by the action of phosphorus pentachloride, tribromide, or tri-iodide suspended in chloroform on the corresponding alcohols, or, where X = F, by the action of 1-bromo-2-fluoroethane on the secondary amines. They inhibit the action of adrenaline and of histamine more or less save when R = Ph or X = F. The relevance of these observations to the mode of pharmacological action of the compounds is discussed.

REPORTS by Loew and Micetich (*J. Pharmacol.*, 1948, **94,** 339; 1949, **95,** 448) and by Nickerson and Gump (*ibid.*, 1949, **97,** 25) that certain *N*-substituted 2-halogenoethylamines (*e.g.*, I, II; R = Et, X = Cl) inhibited the action of histamine and of adrenaline led us to undertake a systematic study, utilising all the halogens, of certain of these compounds in which one of the substituents is a 1(or 2)-naphthylmethyl group. We had already made some progress with the synthesis of another type of histamine antagonist also derived from naphthalene (Chapman, James, and Williams, *J.*, 1952, 4024).

(I) 1-$C_{10}H_7 \cdot CH_2 \cdot NR \cdot CH_2 \cdot CH_2X$ 2-$C_{10}H_7 \cdot CH_2 \cdot NR \cdot CH_2 \cdot CH_2X$ (II)

Our object was threefold: first, to examine the dependence of pharmacological activity on mobility of the halogens by systematic variation of the halogen, including fluoro-compounds in which the fluorine could be confidently predicted to be immobile; secondly, to examine the hypothesis advanced by Nickerson and Gump (*loc. cit.*), that the pharmacologically active species is a substituted ethyleneiminium ion, by varying the structure so as to inhibit loss of halogen, and by studying the kinetics of the cyclisation where it did occur. The kinetic work will be reported later. Cyclisation was inhibited by a phenyl substituent which so reduced electron availability at the nitrogen atom that the compounds were stable in solution in aqueous acetone even at elevated temperatures. Finally, we wished to examine the influence of the structure of the carbon skeleton on pharmacological activity, and the claim that this type of compound irreversibly inhibited the action of histamine. We have worked in collaboration with J. D. P. Graham and G. P. Lewis, Department of Pharmacology, Welsh National School of Medicine, Cardiff.

At the inception of this investigation no chemical details of the compounds examined pharmacologically had been published. Since then reports of some of the compounds we have synthesised have appeared (Rieveschl and Coleman, U.S.P. 2,573,605; cf. Gump and Nikowitz, *J. Amer. Chem. Soc.*, 1950, **72,** 1309; Kerwin and Ulyott and their collaborators, *ibid.*, 1951, **73,** 4162, 5682; Geissman, Hochman, and Fukuto, *ibid.*, 1952, **74,** 3313). Preliminary accounts of our own work have been given (Chapman, James, Graham, and Lewis, *Chem. and Ind.*, 1951, 633; 1952, 805). Geissman *et al.* (*loc. cit.*) have overlooked this in claiming priority for their synthesis of *N*-ethyl-*N*-2-iodoethyl-1′-naphthylmethylamine hydriodide.

Condensing 1-naphthylmethyl chloride or 2-naphthylmethyl bromide (Chapman and Williams, *J.*, 1952, 5044) with 2-anilino-, 2-ethylamino-, or 2-methylamino-ethanol gave the alcohols corresponding to the required halogeno-compounds. The alcohols were converted into chlorides by the action of phosphorus pentachloride in dry chloroform, into bromides by using phosphorus tribromide similarly, and into iodides by using phosphorus tri-iodide. The iodide (I; R = Ph) was obtained by Finkelstein's reaction (*Ber.*, 1910, **43,** 1528) from the bromo-compound (cf. Geissman *et al.*, *loc. cit.*). The compounds were usually obtained as hydrogen halide salts. Synthesis of the fluoro-compounds proved more difficult. Condensation of 1-naphthylmethyl chloride or 2-naphthylmethyl bromide with an excess of anhydrous ethylamine or methylamine gave *N*-ethyl(or methyl)-1- or -2-naphthylmethylamines. By utilising the difference in reactivity between CH_2F

and CH_2Br, these secondary amines could be converted into the required fluorine-containing tertiary amines by condensation with 0·5 mol. of 1-bromo-2-fluoroethane in boiling ethyl methyl ketone. Only one of these (namely, I; R = Me, X = F) readily gave crystalline salts.

The pharmacological properties of these compounds are fully described by Graham and Lewis (*Brit. J. Pharmacol.*, 1953, **18**, 54). When R = Ph, or when R = Me or Et and X = F, the compounds (I and II) do not inhibit the action of adrenaline, and antihistamine activity is very small. Mobility of the halogen is clearly a necessary condition for pharmacological activity. The same condition is, of course, also necessary but not sufficient for cyclisation to an ethyleneiminium ion. Moreover, variation of halogen is as important as other structural changes in influencing activity (for details see Graham and Lewis, *loc. cit.*).

Evidence relating to the formation, structure and stability, and pharmacological rôle of ethyleneiminium ions derived from these halogeno-amines will be discussed later.

Experimental

Preparation of Intermediates.—1-Naphthylmethyl chloride was prepared by the method given in " Organic Reactions," John Wiley and Sons, Inc., New York, 1942, Vol. 1, p. 70, and 2-naphthylmethyl bromide by Chapman and Williams' method (*J.*, 1952, 5044). 2-Anilinoethanol was prepared by Dashen and Brewster's method (*Trans. Kansas Acad. Sci.*, 1937, **40**, 103), *viz.*, interaction of aniline and 40% (w/v) aqueous ethylene chlorohydrin at 100° for 6 hr. 2-Ethyl- and 2-methyl-aminoethanol were prepared by Knorr and Schmidt's and Knorr and Matthes' methods respectively (*Ber.*, 1898, **31**, 1072, 1069). 1-Bromo-2-fluoroethane was prepared by Saunders, Stacey, and Wilding's method (*J.*, 1949, 773) or by Hoffmann's method (*J. Org. Chem.*, 1950, **15**, 430).

2-(N-1′-*Naphthylmethyl*-N-*phenylamino*)*ethanol* (I; R = Ph, X = OH).—1-Naphthylmethyl chloride (26 g., 0·15 mole) was added with stirring to a mixture of 2-anilinoethanol (26 g., 0·19 mole), water (50 c.c.), and sodium hydrogen carbonate (16 g., 0·19 mole). After the initial reaction had subsided the mixture was heated at 100° (4 hr.) and, after cooling, ethanol was added until the mixture was homogeneous. On further cooling the crude substituted aminoethanol separated and was filtered off. On exposure to air it rapidly became green, but could be decolorised chromatographically on alumina. The crude material, m. p. 77—85°, is adequate for subsequent syntheses.

2-(N-1′-*Naphthylmethyl*-N-*phenylamino*)*ethanol picrate* (from ethanol) had m. p. 128·5—129·5° (Found: C, 59·0; H, 4·6; N, 11·3. $C_{25}H_{22}O_8N_4$ requires C, 59·3; H, 4·4; N, 11·1%).

N-2-*Halogenoethyl*-N-*phenyl*-1′-*naphthylmethylamines* (I; R = Ph, X = Cl, Br, or I).—Adding, during 1 hr., a solution, which had been decolorised chromatographically, of *N*-1′-naphthylmethyl-*N*-phenyl-2-aminoethanol (13·6 g., 0·05 mole) in dry (K_2CO_3) chloroform (50 c.c.) to a stirred suspension of phosphorus pentachloride (10·3 g., 0·05 mole) in dry chloroform at 0°, followed by boiling for 2—3 hr. gave, after distillation of chloroform and phosphoryl chloride at 15 mm., N-2-*chloroethyl*-N-*phenyl*-1′-*naphthylmethylamine*, a green oil, which on crystallisation from ethanol had m. p. 103·5—104° (yield 50%) (Found: C, 76·7; H, 6·05; N, 4·9; Cl, 12·0. $C_{19}H_{18}NCl$ requires C, 77·1; H, 6·1; N, 4·75; Cl 12·0%).

N-2-*Bromoethyl*-N-*phenyl*-1′-*naphthylmethylamine* (crystallised from ethanol or acetone) was prepared similarly in 65% yield (a 50% excess of phosphorus tribromide was used), had m. p. 128° (Found: C, 67·2; H, 5·5; N, 3·9; Br, 23·3. $C_{19}H_{18}NBr$ requires C, 67·0; H, 5·3; N, 4·1; Br, 23·5%). This compound was converted (96% yield) into N-2-*iodoethyl*-N-*phenyl*-1′-*naphthylmethylamine* [crystallised from acetone or light petroleum (b. p. 60—80°)], m. p. 152·5—153°, by heating it with sodium iodide in acetone (cf. Finkelstein, *Ber.*, 1910, **43**, 1528) (Found: C, 58·9; H, 4·8; N, 3·7; I, 32·9. $C_{19}H_{18}NI$ requires C, 58·9; H, 4·7; N, 3·6; I, 32·8%).

2-[N-*Ethyl*(*or Methyl*)-N-1′-*naphthylmethylamino*]*ethanol* (cf. B.P. 641,454).—Stirring 2-ethylaminoethanol (60 g., 0·67 mole), water (150 c.c.), 1-naphthylmethyl chloride (120 g., 0·67 mole), and potassium carbonate (100 g., 0·85 mole) at 100° for 8 hr. gave, after acidification, extraction of neutral material with ether, and basification, a 72% yield of 2-(*N*-ethyl-*N*-1′-naphthylmethylamino)ethanol, b. p. 122°/0·001 mm. (lit., 187°/5 mm.), n_D^{20} 1·5900 [*picrate*, m. p. 103·5—104° (Found: C, 54·7; H, 4·9; N, 12·6. $C_{21}H_{22}O_8N_4$ requires C, 55·0; H, 4·8; N, 12·2%)]. *N*-2-(Methyl-*N*-1′-naphthylmethylamino)ethanol, b. p. 125°/0·004 mm. (lit., 172°/5 mm.), was similarly prepared (61%) [*picrate*, m. p. 96° (Found: C, 53·8; H, 4·4; N, 12·4. $C_{20}H_{20}O_8N_4$ requires C, 54·1; H, 4·5; N, 12·6%)].

N-*Ethyl*(*or Methyl*)-1′-*naphthylmethylamine*.—1-Naphthylmethyl chloride (30 g., 0·17 mole) was added dropwise to anhydrous ethylamine (50 g., 0·90 mole) at its b. p., under a reflux condenser cooled to −10°, after which the mixture was kept at room temperature for 12 hr. when ethylamine hydrochloride separated. The product was acidified with dilute hydrochloric acid, any insoluble material being extracted with ether. The oily base was then liberated with aqueous sodium hydroxide, extracted with ether, and dried (Na_2SO_4), the ether removed, and the N-*ethyl*-1-*naphthylmethylamine* (65%) distilled; it had b. p. 88°/0·0007 mm., n_D^{20} 1·6180 [*hydrochloride*, m. p. 171° (Found: C, 69·4; H, 7·2; N, 6·4; Cl, 16·2. $C_{13}H_{15}N$,HCl requires C, 70·4; H, 7·2; N, 6·3; Cl, 16·0%); *hydrobromide*, m. p. 143° (Found: Br, 29·4. $C_{13}H_{15}N$,HBr requires Br, 30·0%)].

N-*Methyl*-1-*naphthylmethylamine*, prepared similarly (69%), had b. p. 90°/0·03 mm., n_D^{20} 1·6180 [*hydrochloride*, m. p. 185° (Found: C, 69·6; H, 6·85; N, 6·7; Cl, 16·9. $C_{12}H_{13}N$,HCl requires C, 69·4; H, 6·8; N, 6·7; Cl, 17·1%)].

N-*Ethyl*(*or Methyl*)-N-2-*halogenoethyl*-1′-*naphthylmethylamines* (I; R = Et or Me; X = F, Cl, Br, or I).—*N*-Ethyl-*N*-1′-naphthyl-2-aminoethanol (21·8 g., 0·095 mole) in dry chloroform was added dropwise to phosphorus pentachloride (20·8 g., 0·1 mole) suspended in dry chloroform, and the mixture boiled until no more hydrogen chloride was evolved. Chloroform and phosphoryl chloride were distilled off at 15 mm., and the product crystallised from dry ethanol (yield 95%).

N-2-Chloroethyl-*N*-ethyl-1′-naphthylmethylamine hydrochloride had m. p. 166·5—167° (lit., 171°) (Found: C, 63·2; H, 6·8; N, 4·9; Cl, 24·9. Calc. for $C_{15}H_{18}NCl$,HCl: C, 63·4; H, 6·7; N, 4·9; Cl, 24·9%).

N-2 Chloroethyl-*N*-methyl-1′-naphthylmethylamine hydrochloride, prepared similarly (100%), had m. p. 187° (lit., 198°) (Found: C, 61·8; H, 6·5; N, 5·5; Cl, 25·9. Calc. for $C_{14}H_{16}NCl$,HCl: C, 62·2; H, 6·3; N, 5·2, Cl, 26·2%).

N-2-Bromoethyl-*N*-ethyl-1′-naphthylmethylamine hydrobromide was similarly prepared, by using phosphorus tribromide (0·15 mol.) [Rieveschl and Coleman (*loc. cit.*) heated the corresponding substituted aminoethanol with 40% aqueous hydrobromic acid to obtain the same product], m. p. 167° (lit., 167°) (yield 94%) (Found: C, 47·9; H, 5·3; N, 3·9; Br, 42·5. Calc. for $C_{15}H_{18}NBr$,HBr: C, 48·3; H, 5·1; N, 3·75; Br, 42·8%).

N-2-*Bromoethyl*-N-*methyl*-1′-*naphthylmethylamine hydrobromide*, similarly prepared (63%), had m. p. 191° (Found: C, 46·9; H, 4·8; N, 4·1; Br, 44·0. $C_{14}H_{16}NBr$,HBr requires C, 46·8; H, 4·8; N, 3·9; Br, 44·5%).

N-*Ethyl*-N-2-*iodoethyl*-1′-*naphthylmethylamine hydriodide* was similarly prepared by using phosphorus tri-iodide, the product being precipitated from ethanol with dry (sodium) ether and slowly recrystallised from dry ethanol (yield 56%); it had m. p. 165·5—166° (Found: C, 38·5; H, 4·2; N, 3·2; I, 54·3. $C_{15}H_{18}NI$,HI requires C, 38·6; H, 4·1; N, 3·0; I, 54·4%). A mixture of red phosphorus and iodine was found unsuitable for this preparation.

N-2-*Iodoethyl*-N-*methyl*-1′-*naphthylmethylamine hydriodide*, prepared similarly (49%), had m. p. 147·5 (Found: C, 36·7; H, 3·7; N, 2·9; I, 56·4. $C_{14}H_{16}NI$,HI requires C, 37·1; H, 3·8; N, 3·1; I, 56·0%).

N-*Ethyl*(*or Methyl*)-N-2-*fluoroethyl*-1′-*naphthylmethylamine*.—1-Bromo-2-fluoroethane (14·1 g., 0·11 mole) and *N*-ethyl-1-naphthylmethylamine (42 g., 0·22 mole) were heated under reflux in ethanol at the b. p. (63 hr.), the ethanol distilled at 15 mm., and the residue made alkaline with sodium hydroxide. The resultant oil was extracted with ether and, after drying (Na_2SO_4) and removal of ether, the mixture was acetylated by boiling acetic anhydride and a trace of sulphuric acid (4 hr.). The product was poured into ice-water, the insoluble material extracted with ether, the residue made alkaline, the oil extracted with ether and dried (Na_2SO_4), and the ether removed.

N-*Ethyl*-N-2-*fluoroethyl*-1′-*naphthylmethylamine* was then distilled (b. p. 116—120°/0·0018 mm.; yield, 6 g., 25% based on 1-bromo-2-fluoroethane) (Found: C, 77·4; H, 7·9; N, 6·2. $C_{15}H_{18}NF$ requires C, 77·9; H, 7·8; N, 6·8%). This base does not readily form crystalline salts with mineral acids or the stronger organic acids and only with difficulty forms a picrate, m. p. 144·5°.

N-Methyl-1-naphthylmethylamine (15 g., 0·08 mole) was boiled under reflux with 1-bromo-2-fluoroethane (14 g., 0·11 mole) and sodium hydrogen carbonate (9·3 g., 0·11 mol.) in ethyl methyl ketone (50 c.c.) for 35 min. The hot reaction mixture was filtered, and excess of 1-bromo-2-fluoroethane and solvent were removed at 15 mm.

N-2-*Fluoroethyl*-N-*methyl*-1′-*naphthylmethylamine* was then distilled (b. p. 99—102°/0·001 mm.; n_D^{20} 1·5840; yield 75%) (Found: C, 77·5; H, 8·1; N, 6·7. $C_{14}H_{16}NF$ requires C, 77·4;

H, 7·4; N, 6·45%). The *hydrochloride* (from dry ethanol), m. p. 143° (Found: C, 66·4; H, 7·2; N, 5·55; Cl, 14·0. $C_{14}H_{16}NF,HCl$ requires C, 66·3; H, 6·8; N, 5·5; Cl, 14·0%), was obtained by the action of dry hydrogen chloride on the base dissolved in benzene.

2-[N-*Ethyl*(*or Methyl*)-N-2′-*naphthylmethylamino*]*ethanol* (II; R = Et or Me, X = OH).—2-Naphthylmethyl bromide (125 g., 0·57 mole) was condensed with 2-ethylaminoethanol (50 g., 0·56 mole) as for the α-isomer, to give 2-(N-*ethyl*-N-2′-*naphthylmethylamino*)*ethanol* (69%), b. p. 138°/0·007 mm., n_D^{18} 1·5896 (Found: N, 5·85. $C_{15}H_{19}ON$ requires N, 6·1%). 2-(N-*Methyl*-N-2′-*naphthylmethylamino*)*ethanol*, b. p. 120°/0·003 mm., n_D^{20} 1·6014, was similarly prepared (62%) (Found: N, 6·5. $C_{14}H_{17}ON$ requires N, 6·5%).

N-*Ethyl*(*or Methyl*)-2-*naphthylmethylamine*.—Condensing ethylamine or methylamine with 2-naphthylmethyl bromide dissolved in an equal weight of benzene, but otherwise as in the preparation of the α-isomers, gave *N*-ethyl-2-naphthylmethylamine (50%), b. p. 89—92°/0·002 mm., n_D^{18} 1·6099 [*hydrochloride*, m. p. 230° (Found: C, 70·6; H, 7·4; N, 6·0; Cl, 15·95%)], and *N*-methyl-2-naphthylmethylamine (40%), b. p. 90°/0·02 mm., n_D^{14} 1·6168 [*hydrochloride*, m. p. 227° (Found: C, 69·4; H, 6·85; N, 6·7; Cl, 16·9%)], respectively. If pure solid 2-naphthylmethyl bromide was condensed with anhydrous ethylamine, a mixture of the above secondary amine with the corresponding tertiary amine was produced.

N-*Ethyl*(*or Methyl*)-N-2-*halogenoethyl*-2′-*naphthylmethylamines* (II; R = Et or Me, X = F, Cl, Br, or I).—The following were prepared as for the α-isomers, except where stated. N-2-*Chloroethyl*-N-*ethyl*-2′-*naphthylmethylamine hydrochloride*, m. p. 191·5° (78%) (Found: C, 63·6; H, 6·8; N, 4·8; Cl, 24·8%). N-2-*Chloroethyl*-N-*methyl*-2′-*naphthylmethylamine hydrochloride*, m. p. 176·5° (80%) (Found: C, 61·8; H, 6·5; N, 5·3; Cl, 26·2%). N-2-*Bromoethyl*-N-*ethyl*-2′-*naphthylmethylamine hydrobromide*, m. p. 196·5° (67%) (Found: C, 48·6; H, 5·4; N, 3·7; Br, 43·6%). N-2-*Bromoethyl*-N-*methyl*-2′-*naphthylmethylamine hydrobromide*, m. p. 183·5° (72%) (Found: C, 47·1; H, 5·3; N, 4·05; Br, 43·9%). N-*Ethyl*-N-2-*iodoethyl*-2′-*naphthylmethylamine hydriodide*, m. p. 179° (54%) Found: C, 38·8; H, 4·2; N, 3·1; I, 54·6%). N-2-*Iodoethyl*-N-*methyl*-2′-*naphthylmethylamine hydriodide*, m. p. 189° (55%) (Found: C, 37·2; H, 3·7; N, 3·2; I, 56·2%).

Experiments with Mr. J. F. A. Williams, B.Sc.—N-*Ethyl*(*or Methyl*)-N-2-*fluoroethyl*-2′-*naphthylmethylamine*. *N*-Ethyl-2-naphthylmethylamine (25 g., 0·13 mole) and 1-bromo-2-fluoroethane (8·6 g., 0·067 mole) in ethyl methyl ketone (30 c.c.) were boiled for 4 hr. The mixture was filtered and cooled, dry ether (100 c.c.) was added, and the product again filtered. The solvents were removed, the residue was dissolved in 6N-hydrochloric acid, and insoluble material extracted with methylene dichloride. The residue was made alkaline with sodium hydroxide, the oil formed extracted with ether and dried (Na_2SO_4), the ether removed, and the residue distilled, giving N-*ethyl*-N-2-*fluoroethyl*-2′-*naphthylmethylamine*, b. p. 112°/0·004 mm., n_D^{22} 1·5680 (yield, 52%) (Found: C, 78·3; H, 7·80; N, 6·35%).

N-2-*Fluoroethyl*-N-*methyl*-2′-*naphthylmethylamine*, b. p. 115°/0·04 mm., n_D^{20} 1·5772 (yield, 52%) (Found: C, 76·6; H, 7·25; N, 6·25%), was prepared similarly.

N-1-Naphthylmethylaniline was prepared as an intermediate for a synthesis which proved unsuccessful, as follows. Aniline (372 g., 4 moles), 1-naphthylmethyl chloride (176·5 g., 1·0 mole), and water (100 c.c.) were heated with stirring at 100° for 8 hr. The cooled mixture was filtered, and the oily layer separated and washed with aqueous sodium chloride solution. After drying (Na_2SO_4), the aniline was removed at 15 mm., and N-1-*naphthylmethylaniline* (220 g., 94%) was distilled and crystallised from ethanol; it had m. p. 64°, b. p. 162—164°/0·003 mm. (Found: C, 87·5; H, 6·7; N, 6·0. $C_{17}H_{15}N$ requires C, 87·5; H, 6·5; N, 6·0%).

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