769. *Synthesis of* NN-*Dialkyl*-N'-*benzyl*(*or -ethyl*)-N'-1(*or* 2)-*naphthylethylenediamines as Potential Histamine Antagonists.*

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The preparation and pharmacological properties are described of eight fully substituted ethylenediamines containing the group $\cdot[CH_2]_2\cdot NR_2$ (R = Me, Et), and bearing 1- or 2-naphthyl radicals, and ethyl or benzyl radicals on the second nitrogen atom. None of them is very active as a histamine antagonist.

DURING the last two decades the synthesis of compounds specifically antagonising the effects of histamine on the animal organism has been intensively studied (for recent reviews see Idson, *Chem. Reviews*, 1950, **47**, 307; Adamson, *Chem. and Ind.*, 1951, 2). The object of the investigation to be described is to explore a small previously unexamined portion of the field.

Ethylenediamines fully substituted on the nitrogen atoms were early shown to be active against histamine (Staub, *Ann. Inst. Pasteur*, 1939, **63**, 400, 420, 485), and in particular " Antergan " (I) proved to have properties which, despite unwanted side effects, marked the first significant step in the therapy of allergic diseases.

$Ph\cdot N(CH_2Ph)\cdot[CH_2]_2\cdot NMe_2$ (I) $\quad 1\text{-}C_{10}H_7\cdot NR'\cdot[CH_2]_2\cdot NR_2$ (II) $\quad 2\text{-}C_{10}H_7\cdot NR'\cdot[CH_2]_2\cdot NR_2$ (III)

It seemed worthwhile, therefore, to see whether loading one aryl residue more heavily than previously, as in (II) and (III) (R' = CH_2Ph; R = Me, Et), would lead to a substance with an action more persistent than that of " Antergan." In a related field an analogous structural alteration had been shown to give an increase in activity, *viz.*, " Dibenamine," $(CH_2Ph)_2N\cdot CH_2\cdot CH_2\cdot Cl$, is less active than $1\text{-}C_{10}H_7\cdot CH_2\cdot NEt\cdot CH_2\cdot CH_2Cl$ (Nickerson and Gump, *J. Pharmacol.*, 1949, **67**, 25). After most of the work had been completed, there appeared an account of a more comprehensive investigation on similar lines (Grail, Tenenbaum, Tolstoouhov, Duca, Reinhard, Anderson, and Scudi, *J. Amer. Chem. Soc.*, 1952, **74**, 1313), to which the present paper is supplementary.

Synthesis of compounds of the types (II) and (III) gave no trouble when R' = CH_2Ph, R = Me or Et, and of (II) when R' = Et, R = Me or Et. Heating secondary alkylarylamines with sodamide in toluene or xylene yields sodium salts, which may be expeditiously condensed with 2-dialkylaminoethyl chlorides to yield the required compounds (cf. Leonard and Solmssen, *ibid.*, 1948, **70**, 2066). However, *N*-ethyl-2-naphthylamine presented unexpected difficulties, for the intermediate sodium salt proved unstable towards even traces of oxygen. The preparation and handling this salt are described in the Experimental section.

In a provisional pharmacological report, J. D. P. Graham, G. P. Lewis, and R. S. Tonks, of the Department of Pharmacology, Welsh National School of Medicine, Cardiff, report that the structural variation studied has virtually abolished anti-histamine activity, and that in accordance with common experience the side chain $\cdot[CH_2]_2\cdot NMe_2$ affords greatest activity. For the compounds (II) and (III) where R' = benzyl, replacing 1-naphthyl by 2-naphthyl or R = Me by R = Et roughly halves the toxicity in each case, whereas the opposite is true for compounds in which R' = Et. A fuller account of the

pharmacological investigation will be published elsewhere, but preliminary quantitative data are given in the Experimental section.

Because of the insolubility and lack of the desired activity of this class of compound, the investigation is being developed in other directions.

Experimental

Analyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected. $L.D._{50}$'s after 1 hour (mg. per kg., mice), by intra-peritoneal administration in phosphate-citrate buffer at pH 5·4, are given below.

2-Dimethyl- and 2-Diethyl-aminoethyl Chloride Hydrochloride.—A procedure similar to that described in *Org. Synth.*, **31**, 37, but worked out before that account appeared, was adopted after considerable investigation, details in the literature being unsatisfactory. We found it advisable, however, to distil the thionyl chloride before use to remove hydrogen chloride, to dry commercial 2-dialkylaminoethanols over barium oxide, then fractionate them (25-cm. Fenske column), and to carry out the reaction in dry benzene. The free bases were best liberated from their salts by Knorr's method (*Ber.*, 1904, **37**, 3511).

N-Benzyl-N'N'-dimethyl-N-1-naphthylethylenediamine (II; R' = CH_2Ph, R = Me).—1- and 2-Benzylaminonaphthalene were prepared by Zechmeister and Truka's method (*Ber.*, 1930, **63**, 2883), *viz.*, reduction of the corresponding benzylidene compounds with magnesium and methanol, in 89 and 93% yields respectively. Sodamide (4·1 g., 0·11 mol.) was stirred with a boiling solution of 1-benzylaminonaphthalene in dry toluene (5 hours), whereupon the yellow sodium salt separated. A solution of 2-dimethylaminoethyl chloride (10·8 g., 0·11 mol.) in dry toluene (10 c.c.) was added dropwise (4 hours) and the mixture boiled for a further 6 hours. After filtration and removal of toluene at 15 mm., an excess of hydrochloric acid (50% w/v) was added and unchanged 1-benzylaminonaphthalene filtered off. Addition of aqueous sodium hydroxide, extraction with ether, drying (Na_2SO_4), and removal of ether yielded (61%) as a viscous yellow oil, *N-benzyl-N'N'-dimethyl-N-1-naphthylethylenediamine*, b. p. 146°/0·007 mm., n_D^{20} 1·6090, $L.D._{50}$ 135 (Found: C, 82·7; H, 8·3; N, 8·4. $C_{21}H_{24}N_2$ requires C, 82·8; H, 7·9; N, 9·2%); the *picrate* (from ethanol) had m. p. 173·5° (Found: C, 60·9; H, 5·0; N, 13·6. $C_{27}H_{27}O_7N_5$ requires C, 60·7; H, 5·1; N, 13·1%); the *monohydrobromide* (from alcohol) had m. p. 170° (Found: Br, 21·1. $C_{21}H_{24}N_2$,HBr requires Br, 20·7%).

N-Benzyl-N'N'-dimethyl-N-2-naphthylethylenediamine (III; R' = CH_2Ph, R = Me) was prepared (65%) as was the 1-naphthyl compound, save that the sodium salt of 2-benzylaminonaphthalene was formed at the b. p. of dry xylene and the mixture cooled to 110° before addition of 2-dimethylaminoethyl chloride, which is unstable at the b. p. of xylene. *N-Benzyl-N'N'-dimethyl-N-2-naphthylethylenediamine* was a viscous yellow oil, b. p. 146°/0·007 mm., n_D^{20} 1·6302, $L.D._{50}$ 265 (Found: C, 82·1; H, 8·0; N, 9·45%). The *picrate* (from acetone–ethanol) had m. p. 110° (decomp.) (Found: N, 12·9%), and the *monohydrobromide* (from ethanol) had m. p. 186° (Found: Br, 20·9%).

N-Benzyl-N'N'-diethyl-N-1-naphthylethylenediamine (II; R' = CH_2Ph, R = Et), prepared (55%) as for the dimethyl analogue, had b. p. 140°/0·003 mm., n_D^{20} 1·5974, $L.D._{50}$ 62·5 (Found: C, 83·6; H, 8·3; N, 8·6. $C_{23}H_{28}N_2$ requires C, 83·1; H, 8·5; N, 8·4%). Its *monohydrobromide monohydrate* (from aqueous ethanol) had m. p. 191° (Found: Br, 18·7. $C_{23}H_{28}N_2$,HBr,H_2O requires Br, 18·5%).

The *2-naphthyl* isomer, prepared (55%) as for the dimethyl analogue, had b. p. 140°/0·0015 mm., n_D^{20} 1·6110, $L.D._{50}$ 128 (Found: C, 82·7; H, 8·7; N, 8·4%).

Its *monohydrobromide* (from ethanol) had m. p. 165° (Found: Br, 20·2. $C_{23}H_{28}N_2$,HBr requires Br, 19·2%).

N-Ethyl-N'N'-dimethyl-N-1-naphthylethylenediamine (II; R' = Et, R = Me).—1-Ethylaminonaphthalene (from British Drug Houses Ltd.; 27·6 g., ~0·16 mol.) was dried (KOH) and redistilled, and was dissolved in xylene (320 c.c.), and sodamide (6·5 g., ~0·16 mol.) was added. The mixture was boiled with stirring for 7 hours, then cooled to ~90°, and dimethylaminoethyl chloride (20 g., 0·14 mol.) slowly added and the mixture boiled for 1 hour. After filtration of the hot liquor and removal of the xylene at 15 mm., the residue was fractionated through a 9" heated Vigreux column, or a 9" column packed with Dixon gauze rings fitted with a variable-temperature vapour-jacket. Refractionation yielded (34%) *N-ethyl-N'N'-dimethyl-N-1-naphthylethylenediamine*, a brown oil with blue fluorescence, b. p. 174—175°/0·13 mm., n_D^{23} 1·5741, $L.D._{50}$ 121 (Found: C, 79·2; H, 9·1; N, 11·7. $C_{16}H_{22}N_2$ requires C, 79·3; H, 9·1; N, 11·6%). It gave a *dipicrate monohydrate*, m. p. 162° (decomp.) (Found: C, 45·9; H, 3·55; N, 15·6. $C_{28}H_{30}O_{15}N_8$ requires C, 46·0; H, 4·11; N, 15·3%).

N-*Ethyl*-N′N′-*dimethyl*-N-2-*naphthylethylenediamine* (III; R′ = Et, R = Me).—This was similarly prepared (15%) from 2-ethylaminonaphthalene (Hickinbottom " Reactions of Organic Compounds," Longmans, Green, & Co., London, 1936, p. 300). It is essential to prepare the sodium salt under oxygen-free nitrogen and advisable to keep the temperature about 50° and not to stir the mixture. The yellow sodium salt is readily formed at room temperature and is noticeably soluble in xylene. The dimethylaminoethyl chloride was added to the mixture at 50° after 4 hours, and the reaction completed at 80° during 1 hour. N-*Ethyl*-N′N′-*dimethyl*-N-2-*naphthylethylenediamine* was a brown oil, with blue fluorescence, especially noticeable in ethanolic solution, and had b. p. 159°/0·08 mm., n_D^{18} 1·6100, L.D.$_{50}$ 52 (Found : C, 79·4; H, 9·0; N, 11·3%). Its *dipicrate* (from ethanol) had m. p. 174—175° (decomp.; sinters at ~160°) (Found : C, 47·8; H, 3·95; N, 15·5. $C_{28}H_{28}O_{14}N_8$ requires C, 47·2; H, 3·55; N, 15·7%).

NN′N′-*Triethyl*-N-1-*naphthylethylenediamine*, prepared (42%) as for the dimethyl analogue, had b. p. 182°/0·13 mm., n_D^{21} 1·5598, L.D.$_{50}$ 65 (Found : C, 80·2; H, 9·3; N, 10·5. $C_{18}H_{26}N_2$ requires C, 80·0; H, 9·6; N, 10·4%). Its *dipicrate* (from ethanol) had m. p. 110—111° (Found : C, 49·3; H, 4·4; N, 14·9. $C_{30}H_{32}O_{14}N_8$ requires C, 48·7; H, 4·3; N, 15·1%).

The 2-*naphthyl* isomer, prepared (16%) under the same rigorous conditions as the dimethyl analogue, had b. p. 180°/0·2 mm., n_D^{17} 1·5950, L.D.$_{50}$ 36 (Found : C, 80·1; H, 9·7; N, 10·7%), and its *dipicrate* (from ethanol) had m. p. 160° (Found : C, 49·4; H, 4·3; N, 15·4%).

The last two bases are similar in colour and fluorescence to the dimethyl analogues.

Pharmacological Activity.—Antihistamine activity determined by the cat blood pressure or guinea-pig aerosol method is very slight for all the compounds except (II; R = Me, R′ = CH_2Ph) which has an activity of about 1/20 of that of " Neoantergan."

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