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Adrenergic Blocking Agents. I. Ethylenediamines[1]

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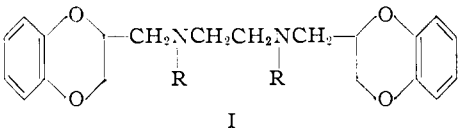
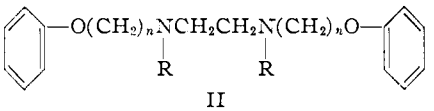
The synthesis of N,N'-substituted ethylenediamines in which the substituents are 1,4-benzodioxan-2-ylmethyl, 2-phenoxyethyl or 3-phenoxypropyl groups as well as that of corresponding derivatives of N,N'-dimethyl and N,N'-diethylethylenediamines is reported. Some of these compounds have marked adrenolytic and sympatholytic activity by oral and parenteral routes of administration.

Ethylenediamines of formulas I and II were prepared as part of a general program on new hypotensive agents which has been under way in these laboratories for several years. In I and II, R may be H, CH_3 or C_2H_5; and in II, n is 2 or 3.

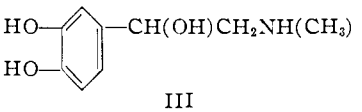


I

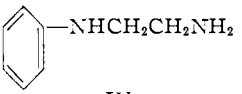


II

Ethylenediamines structurally related to epinephrine (III) often resemble this adrenal hormone in pharmacological activity. For example, N-phenylethylenediamine (IV) has vasopressor activity of a low order.[2] On the other hand, N-alkylation of IV causes a progressive decrease in vasopressor potency and finally the appearance of weak adrenolytic activity.[3] Bovet[4] has pointed out, however,

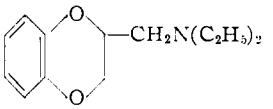


III

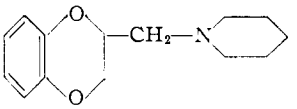


IV

that relatively simple compounds of this type are less effective adrenergic blocking agents than are more complex substances having multiple ring structures such as diethylaminomethylbenzodioxan (883F, V), piperidinomethylbenzodioxan (933F, piperoxan, VI) and certain alkaloids.



V



VI

It occurred to us that ethylenediamines in which both nitrogen atoms carry a benzodioxanylmethyl group should be potent adrenergic blocking agents. It will be seen that molecules like I are composed of two identical halves, each of which closely resembles a known adrenergic blocking agent (such as 883F, V). Such double molecules of formulas I and II are described in this paper; related 1,4-substituted piperazines have also been prepared and are described in paper II.[5]

The reaction of N,N'-dimethyl(or diethyl)-ethylenediamine with haloalkyl compounds in refluxing aqueous sodium hydroxide gave the disubstituted derivatives. 2-Chloromethyl-1,4-benzodioxan reacted with ethylenediamine under these conditions to give the N,N'-disubstituted compound, but in the reaction of phenoxyalkyl bromides with ethylenediamine, the only products isolated were the N,N,N',N'-tetrasubstituted ethylenediamines. To obtain N,N'-bis-(phenoxyalkyl)-ethylenediamines, phenoxyalkyl bromides were treated with ethylenebisbenzenesulfonamide, followed by hydrolysis of the resulting product.

The results of pharmacological studies of some of the new compounds have been reported.[6] Representative data are included in Table I. The most active compounds are the N,N'-bis-(1,4-benzodioxan-2-ylmethyl)- and N,N'-bis-(2-phenoxyethyl)-ethylenediamines. They were shown to retain a large part of their activity when administered orally instead of parenterally to dogs.

Experimental[7]

General Procedure.—An aqueous solution of ethylenediamine (or an N,N'-dialkylethylenediamine) was refluxed with two molecular equivalents of a haloalkyl compound and two or more molecular equivalents of sodium hydroxide for 16 to 48 hours. The product was isolated as the hydrochloride as illustrated for N,N'-bis-(2-phenoxyethyl)-N,N'-diethylethylenediamine.

Yields by this method were usually satisfactory (50–80%) when the halide was a phenoxyalkyl bromide; but with 2-chloromethyl-1,4-benzodioxan, yields were lower (5–30%), and the products were difficult to purify due to the lesser reactivity of this halide and the presence of monoalkylated derivatives. For this reason, modifications of the general method were necessary in some cases, as illustrated for N,N'-bis-(1,4-benzodioxan-2-ylmethyl)-N,N'-diethylethylenediamine.

N,N'-Bis-(2-phenoxyethyl)-N,N'-diethylethylenediamine Dihydrochloride (McN-311).—A mixture of 40.2 g. (0.2 mole) of 2-phenoxyethyl bromide (β-bromophenetole), 18.9 g. (0.1 mole) of N,N'-diethylethylenediamine dihydrochloride[8] and 16 g. (0.4 mole) of sodium hydroxide in 50 ml. of water was refluxed for 48 hours. The cooled reaction mixture was extracted with ether, and the ether extract was shaken with dilute hydrochloric acid. The aqueous acid layer was made alkaline with potassium carbonate and extracted with ether. Addition of hydrogen chloride to the dried ether extract precipitated a crude hydrochloride which

(1) Presented before the Division of Medicinal Chemistry at the 124th Meeting of the American Chemical Society, Chicago, Ill., September 9, 1953.

(2) D. Bovet, Y. de Lestrange and E. Fourneau, *Compt. rend. soc. biol.*, **130**, 1192 (1939).

(3) D. Bovet, Y. de Lestrange and E. Fourneau, *ibid.*, **136**, 386 (1942).

(4) D. Bovet and F. Bovet-Nitti, "Médicaments du Système Nerveux Végétatif," S. Karger, Basel, 1948, pp. 216, 275.

(5) A. P. Swain and S. K. Naegele, THIS JOURNAL, **76**, 5089 (1954).

(6) D. F. Marsh and J. F. O'Leary, *Federation Proc.*, **12**, 348 (1953).

(7) Melting points are uncorrected.

(8) P. Schneider, *Ber.*, **28**, 3077 (1895).

TABLE I

ETHYLENEDIAMINE DIHYDROCHLORIDES, $RR'NCH_2CH_2NRR'\cdot 2HCl$

McN-	R	R'	S[a], mg./kg.	A[b], mg./kg.	L[c], mg./kg.	M.p., °C.[d]	Formula	Nitrogen, %[e] Calcd.	Found
267	$C_9H_9O_2$[f]	H	0.6	0.6	80	288 dec.	$C_{20}H_{24}N_2O_4\cdot 2HCl$	6.5	6.4
323	$PhOCH_2CH_2$	H	4	0.7	160	273 dec.	$C_{18}H_{24}N_2O_2\cdot 2HCl$	7.5	7.4
312	$C_9H_9O_2$[f]	CH_3	4	2	100	224–225	$C_{22}H_{28}N_2O_4\cdot 2HCl$	6.1	6.2
292	$PhOCH_2CH_2$	$PhOCH_2CH_2$	4	4	280	202–203	$C_{34}H_{40}N_2O_4\cdot 2HCl$	4.6	4.6[i]
320	$PhOCH_2CH_2$	CH_3	6	4	120	222 dec.	$C_{20}H_{28}N_2O_2\cdot 2HCl$	7.0	7.0
327	$C_9H_9O_2$[f]	C_2H_5	8	8	180	212 dec.	$C_{24}H_{32}N_2O_4\cdot 2HCl$	5.8	5.7
301	$PhO(CH_2)_3$	CH_3	8	8	120	230–231	$C_{22}H_{32}N_2O_2\cdot 2HCl$	6.5	6.3
311	$PhOCH_2CH_2$	C_2H_5	10	6	150	166–167	$C_{22}H_{32}N_2O_2\cdot 2HCl$	6.5	6.7
315	$PhO(CH_2)_3$	C_2H_5	16	8	80	159–160	$C_{24}H_{36}N_2O_2\cdot 2HCl$	6.1	6.2
296	$PhO(CH_2)_3$	$PhO(CH_2)_3$	> 16[g]	8	< 120[h]	222–223	$C_{38}H_{48}N_2O_4\cdot 2HCl$	4.2	4.2[j]
322	$PhO(CH_2)_3$	H	> 30[g]	16	55	257 dec.	$C_{20}H_{28}N_2O_2\cdot 2HCl$	7.0	6.8
				$RR'NCH_2CH_2NHC_2H_5\cdot 2HCl$					
329	$C_9H_9O_2$[f]	H	8	4	280	252–253 dec.	$C_{16}H_{20}N_2O_2\cdot 2HCl$	9.1	9.2
339	$C_9H_9O_2$[f]	C_2H_5	12	>32[g]	180	129 dec.	$C_{15}H_{24}N_2O_2\cdot 2HCl$	8.3	8.3

[a] Sympatholytic activity; i.v. dose required to prevent 50% of the pressor rise resulting from bilateral carotid occlusion in α-chloralose-anesthetized dogs. [b] Adrenolytic activity; i.v. dose required to prevent 50% of the pressor response (30–60 mm.) of small doses of epinephrine in α-chloralose-anesthetized dogs. [c] Toxicity following intraperitoneal injection in white mice. [d] Uncorrected. [e] Semimicro Kjeldahl. [f] 1,4-Benzodioxan-2-ylmethyl. [g] Less than 50% depression of the pressor rise was obtained at this dose, the highest tested. [h] Not checked at lower doses. [i] Cl, calcd., 11.6; found, 11.5. [j] Calcd.: C, 68.15; H, 7.53. Found: C, 67.50; H, 7.65.

was crystallized twice from a mixture of methanol and ether; yield 32.7 g. (76%), m.p. 166–167°.

Anal. Calcd. for $C_{22}H_{32}N_2O_2\cdot 2HCl$: N, 6.5. Found: N, 6.7.

N-(1,4-Benzodioxan-2-ylmethyl)-N,N'-diethylethylenediamine Dihydrochloride (McN-339) and N,N'-Bis-(1,4-benzodioxan-2-ylmethyl)-N,N'-diethylethylenediamine Dihydrochloride (McN-327).—A mixture of 37 g. (0.2 mole) of 2-chloromethyl-1,4-benzodioxan,[9] 16 g. (0.4 mole) of sodium hydroxide in 50 ml. of water and 18.9 g. (0.1 mole) of N,N'-diethylethylenediamine dihydrochloride was refluxed for 64 hours. The reaction mixture was worked up as described in the general procedure, but the resulting sticky solid dihydrochloride could not be purified by the usual crystallization technique. Instead, the bases were recovered by treatment of the product with excess sodium hydroxide solution and extraction into ether. Distillation of the residue after removal of the ether gave 7.8 g. (29% based on the amine) of **N-(1,4-benzodioxan-2-ylmethyl)-N,N'-diethylethylenediamine**, b.p. 130–134° (0.3–0.4 mm.). Addition of hydrogen chloride to a portion of this base dissolved in ether gave 1.8 g. of the **dihydrochloride (McN-339)**, m.p. 129° dec. after three crystallizations from a mixture of acetone and ether.

Anal. Calcd. for $C_{15}H_{24}N_2O_2\cdot 2HCl$: N, 8.3. Found: N, 8.3.

An ether solution of the dark residue from the distillation was treated with hydrogen chloride. The precipitate was recrystallized to yield 2.1 g. (4.3%) of **N,N'-bis-(1,4-benzodioxan-2-ylmethyl)-N,N'-diethylethylenediamine dihydrochloride**, m.p. 215° dec.

Anal. Calcd. for $C_{24}H_{32}N_2O_4\cdot 2HCl$: N, 5.8. Found: N, 5.7.

N-Benzodioxanylmethyl-N'-ethylethylenediamine (McN-329) was prepared similarly, but none of the disubstituted derivative was isolated. On the other hand, in the preparation of **N,N'-bis-benzodioxanylmethyl-N,N'-dimethylethylenediamine (McN-312)** by the general procedure little or no difficulty was experienced in purifying its dihydrochloride. No attempt was made to separate stereoisomers.

N,N,N',N'-Tetrakis-(2-phenoxyethyl)-ethylenediamine Dihydrochloride (McN-292).—A mixture of 6.3 g. (0.1 mole) of a 95% solution of ethylenediamine, 8 g. (0.2 mole) of sodium hydroxide in 25 ml. of water and 40.2 g. (0.2 mole) of 2-phenoxyethyl bromide was heated at 110° for 48 hours. The reaction mixture was diluted with water and extracted with ether. Addition of dilute hydrochloric acid to the ether extract caused a solid to separate. After one crystallization from methanol, the product weighed 20.9 g. (68% based on the halide). A second crystallization gave 15.1 g., m.p. 202–203°.

Anal. Calcd. for $C_{34}H_{40}N_2O_4\cdot 2HCl$: Cl, 11.6; N, 4.6. Found: Cl, 11.5; N, 4.6.

N,N'-Bis-(2-phenoxyethyl)-N,N'-ethylenebisbenzenesulfonamide (McN-297).—A solution of 34.0 g. (0.1 mole) of N,N'-ethylenebisbenzenesulfonamide,[10] 50.2 g. (0.2 mole) of 2-phenoxyethyl bromide and 8 g. (0.2 mole) of sodium hydroxide in 25 ml. of water and 100 ml. of methanol was refluxed for 7 hours. Crystals which separated on cooling were collected, washed with a little methanol and crystallized from acetone. The yield (18.8 g., 32%) might have been improved by working up the entire reaction mixture. Crystallization of 2 g. of the product from acetone gave 1.1 g., m.p. 136–137°.

Anal. Calcd. for $C_{36}H_{32}N_2O_6S_2$: C, 62.05; H, 5.55; N, 4.8. Found: C, 62.00; H, 5.57; N, 4.8.

N,N'-Bis-(3-phenoxypropyl)-N,N'-ethylenebisbenzenesulfonamide (McN-298) was prepared similarly, m.p. 156–157°.

Anal. Calcd. for $C_{32}H_{36}N_2O_6S_2$: C, 63.13; H, 5.96; N, 4.6. Found: C, 63.23; H, 5.97; N, 4.6.

N,N'-Bis-(2-phenoxyethyl)-ethylenediamine Dihydrochloride (McN-323).—A mixture of 24.8 g. (0.03 mole) of N,N'-bis-(2-phenoxyethyl)-N,N'-ethylenebisbenzenesulfonamide, 300 ml. of freshly distilled hydrobromic acid and 40 g. of phenol was refluxed for 1 hour.[11] The cooled mixture was made alkaline with sodium hydroxide and extracted with ether. Addition of hydrogen chloride to the dried ether extract precipitated a sticky solid which was crystallized twice from aqueous methanol to give 1.6 g. (10%) of the final product, m.p. 277° dec.

Anal. Calcd. for $C_{18}H_{24}N_2O_2\cdot 2HCl$: N, 7.5. Found: N, 7.4.

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(9) E. Fourneau, P. Maderni and Y. de Lestrange, *J. pharm. chim.*, [8] **18**, 185 (1933).

(10) P. Schneider, *Ber.*, **28**, 3074 (1895).

(11) H. R. Snyder and R. E. Heckert, THIS JOURNAL, **74**, 2006 (1952).