Hypotensive Agents. 2-(2-Aminoethyl)-piperidine Derivatives

WILLIAM F. MINOR, JUSTIN B. HOEKSTRA, DOROTHEA FISHER, AND JOSEPH SAM[1]

Research Division, Bristol Laboratories, Division of Bristol-Myers Company, Syracuse, New York

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A series of 1-methyl-2-(2-aminoethyl)-piperidines (III) and their bis-quaternary ammonium salts have been prepared and evaluated as hypotensive agents. The majority of the bis-quaternary salts have been found to be hypotensive agents of the ganglionic blocking type. The most active of these bis-quaternary salts were the two isomers of 1,1-dimethyl-5-ethyl-2-(2-morpholinoethyl)-piperidinium iodide methiodide. Nuclear magnetic resonance studies have allowed the assignment of the *trans* configuration to the high-melting isomer and the *cis* configuration to the low-melting compound.

The preparation of compounds of the hexamethonium type in which the alkylene chain is incorporated in a cyclic structure was first described by Norton and Phillips.[2,3] McMillan and co-workers[4] later prepared a variety of such cyclic derivatives, both aromatic and heterocyclic, and found some compounds which possessed hypotensive activity comparable to that of hexamethonium.

More recently Phillips has reported on derivatives of 4-(2-aminoethyl)-piperidine[5] and 3- and 4-(3-aminopropyl)-piperidines.[6] In each of these series certain of the diamines and bis-quaternary salts exhibited pronounced ganglionic blockade in cats.

Shapiro and co-workers[7] have shown that the introduction of an oxygen atom into the alkylene side chain of structures of the types prepared by Phillips may also produce compounds having hypo-

(1) The University of Mississippi School of Pharmacy, Department of Pharmaceutical Chemistry, University, Miss.

(2) S. Norton and A. P. Phillips, *Nature, London*, **172**, 867 (1953).

(3) A. P. Phillips, *J. Am. Chem. Soc.*, **76**, 2211 (1954).

(4) F. H. McMillan, K. A. Kun, C. B. McMillan, and J. A. King, *ibid.*, **78**, 4077 (1956).

(5) A. P. Phillips, *ibid.* **79**, 2836 (1957). The pharmacology of this series of compounds was reported by K. I. Colville and R. V. Fanelli, *J. Am. Pharm. Ass. (Sci. Ed.)*, **45**, 727 (1956).

(6) A. P. Phillips, *J. Am. Chem. Soc.*, **79**, 5754 (1957).

(7) (a) S. L. Shapiro, H. Soloway and L. Freedman, *ibid.*, **80**, 2743 (1958);(b) S. L. Shapiro, H. Soloway, H. Shapiro and L. Freedman, *J. Org. Chem.*, **25**, 291 (1960).

tensive activity, notably 2-(2-dialkylaminoethoxy)-methyl-1-methylpiperidines and 2-(3-dimethylaminopropoxy)-methyl-1-methylpiperidine, which show equal or better activity as free amines than as their bis-quaternary salts.

The above communications deal with compounds having five or six atoms between the nitrogens, indicating close adherence to the models of pentamethonium and hexamethonium. However, it has been shown by Gray and co-workers[8] that a carbon chain of such length does not necessarily produce maximum hypotensive activity, but rather that such activity may often be obtained with a two- or three-carbon alkylene chain between nitrogen atoms, when one of the nitrogens is contained in a cyclic system.

In a previous paper[9] we reported the preparation of a few 1-methyl-3-heterocyclic-aminomethylpiperidines and their bis-methiodide salts, compounds having two- and three-carbon chains between nitrogens. Neither these compounds, nor apparently those of the same type prepared earlier by Weston, Sommers, and Beck,[10,11] exhibited any appreciable hypotensive activity. It has been shown[12] more recently that certain 9-(1-methyl-2-, 3- and 4-piperidylmethyl)-carbazoles induce increases in blood pressure.

The purpose of our investigation has been to determine the hypotensive effect of a number of bis-amines of the general formula III (see Chemistry section), and bis-quaternary salts[13] thereof, in which one of the three carbons between the nitrogen atoms is included in the piperidine nucleus. The majority of the compounds have an ethyl group in the 5-position of the piperidine nucleus. Shapiro, Soloway, and Freedman[14] have described four bis-methiodides analogous to those of Table III, where R_1 is H or ethyl and B is the 10-phenothiazinyl or 9-carbazolyl moiety. These compounds were reported to cause some depression of motor activity in the rat.

Chemistry.—Figure 1 shows the reaction of 2-vinylpyridine[10,15] and

(8) A. P. Gray, E. E. Spinner, D. C. Schlieper, W. L. Archer, and C. J. Cavallito, *J. Am. Chem. Soc.*, **77**, 3533, 3536 (1955); **79**, 3805 (1957).

(9) J. Sam, W. F. Minor and Y. G. Perron, *ibid.* **81**, 710 (1959). See also J. Sam, U. S. Patent 2,870,148 (Jan. 20, 1959).

(10) A. H. Sommers, M. Freifelder, H. B. Wright, and A. W. Weston, *ibid.*, **75**, 57 (1953).

(11) A. W. Weston, A. H. Sommers, and K. M. Beck, U. S. Patent 2,684,965 (July 27, 1954).

(12) O. Nieschulz, I. Hoffmann, and K. Popendiker, *Arzneimittel-Forsch.*, **9**, 219 (1959).

(13) J. Sam, U. S. Patent 2,922,786 (Jan. 26, 1960).

(14) S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Pharm. Ass. (Sci. Ed.)*, **46**, 333 (1957).

(15) H. E. Reich and R. Levine, *J. Am. Chem. Soc.*, **77**, 4913, 5434 (1955).

5-ethyl-2-vinylpyridine[16] with primary and secondary amines was used to prepare the substituted 2-(2-aminoethyl)-pyridines (I) (Table I). Hydrogenation of the compounds of type I in glacial acetic acid over platinum oxide gave the corresponding piperidines (II) (Table II), which were methylated with formic acid and formaldehyde to provide III (Table II). 5-Ethyl-2-(2-morpholinoethyl)-piperidine was allowed to react with ethyl iodide and β-phenethyl bromide in the presence of potassium carbonate to give the corresponding 1-ethyl- and 1-β-phenethylpiperidines (Table II). The bis-quaternary salts (Table III) of III were obtained readily by treatment of the diamines with alkyl iodides in acetonitrile or methanol.

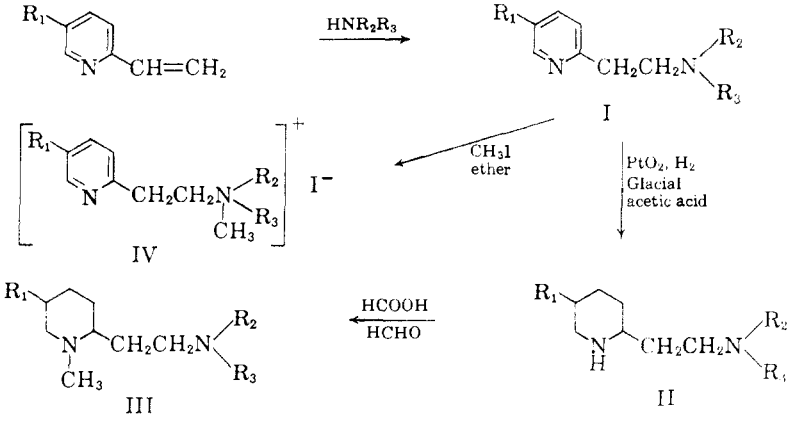


Fig. 1.—R_1 = H or C_2H_5; NR_2R_3 = dialkylamino or heterocyclic amino.

The geometrical isomerism resulting from the presence of the 5-ethyl group in many of the compounds probably has accounted for the persistently low yields of their bis-quaternary salts, which were generally less than 50%. In no case was any concerted effort made to isolate both geometrical isomers. However, quaternization of 5-ethyl-1-methyl-2-(2-morpholinoethyl)-piperidine with methyl iodide in methanol gave two distinct products. The less soluble compound had m.p. 265° (dec.), and the more soluble isomer showed m.p. 136–137° (dec.) (Nos. 8 and 9, respectively, Table III).

On the basis of the nuclear magnetic resonance spectra (Fig. 2)

(16) E. Profft, *Chemiker-Ztg.*, **81**, 427 (1957).

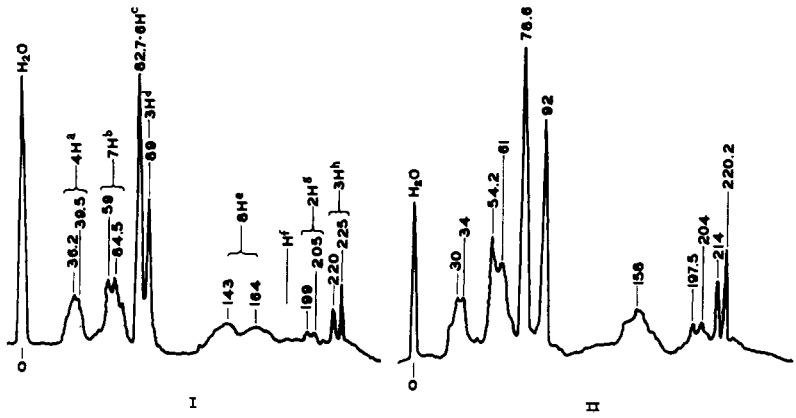
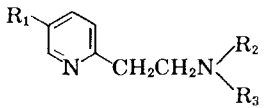


Fig. 2.—Nuclear magnetic resonance spectra of *cis* (II) and *trans* (I) 1,1-dimethyl-5-ethyl-2-(2-morpholinoethyl)-piperidinium iodide methiodide in D_2O with water (0 cps.) as the internal standard. Lettered peaks on I correspond to identically labeled protons in the structural formula I of Fig. 3, the numbers of each type of proton being given also. The resonances in II correspond to those of I except for the significant difference at 158 cps., which is interpreted in the text.

the high-melting, less soluble compound (Table III, No. 9) was assigned a *trans* configuration (Fig. 3, I). This was concluded from the structure of the signals for the H^e-type of hydrogens. The H^e signals for the high-melting isomer show two broad bands, centered at 143 cps. and 164 cps., while those of the low-melting isomer give only one band, centered at 158 cps. The poorer resolution in the latter case indicates that the low-melting compound is the conformationally less pure, or 1,4-*cis*, isomer. In the *cis* isomer each of the H^e-type of hydrogens in the piperidine ring must be expected to exist to an appreciable extent in both the axial and equatorial configurations (Fig. 3, II and III). Therefore the chemical shifts between these hydrogens will be less than in the rigid *trans* isomer, in which each of the H^e hydrogens in the ring will be essentially in only one or the other of the two orientations. The chemical shift between axial and equatorial hydrogens that are otherwise equivalent can be as great as 20 cps. Also, the *cis* isomer can be expected to exist mainly in conformation III (Fig. 3), wherein the H^e hydrogens of the piperidine ring are more weakly coupled with the hydrogens at the 2- and 5-positions than in the *trans* isomer (Fig. 3, I).

TABLE I

2-(2-AMINOETHYL)-PYRIDINES



Cpd.	R_1	NR_2R_3	Yield, %	B.p. °C.	B.p. Mm.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	n_D (° C.)
1	C_2H_5	$N(CH_3)_2$	80	131–133	18	$C_{11}H_{18}N_2$	74.1	73.8	10.2	10.4	1.5000(23)
2	C_2H_5	NHC_2H_5	77	101.5–103	2	$C_{11}H_{18}N_2$	74.1	74.2	10.2	10.2	1.5032(26.5)
3	H	NHC_2H_5[a]	75	70–73	2	$C_9H_{14}N_2$	71.9	72.0	9.4	9.0	1.5070(25.5)
4	H	$N(CH_3)C_2H_5$[b]	54	67–70	2	$C_{10}H_{16}N_2$	73.0	73.4	9.8	9.8	1.5009(26)
5	C_2H_5	$NHCH(CH_3)_2$	70	113–115	4	$C_{12}H_{20}N_2$	74.9	74.6	10.5	10.6	1.4969(26)
6	C_2H_5	Pyrrolidino[c]	86	107–110	0.8	$C_{13}H_{20}N_2$	76.4	76.7	9.9	10.0	1.5181(24)
7	H	Morpholino[d]	89	127–128	3.5	$C_{11}H_{16}N_2O$					1.5250(24.5)
8	C_2H_5	Morpholino[e]	66	120–123	0.8	$C_{13}H_{20}N_2O$	70.9	70.5	9.2	9.1	1.5197(25)
9	C_2H_5	Piperidino[f]	78	135–139	3	$C_{14}H_{22}N_2$	77.0	76.8	10.1	10.3	1.5181(24.5)
10	C_2H_5	5-Ethyl-2-methyl-piperidino	68	144–147	1	$C_{17}H_{28}N_2$	78.4	78.5	10.8	10.9	1.5083(25)
11	C_2H_5	1,2,3,4-Tetrahydro-isoquinolino	53	182–184	0.8	$C_{18}H_{22}N_2$	81.2	81.0	8.3	8.2	1.5699(26)

[a] Prepared as described by H. Reich and R. Levine, *J. Am. Chem. Soc.*, **77**, 5434 (1955). [b] L. A. Walter, W. H. Hunt, and R. J. Fosbinder, *ibid.* **63**, 2771 (1941). [c] Lit.[16] n_D^{20} 1.5199. [d] Prepared as described by H. Reich and R. Levine, *ibid.* **77**, 4913 (1955). [e] Lit.[16] n_D^{20} 1.5195. [f] Lit.[16] n_D^{20} 1.5180.

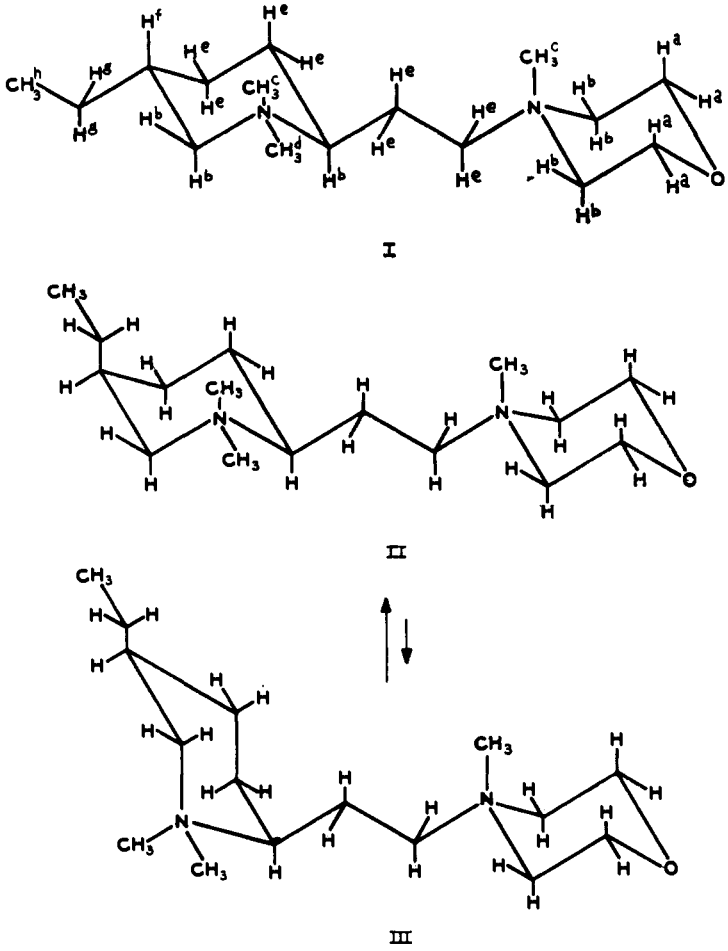
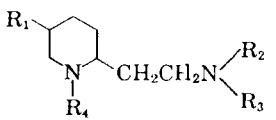


Fig. 3.—Conformational representation of the structures of *cis* (II and III) and *trans* (I) 1,1-dimethyl-5-ethyl-2-(2-morpholinoethyl)-piperidinium iodide methiodide. In structure I the various types of protons are identified.

Some effort was directed toward the conversion of the intermediate pyridines (I) to bis-quaternary salts, but in the majority of these cases only oils were obtained. In two instances, where $-NR_2R_3$ of I is morpholino or pyrrolidino, the corresponding bis-methiodides were isolated in low yields.

TABLE II

2-(2-AMINOETHYL)-PIPERIDINES



Cpd.	R_1	NR_2R_3	R_4	Yield, %	B.p. °C.	B.p. Mm.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	n_D (°C.)
1	H	$N(CH_3)_2$[a]	H	88	103–105	28	$C_9H_{20}N_2$	69.0	69.3	12.9	12.9	1.4634(27)
2	H	$N(CH_3)_2$	CH_3	84	101.5–103	19	$C_{10}H_{22}N_2$	70.5	69.5	13.0	13.4	1.4612(27)
3	C_2H_5	$N(CH_3)_2$	H	75	80–84	25	$C_{11}H_{24}N_2$	71.6	71.6	13.1	12.8	1.4675(27.5)
4	C_2H_5	$N(CH_3)_2$	CH_3	56	121–127	17	$C_{12}H_{26}N_2$	72.6	72.8	13.2	13.1	1.4626(26.5)
5	H	NHC_2H_5	H	94	60–63	1.5	$C_9H_{20}N_2$	69.1	69.6	12.9	12.9	1.4699(26)
6	H	$N(CH_3)C_2H_5$	CH_3	74	80–84	33	$C_{11}H_{24}N_2$	71.6	71.5	13.1	12.9	1.4643(24.5)
7	C_2H_5	NHC_2H_5	H	86	86–90	2	$C_{11}H_{24}N_2$	71.6	72.2	13.1	12.6	1.4709(28)
8	C_2H_5	$N(CH_3)C_2H_5$	CH_3	66	138	18	$C_{13}H_{28}N_2$	73.4	73.1	13.1	13.1	1.4635(26.5)
9	C_2H_5	$NHCH(CH_3)_2$	H	90	100–102	2.5	$C_{12}H_{26}N_2$	72.5	72.4	13.2	13.6	1.4637(24.5)
10	C_2H_5	$N(CH_3)CH(CH_3)_2$	CH_3	66	108.5–112	3	$C_{14}H_{30}N_2$	74.1	73.7	13.4	13.9	1.4661(24.5)
11	C_2H_5	Pyrrolidino	H	76	100	1	$C_{13}H_{26}N_2$	74.2	74.3	12.5	12.1	1.4844(24.5)
12	C_2H_5	Pyrrolidino	CH_3	55	130	3	$C_{14}H_{28}N_2$	74.9	75.1	12.6	12.4	1.4825(25)
13	H	Morpholino[b]	CH_3	92	97	0.5	$C_{12}H_{24}N_2O$	67.9	67.5	11.4	11.2	1.4860(26)
14	C_2H_5	Morpholino	H	93	116	0.8	$C_{12}H_{26}N_2O$	69.0	68.7	11.6	11.7	1.4842(25)
15	C_2H_5	Morpholino	CH_3	85	118	0.7	$C_{13}H_{28}N_2O$	70.0	70.1	11.7	11.5	1.4835(25)
16	C_2H_5	Morpholino	C_2H_5	21	134	1.5	$C_{15}H_{30}N_2O$	70.8	70.9	11.9	11.9	1.4827(26)
17	C_2H_5	Morpholino	$C_6H_5CH_2CH_2$	50	193–197	1.5	$C_{21}H_{34}N_2O$	76.4	76.6	10.4	10.3	1.5220(22)
18	C_2H_5	Piperidino	H	84	131–136	4	$C_{14}H_{28}N_2$	74.8	75.0	12.6	12.2	1.4842(24)
19	C_2H_5	Piperidino	CH_3	80	147.5–150	6	$C_{15}H_{30}N_2$	75.5	75.7	12.7	12.6	1.4813(25)
20	C_2H_5	5-Ethyl-2-methyl-piperidino	H	87	154–159	3	$C_{10}H_{34}N_2$	76.5	76.6	12.9	12.5	1.4812(25)
21	C_2H_5	5-Ethyl-2-methyl-piperidino	CH_3		160–164	3	$C_{18}H_{36}N_2$	77.0	77.1	12.9	13.2	
22	C_2H_5	1,2,3,4-Tetrahydro-isoquinolino	H	72	180–183	2	$C_{19}H_{28}N_2$	79.7	79.5	10.0	10.3	1.5340(27.5)

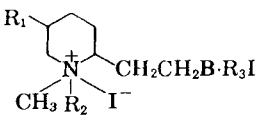
TABLE II (*Continued*)

23	C_2H_5	1,2,3,4-Tetrahydro-isoquinolino	CH_3	62	191.5–195	2	$C_{19}H_{30}N_2$	79.6	79.8	10.6	10.8	1.5316(26.5)		

[a] H. L. Cohen and L. M. Minsk, *J. Am. Chem. Soc.*, **79**, 1759 (1957). [b] The intermediate 2-(2-morpholinoethyl)-piperidine was prepared by the method of A. H. Sommers, M. Freifelder, H. B. Wright, and A. W. Weston, *J. Am. Chem. Soc.*, **75**, 57 (1953).

TABLE III

BIS-QUATERNARY SALTS



								Analyses, %				
					Yield,	M.p.[a]		Carbon		Hydrogen		Crystn.
Cpd.	R_1	R_2	B	R_3	%	°C.	Formula	Calcd.	Found	Calcd.	Found	solvent[b]
1	H	CH_3	$N(CH_3)_2$[c]	CH_3	59	218–220	$C_{12}H_{28}I_2N_2$	31.8	31.6	6.2	6.1	M
2	H	CH_3	$N(CH_3)C_2H_5$	CH_3	68	213–214.5	$C_{13}H_{30}I_2N_2$	33.4	33.4	6.5	6.5	E
3	C_2H_5	CH_3	$N(CH_3)_2$	CH_3	52	257–257.5	$C_{14}H_{32}I_2N_2$	34.8	35.0	6.7	6.7	M
4	C_2H_5	CH_3	$N(CH_3)C_2H_5$	CH_3	41	236–238	$C_{15}H_{34}I_2N_2$	36.2	36.4	6.9	6.9	M-Et
5	C_2H_5	CH_3	$N(CH_3)CH(CH_3)_2$	CH_3	51	244–244.5	$C_{16}H_{36}I_2N_2$	37.6	37.4	7.1	7.0	M-EA
6	C_2H_5	CH_3	Pyrrolidino	CH_3	46	255–256	$C_{16}H_{34}I_2N_2$	37.8	37.7	6.7	6.6	M
7	H	CH_3	Morpholino	CH_3	96	264–265	$C_{14}H_{30}I_2N_2O$	33.8	34.0	6.1	6.0	M
8	C_2H_5	CH_3	Morpholino	CH_3	30	136–137	$C_{16}H_{34}I_2N_2O$	36.8	36.7	6.7	6.9	M
9	C_2H_5	CH_3	Morpholino	CH_3	52	264–264.5	$C_{16}H_{34}I_2N_2O$	36.8	36.8	6.7	6.7	W-A
10	C_2H_5	C_2H_5	Morpholino	C_2H_5	45	254–255	$C_{18}H_{38}I_2N_2O$	39.3	39.4	7.0	7.1	M
11	C_2H_5	CH_3	Piperidino	CH_3	41	245–246	$C_{17}H_{36}I_2N_2$	39.1	39.2	7.0	7.0	W-A

[a] All of the compounds in the table melt with decomposition. [b] M, methanol; E, ethyl alcohol; Et, ether; EA, ethyl acetate; W, water; A, acetone. [c] H. L. Cohen and L. M. Minsk, *J. Am. Chem. Soc.*, **79**, 1759 (1957).

Several mono-methiodides were prepared from compounds of type I by the addition of methyl iodide to ethereal solutions of the diamines. These compounds were assigned structures of type IV (Fig. 1) on the basis of the greater basicity to be expected of the nitrogen terminating the alkyl chain.

Pharmacology.—The compounds described were evaluated in dogs under sodium pentobarbital anesthesia. Blood pressure was recorded from the carotid artery using a mercury manometer. All compounds were administered intravenously in aqueous solution. Control blood pressure responses were obtained for histamine diphosphate (0.003 mg./kg.), acetylcholine chloride (0.003 mg./kg.), and epinephrine hydrochloride (0.001 mg./kg.). The responses to these three agents were checked at five-minute intervals following each successive dose of the compound and compared with the normal responses. If a decrease in blood pressure of any appreciable duration occurred the compound was given to another dog and the degree and duration of action on blood pressure were determined. Blood pressure had to decrease by a minimum of 8% over a two-hour period before the effect was considered significant.

The pyridines listed in Table I did not produce significant hypotension. Half of these compounds, however, did exhibit some antihistaminic activity. Compound 6 was the most active in this respect, completely blocking the response to histamine at half the toxic dose. Compounds 3 and 4 possessed some adrenergic blocking properties. Compound 3 completely reversed the epinephrine response at one-tenth of the toxic dose. The majority of these compounds were toxic in the range of 10.0–40.0 mg./kg.

The piperidines listed in Table II likewise showed no significant hypotensive action. These compounds were toxic in the range of 10.0 to 250.0 mg./kg., with the majority falling in the 10.0–50.0 mg./kg. range. Compound 11 showed antihistaminic activity, completely blocking the response at half the toxic dose. Compounds 13, 20, and 22 potentiated the action of histamine, compound 9 showed a moderate degree of anticholinergic activity and compounds 10, 12, 14, 19, and 20 potentiated the action of epinephrine.

The bis-quaternary compounds listed in Table III all showed significant hypotensive activity with the exception of compound 1. Compounds 8 and 9 possessed the greatest degree of activity. Compound 8 produced a 30% average decrease in blood pressure lasting

more than two hours at one-fiftieth the toxic dose. Compound 9 produced a 21% average decrease in blood pressure for more than two hours at one-twentieth the toxic dose. These compounds were in general less toxic than those listed in Tables I and II. They potentiated the responses to both histamine and epinephrine and possessed considerable ganglionic blocking action. The inclusion of an ethyl group in the 5-position of the piperidine ring yielded compounds having slightly greater activity, but they were also more toxic than the unsubstituted analogs.

Neither the three mono-quaternaries (IV), nor the two bismethiodides prepared from type I compounds, exhibited any appreciable hypotensive activity.

Experimental[17]

Reaction of Amines with Vinylpyridines (Table I).—The procedures of Reich and Levine[15] were employed for the preparation of the compounds in Table I. 2-Vinylpyridine was obtained from Reilly Tar and Chemical Co. and 5-ethyl-2-vinylpyridine from Carbide and Carbon Chemicals Co.

Piperidines (Table II).—The piperidines listed in Table II were obtained by the catalytic reduction of the corresponding pyridines in glacial acetic acid over Adams catalyst. The majority of these reductions proceeded smoothly at 50° and at 50–60 lb. pressure. After removal of catalyst and excess acetic acid the reduction mixtures were made basic with 25% sodium hydroxide. Extraction with ether, drying, and distillation yielded the products. Since many of the compounds were appreciably soluble in water, the general practice was to saturate the basic mixture with potassium carbonate before the ether extraction.

N-Substituted Piperidines (Table II).—The N-methylpiperidines were prepared by methylation of the piperidines[11] with formic acid and formaldehyde. As in the procedure for the unmethylated piperidines the basic aqueous mixtures were saturated with potassium carbonate before extraction, for many of the products were quite water-soluble.

1,5-Diethyl-2-(2-morpholinoethyl)-piperidine.—A mixture of 22.6 g. (0.1 mole) of 5-ethyl-2-(2-morpholinoethyl)-piperidine, 23.4 g. (0.15 mole) of ethyl iodide and 13.8 g. (0.1 mole) of anhydrous potassium carbonate was heated for 20 hr. on a steam-bath. After the addition of 50 ml. of water the mixture was heated for 1 hr., cooled, and extracted three times with ether. The ethereal extracts were combined, dried over anhydrous potassium carbonate and distilled, yielding 6 g. (24%) of the desired product.

5-Ethyl-2-(2-morpholinoethyl)-1-β-phenethylpiperidine.—A mixture of 45.4 g. (0.2 mole) of 5-ethyl-2-(2-morpholinoethyl)-piperidine, 46.3 g. (0.25 mole) of phenethyl bromide and 28 g. (0.2 mole) of anhydrous potassium carbonate in 150 ml. of toluene was refluxed for 17 hr. The mixture then was washed once

(17) Microanalyses are by Richard M. Downing. Melting points are uncorrected.

with water and extracted three times with 6 *N* HCl. The combined extracts were neutralized with 50% sodium hydroxide and extracted with ether; after being washed with saturated sodium chloride solution the ether was dried over anhydrous potassium carbonate and distilled, yielding 33.2 g. (50%) of product, b.p. 194–196° (1.5 mm.). See Table II for analysis.

Bis-quaternary Salts (Table III).—The bis-quaternary salts cited in the Table were prepared by the treatment of each of the corresponding bis-amines, either in methanol or acetonitrile, with an excess of alkyl iodide. In the majority of cases initial cooling of the exothermic reaction was necessary. The resulting mixtures either were allowed to stay at room temperature overnight or heated under reflux for several hours. The products were collected by filtration and recrystallized from suitable solvents, which are given in Table III.

1,1-Dimethyl-5-ethyl-2-(2-morpholinoethyl)-piperidinium Iodide Methiodides (Nos. 8 and 9, Table III).—To a solution of 349.5 g. (1.45 moles) of 5-ethyl-1-methyl-2-(2-morpholinoethyl)-piperidine in 1850 ml. of methanol was added 506 g. (3.56 moles) of methyl iodide and the solution was allowed to stand at 25°. After 24 hr. it was chilled and a white, crystalline solid (A) was collected. When dry this weighed 487 g. (64%) and had m.p. 256–258° (dec.). Further cooling of the filtrate produced a large second crop (B) which weighed 207 g. (27%); m.p. 138–142° (dec.).

Compound A was pulverized and stirred for 10 min. in 1 l. of boiling methanol. It was then recrystallized from water (500 ml.)-acetone (4400 ml.). There was recovered 397 g. (52%) of material of m.p. 264–264.5° (dec.). Further purification did not improve the melting point. Nuclear magnetic resonance spectral studies have allowed the assignment of the *trans* configuration to this compound (see Chemistry section).

Compound B was recrystallized twice from methanol to yield 210 g. (30%) of product having m.p. 136–137° (dec.). On the basis of n.m.r. studies this low-melting isomer has been assigned the *cis* configuration (see Chemistry section).

5-Ethyl-1-methyl-2-(2-pyrrolidinoethyl)-pyridinium Iodide Methiodide.—Treatment of a solution of 10 g. (0.05 mole) of 5-ethyl-2-(2-pyrrolidinoethyl)-pyridine in 50 ml. of absolute ethanol with 20 g. (0.14 mole) of methyl iodide yielded 12 g. of crystalline yellow solid after 24 hr. at 25°. After recrystallization from the same solvent the product had m.p. 154–155°.

Anal. Calcd. for $C_{15}H_{26}I_2N_2$: C, 36.9; H, 5.37. Found: C, 37.0; H, 5.41.

5-Ethyl-1-methyl-2-(2-morpholinoethyl)-pyridinium Iodide Methiodide.—A solution of 22 g. (0.10 mole) of 5-ethyl-2-(2-morpholinoethyl)-pyridine and 35 g. (0.25 mole) of methyl iodide in 100 ml. of acetonitrile was heated under reflux for 3 hr. After an additional day at 25° there was collected 5 g. of product of m.p. 127–130°. After two recrystallizations from methanol the material had m.p. 135–138°.

Anal. Calcd. for $C_{15}H_{26}I_2N_2O$: C, 35.7; H, 5.20. Found: C, 35.6; H, 5.32.

Mono-quaternary Salts of Pyridines of Type I.—The addition of one equivalent of methyl iodide to ethereal solutions of each of the diamines gave the desired products, which were collected by suction filtration and recrystallized from suitable solvents.

2-(2-Pyridyl)-ethyltrimethylammonium iodide was recrystallized from water; m.p. 253–253.5°, yield 80%.

Anal. Calcd. for $C_{10}H_{17}IN_2$: C, 41.1; H, 5.9. Found: C, 41.4, H, 6.0.

2-(5-Ethyl-2-pyridyl)-ethylmethylpyrrolidinium iodide was recrystallized from methanol–ether to give a 97% yield of material of m.p. 128–129°.

Anal. Calcd. for $C_{14}H_{23}IN_2$: C, 48.6; H, 6.7. Found: C, 48.7; H, 6.9.

2-(2-Pyridyl)-ethylmethylmorpholinium iodide was recrystallized from acetone; m.p. 130°, yield 49%.

Anal. Calcd. for $C_{12}H_{19}IN_2O$: C, 43.1; H, 5.7. Found: C, 43.0, H, 5.5.

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16-Substituted Steroids. XVIII.[1] 6,16-Difunctional 3,5-Cyclo-5α-androstanes

JAMES R. RHONE AND MAX N. HUFFMAN

Lasdon Foundation Research Institute of Chemotherapy, Colorado Springs, Colorado

ALLAN J. STANLEY

Department of Physiology, University of Oklahoma School of Medicine, Oklahoma City, Oklahoma

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The preparation of eight cycloandrostane compounds with oxygen functions in 6 and 16-positions (III, IV, V, VI, XII, XIV, XV, and XVIII) is described. Only 3,5-cyclo-5α-androstan-6β,16α-diol (XII) produced transient lowerings in the mean systolic blood pressure of dogs under sodium pentobarbital anesthesia.

In the clinical study of androst-5-en-3β,16α-diol in acute alcoholism, an occasional pronounced lowering of blood pressure has been noted.[2] It was believed of importance to investigate this hypotensive effect further, and a series of related steroids bearing the cyclopropyl ring was prepared.

(1) XVII. M. N. Huffman, M. H. Lott, and A. Tillotson, *J. Biol. Chem.*, **222**, 447 (1956).
(2) C. H. Campbell and M. N. Huffman, *J. Okla. State Med. Assn.*, **48**, 295 (1955).