extraction with water, 0.73 g. of 3,5-dinitrobenzoic acid was recovered upon acidification of extractions obtained using sodium bicarbonate solution, and 2-pyridylmethyl 3,5-dinitrobenzoate was obtained upon neutralizing with sodium carbonate the extractions obtained using 5% hydrochloric acid. The ester recrystallized from ethanol as colorless needles, m.p. 100–101°, 1.00 g. (33%).

Anal. Calcd. for $C_{13}H_9N_3O_6$: C, 51.48; H, 2.99; N, 13.86. Found: C, 51.38; H, 3.15; N, 14.05.

An unidentified dark oil, 0.16 g., was isolated from the neutralized acid extractions by further extraction with ether.

The following variations were used in product isolation. B2: Toluene and a low boiling acid were removed by normal distillation and the product ester distilled *in vacuo*. B3: The reaction mixture in toluene was extracted with 5% sodium bicarbonate solution and then distilled.

Table II contains summarizing data for reactions between two different triazoles and eight different organic acids. Intractable material obtained in experiments with β-naphthol and with cinnamic acid was not further identified.

Upon hydrolysis with hydrochloric acid, 3,5-dinitrobenzoic acid, m.p. and mixture m.p. 203–208°, and 2-pyridylmethanol were obtained from 2-pyridylmethyl 3,5-dinitrobenzoate. A picrate derivative, m.p. 160.5–161°,[8] was prepared from 2-pyridylmethanol.

Saponification of phenyl-2-pyridylmethyl benzoate afforded phenyl-2-pyridylcarbinol, m.p. 74–77°,[11] picrate m.p. 170–171°,[11] and benzoic acid, m.p. and mixture m.p. 121–122°.

(11) A. E. Tschitschibabin, *Ber.*, **37**, 1370 (1904); M. R. F. Ashworth, R. P. Daffern and D. L. Hammick, *J. Chem. Soc.*, 809 (1939).

NEW ORLEANS 18, LA.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE U. S. VITAMIN CORPORATION]

Antihypertensive Agents. I. Dialkylaminoalkoxyalkylpiperidines and Pyrrolidines

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A series of 2-dialkylaminoalkoxyalkyl-1-methylpiperidines and pyrrolidines have been synthesized in the search for bis-tertiary amines with hypotensive activity. Such activity has been found with the 2-(2′-dialkylaminoethoxy)-methyl-1-methyl- and the 2-(3′-dimethylaminopropoxy)-methyl-1-methylpiperidines.

The wide therapeutic usage of hexamethonium and pentapyrrolidinium has indicated irregularities in the oral absorption of these drugs[1] which have been associated in part with the quaternary character of the compounds.

The report by Phillips and his associates[2] of potent hypotensive action in bis-tertiary amines of the type 1-methyl-3-(4′-dimethylaminobutyl)-piperidine dihydrochloride, suggested structural variation of amines of this type. As a result of such studies it was hoped that bis-tertiary amines retaining the hypotensive potential of the clinically useful bis-onium salts without the side effects of these salts, could be obtained.

The scope of the study included variations of the structure I, A_1–Y–A_2·2RX, wherein A_1 = 2-pyridyl, 4-pyridyl, N-methyl-2-piperidyl, N-methyl-4-piperidyl and N-methyl-2-pyrrolidyl; Y = $(CH_2)_n$– and $-(CH_2)_nO(CH_2)_n'-$; A_2 = dimethylamino, diethylamino, pyrrolidino, piperidino, morpholino, hexamethylenimino and tetrahydroquinolino; R = hydrogen and lower alkyl.

The extension of investigations in certain of these directions stimulated work not only by our laboratories, but by others,[3] and particularly by Phillips[4] and his associates, and a large group of the compounds in the category I, Y = $-(CH_2)_n-$, have since been reported in the literature.[5]

This paper will be confined to derivatives of I, Y = oxa-alkylene. The 1-methyl-2-piperidine (and pyrrolidine) alkanols were treated with an excess of the dialkylaminoalkyl halide in the presence of an alkaline condensing agent to yield the desired compounds in moderate yields. The compounds which were prepared, as well as their bis-quaternary salts, have been detailed in Table I.

The required heterocyclic aminoalcohols were accessible through a variety of procedures reported in the literature,[6] and the reactant alkanol amines were prepared following these procedures; 1-methyl-2-hydroxymethylpyrrolidine,[6b] 1-methyl-2-(2-hydroxyethyl)-piperidine,[6f] and the preparation

(1) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," 2nd ed., The Macmillan Co., New York, N. Y., 1955, p. 636.

(2) (a) S. Norton and A. P. Phillips, *Nature*, **172**, 867 (1953); (b) A. P. Phillips, THIS JOURNAL, **76**, 2211 (1954).

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

(4) (a) A. P. Phillips, *ibid.*, **78**, 4441 (1956); (b) **79**, 2836 (1957); (c) **79**, 5754 (1957).

(5) We prepared along parallel synthetic lines and evaluated as hypotensives the following of the Phillips compounds. Good agreement in the physical constants and analyses were obtained in all instances: ref. 4a, Table I, expt. 1, 2; ref. 4b, Table I, cmpd. 10, 11, 12, 14, 15; ref. 4c, Table I, cmpd. 14, 15, 16, 20, 21, 24, 25, 26, 27. Utilizing procedures similar to those of Phillips, several new I, A_1 = N-methyl-4-piperidyl and Y = $-(CH_2)_r-$, were prepared and are reported in Table A.

TABLE A

N-METHYL-4-(3′-TERTIARYAMINOPROPYL)-PIPERIDINES

A_2	RX	Yield, %	M.p., °C.	Nitrogen, % Calcd.	Found
2-MP[h]	HCl	17	295–296	9.0	8.9
2-MP[h]	CH_3I	82[g]	296–297[c3]		
HMI[i]	HCl	71	280–283[c1]	9.0	8.9
HMI[i]	CH_3I	96	265–267[c4]	5.4	5.3
THQ[j]	HCl	58	180–182[c1]	8.1	7.7
THQ[j]	CH_3I	84	133–137[c1]	5.0	4.9

The footnotes have the same significance as in Table I. [g] Calcd.: C, 39.1; H, 7.0. Found: C, 39.1; H, 7.1. [h] 2-MP = 2-methylpiperidino. [i] HMI = hexamethylenimino. [j] THQ = tetrahydroquinolino. None of these compounds showed significant hypotensive activity. We also noted that in the instance of the entire series reviewed in this footnote, the important hypotensive activity, if present, was confined to the bis-methiodides, rather than to the bis-tertiary amines which confirmed Phillips' observation.[4c]

(6) (a) F. F. Blicke and C.-J. Lu, THIS JOURNAL, **77**, 29 (1955); (b) F. F. Blicke, U. S. Patent 2,695,301; (c) R. Paul and S. Tchelitcheff, *Bull. soc. chim. France*, 1139 (1954); (d) E. Profft, *Chem. Tech. (Berlin)*, **8**, 378 (1956); (e) R. E. Feldkamp, U. S. Patent 2,657,211; (f) S. L. Shapiro, H. Soloway and L. Freedman, *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 333 (1957).

TABLE I

DIALKYLAMINOALKOXYALKYLPIPERIDINES AND PYRROLIDINES A_1–Y–A_2·2RX

No.	Y	A_2	RX	Yield, %[d]	B.p. °C.	Mm.	M.p., °C.[b,c]	Formula	Analyses,[a] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Activity[f]
							A_1 = N-methyl-2-piperidyl								
1	$-CH_2O(CH_2)_2-$	$-N(CH_3)_2$		32	64–66	0.25		$C_{11}H_{24}N_2O$	66.0	66.0	12.1	12.1	14.0	13.9	3+
2	$-CH_2O(CH_2)_2-$	$-N(CH_3)_2$	CH_3Br	86			254–255	$C_{13}H_{30}Br_2N_2O$	40.0	40.4	7.8	7.9			3+
3	$-CH_2O(CH_2)_2-$	$-N(C_2H_5)_2$		45	112–115	4		$C_{13}H_{28}N_2O$	68.4	68.3	12.3	11.9	12.3	12.0	3+
4	$-CH_2O(CH_2)_2-$	$-N(C_2H_5)_2$	CH_2Br	100			266–267[c1]	$C_{15}H_{34}Br_2N_2O$					6.7	6.8	2+
5	$-CH_2O(CH_2)_2-$	$-N(CH_2)_4$		42	125–126	4		$C_{13}H_{26}N_2O$	69.0	69.1	11.6	11.3			2+
6	$-CH_2O(CH_2)_2-$	$-N(CH_2)_4$	CH_3Br	18			292–293[c1]	$C_{15}H_{32}Br_2N_2O$					6.7	6.9	2+
7	$-CH_2OCHCH_3CH_2-$	$-N(CH_3)_2$		41	103–106	3.5		$C_{12}H_{26}N_{20}$	67.2	66.5	12.2	12.1	13.1	12.8	1+
8	$-CH_2OCHCH_3CH_2-$	$-N(CH_3)_2$	CH_3Br	100			267–268	$C_{14}H_{32}Br_2N_2O$	41.6	41.8	8.0	7.6	6.9	6.8	0
9	$-CH_2O(CH_2)_3-$	$-N(CH_3)_2$		19	90–93	0.6		$C_{12}H_{26}N_2O$	67.2	66.7	12.2	12.0	13.1	12.7	3+
10	$-CH_2O(CH_2)_3-$	$-N(CH_3)_2$	CH_3Br	100			264[c2]	$C_{14}H_{32}Br_2N_2O$					6.9	7.3	3+
11	$-(CH_2)_2O(CH_2)_2-$	$-N(CH_3)_2$		47	82–84	0.1									0
12	$-(CH_2)_2O(CH_2)_2-$	$-N(CH_3)_2$	HPic.[e]	93			121–123	$C_{24}H_{32}N_8O_{15}$					16.7	16.9	
13	$-(CH_2)_2O(CH_2)_2-$	$-N(CH_3)_2$	CH_3I	64			259–262	$C_{14}H_{32}I_2N_2O$	33.7	33.6	6.5	6.3	5.6	5.6	0
14	$-(CH_2)_2O(CH_2)_2-$	$-N(CH_3)_2$	C_2H_5I	77			209–210	$C_{16}H_{36}I_2N_2O$	36.5	36.3	6.9	6.7	5.3	4.9	2+
15	$-CH_2O(CH_2)_2-$	$-N(CH_3)_2$		54	53–54	0.06									0
16	$-CH_2O(CH_2)_2-$	$-N(CH_3)_2$	HPic.[e]				132–135[c3]	$C_{22}H_{23}N_8O_{15}$	41.0	40.7	4.4	4.1	17.4	17.2	
17	$-CH_2O(CH_2)_2-$	$-N(CH_3)_2$	CH_3I	51			242–245[c4]	$C_{12}H_{28}I_2N_2O$	30.7	30.4	6.0	5.9	6.0	5.9	3+
18	$-CH_2O(CH_2)_2-$	$-N(C_2H_5)_2$		64	86–87	0.3		$C_{12}H_{26}N_2O$					13.0	12.9	0
19	$-CH_2O(CH_2)_2-$	$-N(C_2H_5)_2$	HPic.[e]				216–220	$C_{24}H_{32}N_8O_{15}$					16.7	16.6	
20	$-CH_2O(CH_2)_2-$	$-N(C_2H_5)_2$	CH_3I	14			245–248	$C_{14}H_{32}I_2N_2O$	33.8	33.4	6.5	6.4			
21	$-CH_2O(CH_2)_2-$	$-N(C_2H_5)_2$	C_2H_5I	22			184–187	$C_{16}H_{36}I_2N_2O$					5.3	5.1	0
22	$-CH_2O(CH_2)_3-$	$-N(CH_3)_2$		25	92–93	1		$C_{11}H_{24}N_2O$					14.0	13.8	1+
	Hexamethonium (Control)														3+

[a] Analyses by Weiler and Strauss, Oxford, England. [b] Melting points are not corrected and were obtained on a Fisher–Johns melting point block. [c] The recrystallizing solvent was ethanol unless otherwise indicated. [c1] Isopropyl alcohol. [c2] 1-Propanol. [c3] Acetonitrile. [c4] Methanol. [d] Yields are based on distilled product for the free bases, and the crude (substantially pure) product in the case of the bis-quaternary compounds. [e] Dipicric acid salt. [f] Activities were established by intravenous administration of the compounds to anesthetized (Nembutal, 30 mg./kg.) dogs at dosage levels corresponding to 1/100 $LD_{min.}$ mg./kg. as established in mice. In no instance was a dosage higher than 5 mg./kg. used. The blood pressure response has been classified as 3+ = sustained and marked (20 mm. or more) hypotension; 2+ = sustained and moderate (5–20 mm.) hypotension; 1+ = transient hypotension; and 0 = no response noted. Detailed data for the key structures as to compound number, minimum lethal dose (subcutaneous in mice in mg./kg.), and test dosage in mg./kg. are as follows: 1, 750, 5; 2, 75, 0.75; 3, 450, 4.5; 5, 550 5; 9, 500 5; 10, 40, 0.4; 17, 250, 2.

of 1-methyl-2-hydroxymethyl piperidine has been detailed in the Experimental Section.

Pharmacology.—The oxa-alkylene analogs of the methonium type compounds herein prepared show interesting dependence of structure on noted hypotensive activity. In contrast to the 1-methyl - 4 - (3 - dialkylaminopropyl) - piperidines[5] which required conversion to the bis-quaternary structure to give hypotensive responses, selected members of the oxa-alkylene series show good activity in the form of the bis-tertiary amines. This effect is noted particularly in the structures I, A_1 = M-methyl-2-piperidyl and Y = $-CH_2O(CH_2)_2-$ which show equal or better activity as the bis-tertiary amine than as the bis-quaternary (compound 1 *vs.* 2, 3 *vs.* 4, 5 *vs.* 6). Equally good activity is obtained when Y is varied as $-CH_2O(CH_2)_3-$ (compounds 9 *vs.* 10, 1 *vs.* 9). On the other hand, the compounds I, Y = $-CH_2OCHCH_3CH_2-$ and $-(CH_2)_2O(CH_2)_2-$ are associated with sharp diminution or disappearance of the hypotensive response (compounds 7, 11 *vs.* 1, 9). In this latter group, hypotensive properties are substantially absent even as bis-quaternaries (compounds 8, 13, with some effect noted with 14).

Variation of I as A = N-methyl-2-pyrrolidyl is associated with a marked diminution in the hypotensive effect when compared to the corresponding active piperidyl derivatives (compounds 15 *vs.* 1, 18 *vs.* 3, 22 *vs.* 10). In only one instance (compound 17) was good hypotensive activity noted with the pyrrolidyl derivatives, and this structure required conversion to the bis-quaternary derivative.

Experimental[7]

2-Hydroxymethyl-1-methylpyridinium Bromide.—A solution of 30.5 g. (0.28 mole) of 2-pyridylcarbinol in 150 ml. of acetonitrile was maintained at 10° during the addition of 54 g. (0.56 mole) of methyl bromide. After standing 20 hours, the product, 54 g. (94%), was separated. A sample recrystallized from ethanol melted at 166–169°.

Anal. Calcd. for $C_7H_{10}BrNO$: C, 41.2; H, 4.9; N, 6.9. Found: C, 40.9; H, 4.9; N, 6.7.

(7) Descriptive data shown in Table I are not reproduced in the Experimental Section.

2-Hydroxymethyl-1-methylpiperidine Hydrochloride.—A solution of 49 g. (0.24 mole) of 2-hydroxymethyl-1-methylpyridinium bromide in 200 ml. of ethanol was hydrogenated over 8 hours in a Parr hydrogenator at 4 atmospheres using 6.0 g.[8] of 5% rhodium-on-carbon as the catalyst. Separation of the catalyst and removal of solvent yielded 50 g. (94%) of product. A sample recrystallized from acetonitrile melted at 154–156°.

Anal. Calcd. for $C_7H_{16}BrNO$: C, 40.0; H, 7.7; N, 6.7. Found: C, 39.6; H, 8.0; N, 6.9.

2-(2′-Dimethylaminoethoxymethyl)-1-methylpiperidine (Compound 1).—2-Hydroxymethyl-1-methylpiperidine hydrobromide (16.8 g., 0.08 mole) was dissolved in water, made basic with 40% sodium hydroxide, salted with potassium carbonate and extracted with five 15-ml. portions of toluene. The combined extracts were dried over magnesium sulfate. In a similar manner, 15.8 g. (0.11 mole) of 2-dimethylaminoethyl chloride hydrochloride was converted to a dry toluene solution of the base. Sodium sand was prepared in the usual manner from 1.8 g. (0.08 mole) of sodium in 50 ml. of dry toluene and treated over 3 hours with stirring with the toluene solution of 2-hydroxymethyl-1-methylpiperidine, keeping the temperature below 90°. At the end of this period, the stirred mixture was brought to reflux temperature and the toluene solution of 2-dimethylaminoethyl chloride added dropwise over 1 hour, and then reflux was continued for 7 hours. After removal of sodium chloride, the filtrate concentrated at reduced pressure yielded a residue of 13.8 g. Distillation gave a fraction of 8.1 g. boiling at 58–70° (0.3–0.4 mm.), which on redistillation yielded 5.1 g. (32%) of product boiling at 64–66° (0.25 mm.).

2-(3′-Dimethylaminopropoxymethyl)-1-methylpiperidine (compound 9) was prepared by the procedure above from 21 g. (0.1 mole) of 2-hydroxymethyl-1-methylpiperidine bromide, 20.6 g. (0.13 mole) of 3-dimethylaminopropyl chloride hydrochloride and 2.3 g. (0.1 mole) of sodium. Work-up and distillation gave 4.1 g. (19%) of the product boiling at 90–93° (0.6 mm.).

2-(2′-Trimethylammoniumethoxymethyl)-1-dimethylpiperidinium Dibromide (Compound 2).—A solution of 3.0 g. (0.015 mole) of 2-(2-dimethylaminoethoxymethyl)-1-methylpiperidine in 25 ml. of acetonitrile was cooled in a pressure bottle and 3.8 g. (0.04 mole) of methyl bromide added. Precipitation began within an hour. After standing 20 hours, the product was separated; 5.1 g. (86%), m.p. 253–255°.

Acknowledgment.—The authors are indebted to Dr. G. Ungar for the pharmacologic screening of the compounds.

(8) Experience with several runs indicated an optimum proportion of 2.5 g. of the rhodium–carbon catalyst for every 0.1 mole of the pyridinium compound.

YONKERS 1, NEW YORK

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY]

The Synthesis of Some 4,4′-Disubstituted 2,2′-Bipyridines[1]

BY GERHARD MAERKER AND FRANCIS H. CASE

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2,2′-Bipyridine-1,1′-dioxide has been utilized for the preparation of several 4,4′-disubstituted 2,2′-bipyridines: dinitro-, diamino-, bis-diethylamino-, dibromo-, dimethoxy-, diethoxy-, diphenoxy-, dicarbethoxy-, dicarboxamido-, hydroxyethoxy-. These derivatives all yield colored complexes with Fe(II).

The ability of 1,10-phenanthroline (I) and 2,2′-bipyridine (II) to form highly colored complexes with iron(II) and other metallic ions has long been recognized and has been applied extensively in analytical chemistry for the detection and determination of these cations. In the case of 1,10-phenanthroline, the synthesis of a large number of substituted derivatives of the base has led to the discovery that substitution in the 4- and 7-positions especially has a profound effect upon the stabilities, oxidation–reduction potentials and color intensities of the iron(II) complexes.[2]

The 4- and 4′-positions of 2,2′-bipyridine are situated similarly to the 4- and 7-positions of 1,10-

(1) This work was supported by a grant from the Committee on Research and Publications of Temple University.

(2) W. W. Brandt, F. P. Dwyer and E. C. Gyarfas, *Chem. Revs.*, **54**, 959 (1954).