extracted with ethylene dichloride, and filtered. The filtrate was concentrated and chromatographed on a column of Fisher's alumina. It was developed with ethylene dichloride until it was washed free from yellow material. Later, the porphyrin was eluted with chloroform. After distilling the chloroform, the porphyrin was purified by extracting with 30% hydrochloric acid. Finally it was crystallized from a mixture of chloroform and methanol. Yield, 2.1% of analytically pure porphyrin.

Anal. Calcd. for $C_{36}H_{38}O_8N_4$: C, 66.06; H, 5.81. Found: C, 66.09; H, 6.35. Spectrum in chloroform: λ 653 mμ (log ε, 3.3377); λ 596 mμ (log ε, 3.7009); λ 557 mμ (log ε, 3.7467); λ 522 mμ (log ε, 4.1196).

Silver complex. Twenty milligrams of the porphyrin was dissolved in 1 ml. of pyridine and a concentrated solution of 50 mg. of silver acetate in pyridine was added. The mixture was heated on a steam bath until it gave a pure silver complex spectrum. (Two bands) The solvent was distilled nearly to dryness under reduced pressure. The residue was washed several times with hot water and dried in a desiccator. The dry material was crystallized from a mixture of benzene and methanol. Yield, 17 mg.

Anal. Calcd. for $C_{36}H_{36}O_8N_4Ag$: C, 56.84; H, 4.76. Found: C, 57.19; H, 4.77. Spectrum in chloroform: 592, 552. In pyridine, 595, 559.

Demetallation of the silver complex. In the presence of excess silver powder the following observations were made: (a) No demetallation in boiling benzene or naphthalene. (b) Heating the silver complex in terphenyl under the conditions used for the synthesis brought about complete demetallation as judged spectroscopically with the Hartridge reversion spectroscope. The demetallation can also be brought about in this solvent by heating in a Wood's metal bath for about 2 min., the time required for the test tube to reach the boiling temperature of the terphenyl. Experiments were performed in the presence and absence of added silver and demetallation took place equally well either way.

Acknowledgments. This research was supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund. We also appreciate support received from the National Institutes of Health under Grant A-2877, B. B. C.

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Antihypertensive Agents. III. Dialkylaminoalkoxypiperidines and Related Compounds

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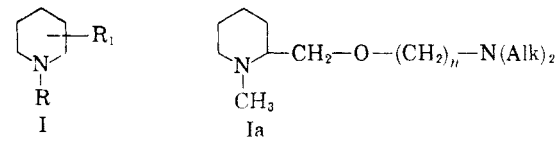
In a previous paper[1] selective effectiveness as hypotensive agents with bistertiary amines of the type I, R = CH_3, R_1 = 2—$CH_2O(CH_2)_nN(Alk)_2$, n = 2 and 3, *i.e.* (Ia), had been noted. In this report the effectiveness of 3- and 4-position analogs of Ia was evaluated. The structure (I), R_1 = 3—$O(CH_2)_nN(Alk)_2$ which retains the two-carbon



I Ia

chain between the piperidine nitrogen and the ether oxygen, characteristic of Ia, was also studied. In addition, replacement of R = CH_3 in Ia by R = $C_6H_5CH_2CH_2$— was investigated. This type of group replacement has been particularly effective in enhancing analgesic properties.[2] The compounds prepared are described in Table I.

The only compound showing even moderate hypotensive activity as the bistertiary amine was compound 7, which is related to Phillips[3] 1-methyl-3-(4′-dimethylaminobutyl)piperidine.

EXPERIMENTAL[4]

N-Alkyl-3-piperidinols. Reductive alkylation of *N*-alkyl-3-piperidinols[5] using formaldehyde and acetaldehyde, respectively, gave *N*-methyl-3-piperidinol (73%), b.p. 103–104° (40 mm.),[6] and *N*-ethyl-3-piperidinol (51%), b.p. 126–128° (40 mm.).[7]

3-(Hydroxymethyl)-1-methylpyridinium bromide. A solution of 56.8 g. (0.52 mol.) of 3-pyridinemethanol in 500 ml. of acetonitrile was cooled to −5° during the addition of 95 g. (1.0 mol.) of methyl bromide. After storage at 20° for 20 hr., 101 g. of product was separated and recrystallized (isopropanol–isopropyl ether) to give 89 g. (84%), m.p. 92–94°.

Anal. Calcd. for $C_7H_{10}BrNO$: C, 41.2; H, 4.9; N, 6.9. Found: C, 40.7; H, 5.2; N, 6.9.

1-Methanol-3-piperidinemethanol hydrobromide was prepared in 70% yield (using the method previously described[1] for the 2-hydroxymethyl analog), m.p. 113–115° (ethanol–methyl ethyl ketone).

Anal. Calcd. for $C_7H_{16}BrNO$: C, 40.0; H, 7.7; N, 6.7. Found: C, 40.3; H, 7.9; N, 6.6.

1-Ethyl-4-piperidinemethanol. A solution of 89.1 g. (0.82 mol.) of 4-pyridinemethanol and 133 g. (1.2 mol.) of ethyl bromide in 800 ml. of acetonitrile was heated under reflux for 24 hr. Removal of the solvent and seeding gave a solid which after trituration with ether yielded 170 g. of crude 4-(hydroxymethyl)-1-ethylpyridinium bromide.

The crude quaternary salt was hydrogenated directly by the method described above[1] and converted to the piperidine base with 40% sodium hydroxide. The reaction mixture was salted with potassium carbonate, extracted with ether, dried (anhydrous magnesium sulfate) and distilled to yield 4-hydroxymethyl-1-ethylpiperidine (31%) b.p. 90–92° (0.15 mm.).

Anal. Calcd. for $C_8H_{17}NO$: C, 67.1; H, 12.0; N, 9.8. Found: C, 66.7; H, 12.0; N, 9.5.

2-Hydroxymethyl-1-phenethylpyridinium bromide. 2-Pyridinemethanol (22 g., 0.2 mol.) and 40.7 g. (0.22 mol.) of phenethyl bromide were dissolved in 250 ml. of acetonitrile

(1) S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, 80, 2743 (1958).

(2) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 294 (1959).

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

(4) Descriptive data shown in the table are not reproduced in the Experimental section.

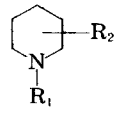
(5) S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Pharm. Assoc., (Sci. Ed.)*, **46**, 333 (1957).

(6) S. Tchelitcheff, U. S. Patent **2,489,546** (Nov. 29, 1949), reports b.p. 79° (15 mm.).

(7) J. H. Biel, H. L. Friedman, H. A. Leiser, and E. P. Sprengeler, *J. Am. Chem. Soc.*, **74**, 1485 (1952), report b.p. 93–95° (15 mm.).

TABLE I

DIALKYLAMINOALKOXYALKYLPIPERIDINES



No.	R_1	R_2	Yield,[a] %	M.P.[b,c(a)] or B.P. (Mm.)	Formula	Analyses[d] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Activity
1[e]	CH_3—	3-$O(CH_2)_2N(CH_3)_2$	11	100–103 (9)								0
2	$2CH_3I$[f]		60	294–297[c(b)]	$C_{12}H_{28}IN_2O$	30.6	30.8	6.0	6.1	6.0	6.0	1+
3	C_2H_5—	3-$O(CH_2)_2N(CH_3)_2$	17	102–106 (8)	$C_{11}H_{24}N_2O$	66.0	65.6	12.1	12.3			0
4	CH_3—	3-$O(CH_2)_3N(CH_3)_2$	50	142–144 (35)	$C_{11}H_{24}N_2O$	66.0	65.8	12.1	11.8	14.0	13.5	0
5	$2CH_3I$[f]		85	214–216	$C_{13}H_{30}I_2N_2O$	32.2	32.2	6.2	6.2	5.8	5.7	1+
6	$2C_2H_5I$[g]		71	171–174	$C_{15}H_{34}I_2N_2O$	35.2	34.9	6.7	7.0			0
7	C_2H_5—	3-$O(CH_2)_3N(CH_3)_2$	38	116–118 (6)	$C_{12}H_{26}N_2O$					13.1	13.1	2+
8	$2CH_3I$[f]		52	197–200	$C_{14}H_{32}I_2N_2O$	33.8	33.8	6.5	6.5	5.6	5.2	3+
9[h]	CH_3—	3-$CH_2O(CH_2)_2N(C_2H_5)_2$	10	113 (2)								0
10	C_2H_5—	4-$CH_2O(CH_2)_2N(C_2H_5)_2$	40	106 (0.9)	$C_{14}H_{30}N_2O$	69.4	69.1	12.5	12.6	11.6	11.6	0
11	$C_6H_5CH_2CH_2$—	2-$CH_2O(CH_2)_2N(C_2H_5)_2$	4	120–124 (0.08)	$C_{20}H_{34}N_2O$	75.4	75.3	10.8	10.2			0

[a] Yields are based on distilled or recrystallized product. [b] Melting points are not corrected and were obtained on a Fisher-Johns melting point block. [c] (a) Recrystallizing solvent is ethanol unless otherwise shown; (b) methanol. [d] Analyses by Weiler and Strauss, Oxford, England. [e] Characterized as the methiodide (Compound 2). [f] Compound is the dimethiodide of bisamine immediately above. [g] Compound is the diethiodide of bisamine immediately above. [h] B. Elpern, U. S. Patent 2,773,876 (Dec. 11, 1956) reports b.p. 113–118° (3.2 mm.).

and heated under reflux for 22 hr. The solvent was removed to give 19 g. (32%), m.p. 150–154°. Recrystallization (ethanol) gave m.p. 158–159°.

Anal. Calcd. for $C_{14}H_{16}BrNO$: C, 57.2; H, 5.5; N, 4.8. Found: C, 57.4; H, 5.7; N, 5.1.

1-Phenethyl-2-piperidinemethanol hydrobromide. A mixture of 14 g. (0.048 mol.) of 2-hydroxymethyl-1-phenethylpyridinium bromide in 250 ml. of ethanol and 1.3 g. of 5% rhodium on carbon afforded complete uptake of hydrogen[1] after 3 hr. The catalyst was removed and the filtrate concentrated to dryness. Crystallization (ethanol-ether) gave 10 g., m.p. 153–154° and recrystallization (ethanol-ether) gave m.p. 157–158°.

Anal. Calcd. for $C_{14}H_{22}BrNO$: C, 56.0; H, 7.4; N, 4.7. Found: C, 56.3; H, 7.1; N, 4.9.

3-(3-Dimethylaminopropoxy)-1-ethylpiperidine (Compound 7). Sodium hydride (3.1 g., 0.13 mol.) was stirred under 50 ml. of dry toluene while a solution of 15.4 g. (0.12 mol.) of 1-ethyl-3-piperidinol in 50 ml. of toluene was added over 40 min. Stirring was continued at 20° for 2 hr. and then under reflux for 2 hr. This solution was treated over 1 hr. with the filtered solution prepared from 38.4 g. (0.24 mol.) of 3-dimethylaminopropyl chloride hydrochloride dissolved in water, made basic with 40% sodium hydroxide, extracted with 150 ml. of toluene and dried (magnesium sulfate). Reflux was continued for 6 hr. When cool, the mixture was filtered and the residue distilled to yield 9.8 g. (38%) of product, b.p. 116–118° (6 mm.).

3-(3-Dimethylaminopropoxy)-1-ethyl-1-methylpiperidinium iodide methiodide (Compound 8). Addition of 3.2 g. (0.015 mol.) of 3-(3-dimethylaminopropoxy)-1-ethylpiperidine in 10 ml. of acetonitrile to a cooled solution of 4.7 g. (0.033 mol.) of methyl iodide in 15 ml. of acetonitrile caused an immediate exothermic reaction. After 20 hr. the precipitated product (4.7 g.) was separated.

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6-Alkylacridizinium Derivatives[1]

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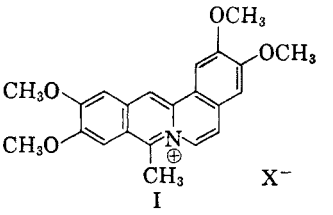
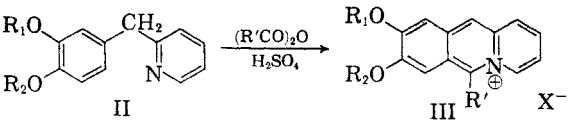
Probably the first reported compound containing the fully aromatic quinolizinium[2] nucleus was the Coralyn (I) of Schneider and Schroeter,[3,4] described in 1920. Coralyn, an 8-methyl-2,3,10,11-tetramethoxybenz[a]acridizinium salt was obtained in 90% yield by the action of sulfoacetic acid (acetic anhydride containing a small amount of sulfuric acid) on papaverine.



I

It seemed likely that 2-(3,4-dialkoxybenzyl)-pyridines (II) might be made to undergo a similar acylative cyclization, affording the first simple 6-alkylacridizinium salts III.



II III

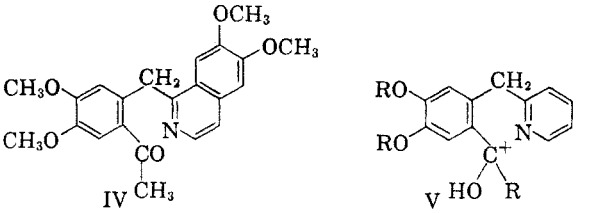
The requisite benzylpyridines (II) were prepared by reaction of 2-pyridyllithium with the appropriate aldehyde, followed by reduction of the crude carbinol. The acylative cyclization was carried out at 100° by means of sulfuric acid in a large excess of the appropriate anhydride, and the results are summarized in Table I.

TABLE I

6-ALKYL-8,9-ALKOXYACRIDIZINIUM SALTS (III)

R_1	R_2	R′	% Yield (as)	Ultraviolet Absorption Maxima, mμ (Perchlorate)		
CH_3	CH_3	CH_3	—[a]	368	382	401
C_2H_5	C_2H_5	CH_3	74[b](ClO_4)	370	384	404
C_2H_5	C_2H_5	C_2H_5	48[c]	370	385	405
—CH_2—		CH_3	25(Pic.)[d]			

[a] A 31% yield of sulfoacetate, m.p. 255–262° (dec.), was recorded, but this salt was never obtained in a state of analytical purity. [b] Product melting at 252–256° (dec.). [c] A part of the yield (25%) was obtained as the perchlorate m.p. 260–264° (dec.), the remainder (23%) as picrate, m.p. 188–192°. [d] No perchlorate of this compound was prepared.



IV V

Schneider and Schroeter[3] adduced evidence to show that the acetylative cyclization of papaverine occurred *via* acetopapaverine (IV). Probably the acylative cyclization of the 2-(3,4-dialkoxybenzyl)pyridine likewise occurs *via* a carbonyl derivative, or more exactly, *via* the conjugate acid V. The Coralyn synthesis can be regarded not only as the prototype of the Woodward synthesis of

(1) Taken in part from a thesis submitted in partial fulfillment of the requirements for the Ph.D. Degree, Duke University, 1958. This research was supported by a research grant (NSF-G2364) of The National Science Foundation.

(2) *Chemical Abstracts* nomenclature.

(3) W. Schneider and K. Schroeter, *Ber.* **53B**, 1459 (1920).

(4) W. Schneider and O. Boger, *Ber.*, **54B**, 2021 (1921).