[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES OF THE U. S. VITAMIN & PHARMACEUTICAL CORP.]

3-Oxypiperidine Derivatives

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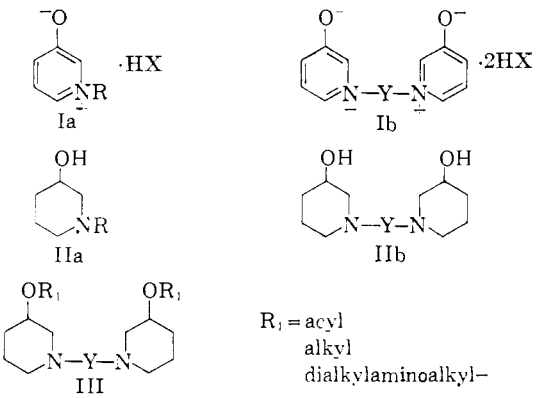
Reduction of 3-oxypyridyl betaines Ia and Ib with rhodium-on-carbon affords the corresponding N-substituted-3-hydroxypiperidine compounds IIa and IIb. The 3-hydroxypiperidines, their 3-oxy derivatives and quaternaries of these structures were examined for pharmacological activity. Significant central nervous system depression, and anti-inflammatory and curare-like activity were found with selected structures.

Formal structural relationships between 3-hydroxypiperidine and the ethanol amines have stimulated examination of derivatives of 3-hydroxypiperidines and related compounds for pharmacological activity, particularly as anti-cholinergic and anesthetic agents.[1-12]

With the availability of 3-oxypyridyl betaines of the type Ia and Ib,[13] reduction to the corresponding hydroxypiperidines of the type IIa and IIb was effected, and IIb was converted to bis-esters and bis-ethers of the type III. Quaternaries of II and III were also prepared.



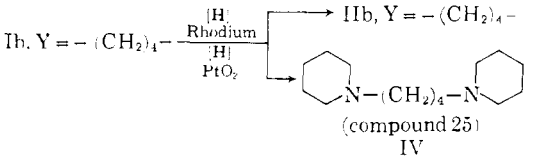
For the reduction[14-16] of betaines (Ia, Ib) to the hydroxypiperidines (IIa, IIb), rhodium-on-carbon proved to be an excellent catalyst. Although Rosenblatt[16] evaluated this catalyst widely for the reduction of phenyl groups we found the pyridine ring to be reduced selectively with no indication of reduction of the phenyl groups (compounds 3, 4, 11–15, 72).

Under the conditions employed, other functional groups on the betaines were not necessarily invulnerable to the hydrogenation. For example, with Ia, R = ω-cyanopentyl, the cyano group was completely reduced to yield IIa, R = ω-aminohexyl, as well as the corresponding bis-amine (compounds 9, 10).

With substituted phenacyl groups on the betaine nitrogen, reduction of the keto group to hydroxyl was invariably observed, (compounds 12–15), and in one instance (compound 11) reduction to the phenethyl group. The kinetic pattern defining the selectivity of these competitive hydrogenations has not been studied any further. When platinum dioxide was employed as the catalyst, with the betaine (Ib, Y = $-(CH_2)_4-$), hydrogenolysis of the piperidine hydroxyl group occurred to yield 1,4-di(1-piperidino)-butane (Scheme I).

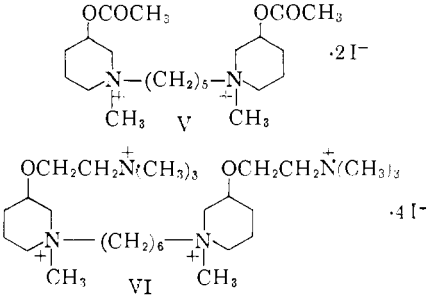
SCHEME I

COMPARISON OF RHODIUM AND PLATINUM DIOXIDE



The compounds IIb were converted to their derivatives (III) by acylation with the acid anhydrides and acid chlorides and alkylation with alkyl halides or dialkylaminoalkyl halides. The compounds prepared have been described in Tables I and II.

Pharmacology.—Of particular interest were structures which were bis cyclic analogs of acetylcholine[3] such as compound 42 (V) and polyfunctional hexamethonium analogs as compound 59 (VI). The



structure VI embodies the 6-atom chain between quaternary nitrogens at three different points within the molecule and was anticipated to have striking effectiveness. The compound proved to be extremely toxic ($LD_{min.}$ 1 mg./kg., s.c.) al-

(1) J. P. Long and H. H. Keasling, *J. Am. Pharm. Assoc.*, (*Sci. Ed.*), **43**, 616 (1954).
(2) F. Leonard and L. Simet, THIS JOURNAL, **77**, 2855 (1955).
(3) F. W. Schueler, *J. Am. Pharm. Assoc.*, (*Sci. Ed.*), **45**, 197 (1956).
(4) A. Lasslo, W. M. Marine and P. D. Waller, *J. Org. Chem.*, **21**, 958 (1956).
(5) L. Dûbravková, I. Ježo, P. Šefčovič and Z. Votický, *Chem. Zvesti*, **10**, 421 (1956) [*C. A.*, **51**, 8085c (1957)].
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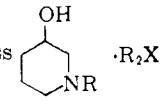
(8) P. Elsner, *Wien. klin. Wochschr.*, **67**, 1 (1955).
(9) J. H. Biel, H. L. Friedman, H A. Leiser and E. P. Sprengeler, THIS JOURNAL, **74**, 1485 (1952).
(10) J. H. Biel, E. P. Sprengeler, H. A. Leiser, J. Horner, A. Drukker and H. L. Friedman, *ibid.*, **77**, 2250 (1955).
(11) S. B. Coan and D. Papa, *J. Org. Chem.*, **20**, 774 (1955).
(12) K. Kamijo and G. B. Koelle, *J. Pharmacol. Exp. Therap.*, **112**, 444 (1954).
(13) S. L. Shapiro, K. Weinberg and L. Freedman, THIS JOURNAL, **81**, 5140 (1959).
(14) C. J. Cavallito and T. H. Haskell, *ibid.*, **66**, 1166 (1944).
(15) J. H. Biel, U. S. Patent 2,802,007, August 6, 1957.
(16) E. F. Rosenblatt, U. S. Patent 2,675,390, April 13, 1954.

TABLE I

3-OXYPIPERIDINES  ·R_2X

No.	R	R_2X	M.p.[a] or b.p., °C. (mm.)	RS[b]	Yield, %	Formula	Analyses,[c] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1[d]	C_2H_5–	HBr	144-146	A	81	$C_7H_{16}BrNO$	40.0	40.2	7.6	7.7	6.7	6.9
2	C_2H_5–	HPic.[e]	81–83	A		$C_{13}H_{18}N_4O_8$	43.6	43.6	5.0	5.0		
3	$C_6H_5CH_2$–	HCl	167–170	B	53	$C_{12}H_{18}ClNO$	63.3	63.5	7.9	8.0		
4	p-$ClC_6H_4CH_2$–	HCl	212–214	C	56	$C_{12}H_{17}Cl_2NO$	55.0	55.5	6.5	6.6	5.3	5.0
5	$(CH_3)_2N(CH_2)_2$–	2HCl	267–268	D	60	$C_9H_{22}Cl_2N_2O$	44.1	43.8	9.0	9.0		
6	$(CH_3)_2N(CH_2)_3$–	2HCl	222–226	C	48	$C_{10}H_{24}Cl_2N_2O$	46.3	45.6	9.3	9.4	10.8	10.6
9	$H_2N(CH_2)_6$–		110–112 (0.08)		24	$C_{11}H_{24}N_2O$	66.0	65.6	12.1	11.8	14.0	13.8
10	[f]		220–230 (0.2)		12	$C_{22}H_{46}N_2O_2$	68.9	68.4	11.8	11.4	11.0	10.8
11	$C_6H_5CH_2CH_2$–		66–68	E	2	$C_{13}H_{19}NO$	76.1	75.6	9.3	9.3	6.8	6.8
12	$C_6H_5CH(OH)CH_2$–		140–150 (0.05)		52	$C_{13}H_{19}NO_2$	70.6	69.5	8.7	8.7	6.3	6.4
13	p-$BrC_6H_4CH(OH)CH_2$–		125–140 (0.2)		8	$C_{13}H_{18}BrNO_2$	52.0	52.2	6.0	6.1	4.7	4.9
14	p-$ClC_6H_4CH(OH)CH_2$–		104–106	F	6	$C_{13}H_{18}ClNO_2$[g]					5.5	5.4
15	p-$C_6H_5C_6H_4CH(OH)CH_2$–		196–206 (0.05)		18	$C_{19}H_{23}NO_2$	76.7	76.5	7.8	7.8	4.7	4.9

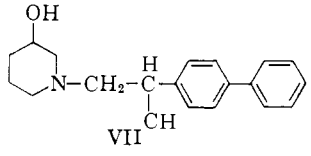
[a] Melting points are not corrected. [b] RS = recrystallizing solvent and includes additional solvents of Table II; A = ethyl acetate–ether; B = ethanol–ethyl acetate; C = methanol–ethyl acetate; D = methanol; E = hexane; F = heptane; G = ethanol; H = water; I = ethanol–hexane; J = ethyl acetate; K = ethanol–water; L = acetone–water; M = *n*-butanol; N = pentane; O = methanol–water. [c] Analyses by Weiler and Strauss, Oxford, England. [d] The benzoate hydrochloride melted 196–198°; R. H. Reitsema, THIS JOURNAL, **71**, 2041 (1949), reports m.p. 197–198°. [e] HPic. is the picric acid salt. [f] Bis-[ω-(3-hydroxy-1-piperidino)-hexyl]-amine. [g] Chlorine. Calcd. 13.9, found 14.1.

though no hypotensive effects were noted. Polyquaternary ammonium salts have been examined by Blicke[17] and Edwards.[18]

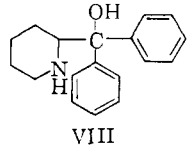
The compounds prepared were for the most part investigated for broad spectrum pharmacological responses and some of the more interesting effects are summarized.

The following compounds potentiated adrenalin[19a]: 6, 8, 15, 19, 28, 35, 39, 40, 44 and 51, while 58 and 63 had adrenergic blocking effects. Moderate ganglionic blocking action[19a] was shown by compound 44 and partial block was found with 8, 15, 28 and 36. In general, the compounds did not have profound lasting blood pressure[19b] effects although compounds 15, 28, 39 and 46 showed slight, lasting hypotension.

Compound 15 ($LD_{min.}$ 750 mg./kg., s.c.) at 20 mg./kg. reduced the motor activity of rats[19c] 43%. This compound (VII) bears a formal relationship to α-(2-piperidyl)-benzhydrol[20] (VIII).



VII



VIII

Depression in motor activity was also noted with compounds 7 and 59. Anti-inflammatory activity[19d] of 17 units/gram was obtained with compound 70, and other compounds showing lesser effectiveness were 57, 61, 39, 17, 35, 41, 43 and 46.

Curare-like effects[19e] approximating 1/10 the activity of decamethonium were noted with compounds 58, 66, 67, 69 and 70, the effect with 69 being irreversible.

Experimental[21]

N-(p-Chlorobenzyl)-3-hydroxypiperidine Hydrochloride (Compound 4).—A solution of 38.4 g. (0.15 mole) of N-(p-chlorobenzyl)-3-oxypyridyl betaine hydrochloride in 250 ml. of methanol and 2 g. of rhodium-on-carbon catalyst[22] was hydrogenated (starting at 50 p.s.i.) in the Parr hydrogenator for 4 hours at 20° at which point the theoretical (3 equivalents) uptake of hydrogen had occurred. The reaction mixture was filtered and 300 ml. of ether was added to the filtrate, whereupon 17 g. of product separated. The filtrate was concentrated to 125 ml. and upon addition of 260 ml. of ether a further crop of 15.5 g. (total yield 32.5 g., 83%) was obtained, m.p. 210–212°.

In a similar manner, complete hydrogen uptake was effected for the following: compounds 1 (1.75 hours), 3 (4.5 hours), 5 (1.5 hours), 6 (1 hour).

N-ω-Aminohexyl-3-hydroxypiperidine (Compound 9) **and Bis-[(3-hydroxy-1-piperidyl)-hexyl]-amine** (Compound 10).—A solution of 10.9 g. (0.048 mole) of N-ω-cyanopentyl-3-oxypyridyl betaine hydrochloride in 200 ml. of methanol and 2 g. of rhodium-on-carbon was hydrogenated over 9 hours, whereupon 18.2 pounds of hydrogen was absorbed (theory for 5 equivalents of hydrogen, 21.8 pounds). The catalyst was removed and washed with 150 ml. of water, and the combined filtrate and wash solution concentrated to remove the methanol. The aqueous solution of the products was basified (6 *N* sodium hydroxide) and extracted with two 100-ml. portions of chloroform. The combined chloroform extracts were dried (magnesium sulfate), filtered, the chloroform removed and the residue distilled to give compounds 9 and 10.

N-(β-Phenethyl)-3-hydroxypiperidine (Compound 11) **and N-(β-Hydroxy-β-phenethyl)-3-hydroxypiperidine** (Compound 12).—A solution of 40.8 g. (0.164 mole) of N-phenacyl-3-oxypyridyl betaine hydrochloride in 250 ml. of methanol, plus 2 g. of rhodium-on-carbon was hydrogenated over 13 hours, whereupon 62.3 pounds of hydrogen was absorbed (theory for 4 equivalents of hydrogen, 59.5 pounds; for 5 equivalents, 74.6 pounds). The reaction mixture was

(17) F. F. Blicke and E. B. Hotelling, THIS JOURNAL, **76**, 2422, 2427 (1954).

(18) (a) D. Edwards, J. J. Lewis, J. B. Stenlake and M. S. Zoha, *J. Pharm. Pharmacol.*, **9**, 1004 (1957); (b) **10** (Suppl.), 106T, 122T (1958).

(19) Methods of testing: (a) S. L. Shapiro, H. Soloway, E. Chodos and L. Freedman, THIS JOURNAL, **81**, 203 (1959); (b) S. L. Shapiro, H. Soloway and L. Freedman, *ibid.*, **80**, 2743 (1958); (c) S. L. Shapiro, I. M. Rose, E. Roskin and L. Freedman, *ibid.*, **80**, 1648 (1958); (d) S. L. Shapiro, H. Soloway and L. Freedman, *J. Am. Pharm. Assoc. (Sci. Ed.)*, **46**, 333 (1957); (e) S. L. Shapiro, H. Soloway, E. Chodos and L. Freedman, THIS JOURNAL, **81**, 201 (1959).

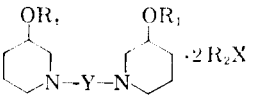
(20) B. B. Brown and H. W. Werner, *J. Pharmacol. Exp. Therap.*, **110**, 180 (1954).

(21) Descriptive data shown in the tables are not herein reproduced. The betaines used as the initial reactants have been described in the accompanying paper (ref. 13).

(22) Rhodium (5%)-on-carbon was obtained from Baker and Co., Inc., Newark, N. J., and was used directly without further treatment.

TABLE II

N,N′-POLYMETHYLENE-(BIS-3-OXYPIPERIDINES)



No.	R_1	R_2X	M.p.[a] or b.p., °C. (mm.)	RS[b]	Yield, %	Formula	Analyses,[c] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
						Y = $-(CH_2)_3-$						
16	H	..	146–151 (0.07)		50	$C_{13}H_{26}N_2O_2$	64.4	64.0	10.8	11.1	11.6	12.0
17	H	CH_3I	245–247	G	56	$C_{15}H_{32}I_2N_2O_2$	34.2	33.7	6.1	6.1	5.3	5.1
18	CH_3CO-	..	138–140 (0.05)		45	$C_{17}H_{30}N_2O_4$	62.6	62.7	9.3	9.3		
19	C_2H_5CO-	..	146–151 (.03)		48	$C_{19}H_{34}N_2O_4$	64.4	64.1	9.7	9.9	7.9	8.0
20	n-C_3H_7CO-	..	156–162 (.05)		57	$C_{21}H_{38}N_2O_4$	65.9	65.6	10.0	9.8	7.3	6.9
21	i-C_3H_7CO-	..	156–158 (.03)		50	$C_{21}H_{38}N_2O_4$	65.9	65.8	10.0	9.8	7.3	6.8
22	i-C_3H_7CO-	MT[i]	216–218	D		$C_{35}H_{54}N_2O_{10}S_2$	57.9	58.2	7.4	7.5	3.9	4.3
23	C_2H_5-	..	124 (0.02)		23	$C_{17}H_{34}N_2O_2$	68.4	68.1	11.5	11.4	9.4	8.9
24	$(CH_3)_2N(CH_2)_2-$	..	160–165 (0.15)		48	$C_{21}H_{44}N_4O_2$	65.6	65.1	11.5	11.3	14.6	15.1
						Y = $-(CH_2)_4-$						
25[j]	H	..	114–120 (0.05)		46							
26[k]	H	HPic.[e]	189–190	H		$C_{26}H_{34}N_8O_{14}$	45.8	45.9	5.0	4.9		
27	H	..	108–110	F	60	$C_{14}H_{28}N_2O_2$	65.6	65.7	11.0	10.9	10.9	11.3
28	H	HCl	263–265	C	56	$C_{14}H_{30}Cl_2N_2O_2$	51.1	50.9	9.1	9.4	8.5	8.8
29	H	HBr	261–262	C	40	$C_{14}H_{30}Br_2N_2O_2$					6.7	7.0
30	H	CH_3I	235–237	C	48	$C_{16}H_{34}I_2N_2O_2$					5.2	5.2
31	CH_3CO-	..	150–152 (0.02)		49	$C_{18}H_{32}N_2O_4$	63.5	64.1	9.55	9.7	8.2	7.8
32	C_2H_5CO-	HCl	270–275	I	37	$C_{20}H_{38}Cl_2N_2O_4$	54.4	54.2	8.6	8.6		
33	n-C_3H_7CO-	..	170–174 (0.02)		58	$C_{22}H_{40}N_2O_4$	66.6	66.6	10.2	10.0	7.1	6.9
34	i-C_3H_7CO-	..	156–162 (.02)		34	$C_{22}H_{40}N_2O_4$	66.8	66.8	10.2	10.2	7.1	7.0
35	C_2H_5-	..	139–146 (.1)		35	$C_{18}H_{36}N_2O_2$	69.2	68.9	11.6	11.7	8.9	8.9
36	$(CH_3)_2N(CH_2)_2-$		148–165 (.03)		21	$C_{22}H_{46}N_4O_2$	66.3	66.4	11.6	11.2	14.1	14.0
37	$(CH_3)_2N(CH_2)_2-$	$-CH_3I$[l]	158–160	J	42	$C_{26}H_{58}I_4N_4O_2$					5.8	5.3
						Y = $-(CH_2)_5-$						
38	H	..	176–180 (0.3)									
39	H	HBr	173–175	B	61	$C_{15}H_{32}Br_2N_2O_2$					6.5	6.8
40	H	CH_3I	257–258	G	73	$C_{17}H_{36}I_2N_2O_2$					5.1	4.9
41	CH_3CO-	..	158–164 (0.05)		74	$C_{19}H_{34}N_2O_4$					7.9	8.3
42	CH_3CO-	CH_3I	108–113	[m]		$C_{21}H_{40}I_2N_2O_4$	39.4	38.8	6.3	6.7	4.4	3.6
43	C_2H_5CO-		168–172 (0.04)		60	$C_{21}H_{38}N_2O_4$	65.9	66.4	10.0	10.0	7.3	7.2
44	n-C_3H_7CO-		177–184 (.03)		55	$C_{23}H_{42}N_2O_4$	67.3	67.4	10.2	10.2	6.8	6.7
45	i-C_3H_7CO-		178–188 (.04)		50	$C_{23}H_{42}N_2O_4$	67.3	67.2	10.2	10.1	6.8	6.7
46	C_2H_5-		140–150 (.01)		34	$C_{19}H_{38}N_2O_2$					8.6	8.8
47	$(CH_3)_2N(CH_2)_2-$		168–175 (.1)		34	$C_{23}H_{48}N_4O_2$	66.9	67.2	11.7	11.7	13.6	13.7
48	$(CH_3)_2N(CH_2)_2-$	CH_3I[l]	250–254	K	34	$C_{27}H_{60}I_4N_4O_2$[n]	33.1	32.7	6.1	6.2	5.7	5.8
						Y = $-(CH_2)_6-$						
49	H	..	91–93	E		$C_{16}H_{32}N_2O_2$					9.9	9.9
50	H	HBr	219–221	C	82	$C_{16}H_{34}Br_2N_2O_2$					6.3	6.1
51	H	CH_3I	182–184	G	71	$C_{18}H_{38}I_2N_2O_2$					4.9	4.9
52	CH_3CO-	..	67–69	L	8	$C_{20}H_{36}N_2O_4$	65.2	65.5	9.9	9.6	7.6	8.0
53	C_2H_5CO-	..	176–182 (0.03)		53	$C_{22}H_{40}N_2O_4$	66.6	66.7	10.2	10.0	7.1	6.8
54	n-C_3H_7CO-	..	188–190 (.03)		56	$C_{24}H_{44}N_2O_4$	67.9	67.9	10.5	10.1	6.6	6.8
55	i-C_3H_7CO-	..	180–185 (.02)		88	$C_{24}H_{44}N_2O_4$	67.9	68.4	10.5	10.3	6.6	6.6
56	p-$NO_2C_6H_4CO-$	HPic.[e]	224–225	M		$C_{42}H_{42}N_{10}O_{22}$	48.5	48.5	4.2	4.0	13.5	13.1
57	C_2H_5-	..	150–158 (0.08)		29	$C_{20}H_{40}N_2O_2$	70.5	70.6	11.8	11.6	8.2	8.3
58[o]	$(CH_3)_2N(CH_2)_2-$	..	186–190 (0.16)		16							
59	$(CH_3)_2N(CH_2)_2-$	CH_3I[l]	258–261	C	20	$C_{28}H_{62}I_2N_4O_2$	33.7	33.2	6.2	6.5	5.6	6.1
						Y = $-CHCH_3(CH_2)_2CH_3CH-$						
60	H	..	162–168 (0.05)		59	$C_{16}H_{32}N_2O_2$	67.6	67.7	11.3	11.1	9.9	9.9
61	CH_3CO-	..	158–162 (0.03)		81	$C_{20}H_{36}N_2O_4$	65.2	64.9	9.9	9.9	7.6	8.0
						Y = $-(CH_2)_{10}-$						
62	H	..	79–81	N		$C_{20}H_{40}N_2O_2$					8.2	7.9
63	H	HBr	189–193	C	33	$C_{20}H_{42}Br_2N_2O_2$	47.8	47.6	8.4	8.6	5.6	5.8
64	H	CH_3I	165–175	[p]		$C_{22}H_{44}I_2N_2O_2$	42.3	41.9	7.4	7.6	4.5	4.7
65	CH_3CO-	..	76–78	O	24	$C_{24}H_{44}N_2O_4$	67.9	68.2	10.5	10.2	6.6	6.7

TABLE II (*Continued*)

No.	R_1	R_2X	M.p.[a] or b.p., °C. (mm.)	RS[b]	Yield, %	Formula	Analyses,[c] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
66	C_2H_5CO-	..	196–204 (0.03)		64	$C_{26}H_{48}N_2O_4$	69.0	69.2	10.7	10.9		
67	n-C_3H_7CO-	..	208–210 (0.08)		28	$C_{28}H_{52}N_2O_4$					5.8	5.8
68	n-C_3H_7CO-	MT[j]	125–127	M	6	$C_{44}H_{72}N_2O_{10}S_2$	62.0	61.8	8.5	8.4	3.3	3.0
69	i-C_3H_7CO-		198–208 (0.02)		34	$C_{28}H_{52}N_2O_4$	70.0	70.2	10.9	10.8	5.8	6.2
70	C_2H_5-		180–188 (0.2)		44	$C_{24}H_{48}N_2O_2$					7.1	6.9
			Y = p,p'-$CH_2C_6H_4CH_2-$									
71	H		140–143	F		$C_{18}H_{28}N_2O_2$	71.0	70.9	9.3	9.2		
72	H	HCl	309–310	K	35	$C_{18}H_{30}Cl_2N_2O_2$	57.3	57.2	8.0	8.1		

[a–h] Footnotes are the same as for Table I. [i] MT = methyl p-toluenesulfonate quaternary. [j] Using platinum dioxide as the hydrogenation catalyst, the hydroxyl groups were removed to yield 1,4-di-(1-piperidino)-butane; see picrate for analysis. [k] Dipicrate of preceding compound. [l] Compound is tetramethiodide. [m] Compound was quite hygroscopic and was triturated with hexane, dried, and submitted for analyses which, however, were not completely acceptable. [n] Iodine calcd., 51.8, found 51.5. [o] Not obtained analytically pure. [p] Not recrystallized.

worked up as described above using ether as the extracting solvent and the residue obtained was distilled. The portion (5.0 g.) distilling at 90–95° (0.09 mm.) became semi-crystalline on standing. The crystalline material was separated from a supernatant orange oil by decantation and recrystallized from hexane. There was obtained 0.4 g. of product (compound 11), m.p. 66–68°. The other fraction (compound 12) of 22 g. boiled at 140–150° (0.05 mm.).

For compound 13, hydrogenation of the corresponding betaine for 16 hours gave but 51% of the theoretical hydrogen uptake for 4 equivalents of hydrogen and an ultimate yield of but 8% of the product. Similarly, compound 14, after 11 hours of hydrogenation showed but 73% of the theoretical hydrogen uptake for 4 equivalents of hydrogen, and ultimately isolation of the product in 6% yield. In the preparation of compound 15, the theoretical hydrogen uptake was obtained after 11 hours of hydrogenation, with 18% yield of the product.

General Procedure for Preparation of the Bis-[α,ω-N-(3-hydroxypiperidino)]-alkanes.—A solution of 0.1 mole of the corresponding betaine hydrohalide in 250 ml. of methanol, plus 2 g. of rhodium-on-carbon was hydrogenated as above. The compound number/hours of hydrogenation/% of theoretical uptake of 6 equivalents of hydrogen are shown as follows: 16/4/88; 28/1/91; 39/6/100; 50/5/98; 60/1.5/91; 63/2/96; 72/7/98. The uptake of 6 equivalents of hydrogen in the preparation of compound 72 is indicative that the two pyridine rings of the corresponding betaine are being reduced to the exclusion of the phenyl ring.

The compounds were either isolated as the hydrohalide salt or converted to the corresponding base by familiar procedures.

α,ω-Bis-(3-Hydroxypiperidino)-propane Dimethiodide (Compound 17).—A solution of 2 g. of compound 16 in 10 ml. of ethanol and 10 ml. of methyl iodide was heated under reflux for 1 hour. After standing for 20 hours, the formed crystals, 4.26 g. (98%), were separated, m.p. 244–246°.

α-ω-Bis-[3-(isobutyroxypiperidino]-propane (Compound 21).—A solution of 3.9 g. (0.0161 mole) of compound 16 in 20 ml. of pyridine was treated dropwise with stirring with 7.4 g. (excess) of isobutyryl chloride over a period of 30 minutes. After standing 20 hours, the crystalline precipitate (11.5 g.) was separated, dissolved in 15 ml. of water and 60 ml. of ether, and 1 N sodium hydroxide added until pH 8. After shaking, the ether layer was separated, the aqueous layer extracted with an additional 50 ml. of ether and the combined ether extracts were dried (magnesium sulfate), filtered, the ether evaporated and the residue distilled. The product (3.06 g.) was obtained as the fraction boiling at 156–158° (0.03 mm.).

Treatment of this product (1.2 g.) in 8 ml. of acetonitrile with 5 ml. of methyl p-toluenesulfonate afforded a crystalline product after standing 10 days. This was then separated (0.2 g.) and recrystallized to give the bis-(methyl tosylate quaternary), (compound 22).

α,ω-Bis-[3-Dimethylaminoethoxy-piperidino]-propane (Compound 24).—Compound 16 (10.5 g., 0.043 mole) in 90 ml. of toluene at 50°, was treated with 2.54 g. (0.105 mole) of sodium hydride and the mixture stirred under reflux for 2 hours.

A solution of 20.9 g. (0.145 mole) of dimethylaminoethyl chloride hydrochloride in 45 ml. of water was treated with 75 ml. of 6 N sodium hydroxide and the free base extracted with 2 × 20 ml. of toluene. The toluene extract was dried (magnesium sulfate) and after filtration added to the refluxing reaction mixture above. Reflux and stirring were continued for 20 hours. When cool, the reaction mixture was centrifuged, the supernatant decanted, the toluene evaporated and the residue distilled. There was obtained 7.86 g. of product (48%), b.p. 160–165° (0.155 mm.).

α,ω-Bis-[3-(acetoxy-piperidino]-pentane (Compound 41).—A solution of 4.7 g. (0.019 mole) of compound 38 in 49 ml. of acetic anhydride was maintained at 20° for 6 days. The excess of the anhydride was removed and the residue dissolved in 30 ml. of ether. After addition of 15 ml. of water, 1 N sodium hydroxide was added with shaking, to pH 8. The ether layer was separated and the aqueous layer extracted with an additional 25 ml. of ether. The ether extracts were combined, dried (magnesium sulfate), filtered, the ether removed and the residue distilled to yield the product, b.p. 158–164° (0.05 mm.).

Using this compound, its corresponding dimethiodide (compound 42) was prepared by treatment of 177 mg. (0.0005 mole) in 5 cc. of hexane to which was added 1 ml. of a hexane solution prepared from 1.2 g. of methyl iodide in 10 cc. of hexane. After standing in the dark for 4 days, the formed precipitate was separated by centrifugation, triturated with additional hexane, re-centrifuged and the product separated. This product was quite hygroscopic and resisted further purification.

α,ω-Bis-(3-ethoxypiperidino)-decane (Compound 70).—A solution of 7.6 g. (0.022 mole) of compound 62 in 100 ml. of toluene at 50° was treated with 1.2 g. of sodium hydride (0.04 mole) and the mixture stirred under reflux for 2 hours. When cool, 7.2 g. (0.046 mole) of ethyl iodide was added and the reaction mixture stirred under reflux for 3 hours. The formed sodium iodide was separated, the filtrate concentrated under vacuum and the residue distilled.

α,ω-Bis-(piperidino)-butane (Compound 25).—A mixture of 15.85 g. (0.05 mole) of N,N'-tetramethylene-bis-3-oxypyridyl betaine dihydrochloride in 250 ml. of ethanol and 0.5 g. of platinum dioxide was hydrogenated for 9 hours, whereupon 29.8 pounds of hydrogen had been absorbed (theory for 6 equivalents of hydrogen, 27.3 pounds). The reaction mixture was worked up as described for the previous hydrogenations and the product (4.5 g.), b.p. 114–120° (0.05 mm.), crystallized on standing, m.p. 82°. Upon recrystallization (heptane) it melted at 107–110°. The compound was characterized as its picrate (compound 26).

Hydrogenation of N,N'-(1,4-Buta-2-enylene)-bis-3-oxypyridyl Betaine Dihydrobromide.—After 27 hours of hydrogenation, this compound (0.132-mole run) absorbed 79.8 pounds of hydrogen (theory for 7 equivalents of hydrogen including the double bond in the hydrocarbon linking element, 84 pounds). The workup of the product in the usual manner yielded upon conversion to the base, 27 g. (80%) of compound 27, m.p. 86–91°, indicating the saturation of the double bond (recrystallization (heptane), m.p. 108–112°).

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