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Spiranes. VII. Spiroethers

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In the course of an extended study of spiro compounds (2), a series of bis(hydroxyalkyl) and bis-(haloalkyl) derivatives of alicyclic and heterocyclic materials was prepared by essentially standard methods. These derivatives have been demonstrated (2d) to be useful in the synthesis of spiro and polyspiro compounds. The diols (Table I) obtained by lithium aluminum hydride reduction of the precursor diesters (3) were converted in high yield to spiro ethers (Table III) either by heating with sulfuric acid (80%) or hydrobromic acid (48%), as described for the preparation of 3-oxaspiro[5.5]undecane (2d). Treatment of the diols with a mixture of hydrobromic and sulfuric acids (2:1) afforded the dibromides (Table II) accompanied by ether formation. Since the ethers could be cleaved to the dibromide by heating with the same mixture of acids the overall efficiency of the conversion of diol to dibromide was satisfactory (60-70%). 1-Methyl-4,4-bis-(β-hydroxyethyl)piperidine (I), was obtained by lithium aluminum hydride reduction of diethyl 1-methylpiperidine-4,4-diacetate (2c). This compound could not be converted to the dibromide with mixed acid. In this instance it seems likely that intramolecular quaternization occurred leading to the formation of water-soluble products which were not isolated. Treatment of I with thionyl chloride afforded 1-methyl-4,4-bis-(β-chloroethyl)piperidine hydrochloride (II) in high yield, whereas with warm 80% sulfuric acid I gave the ether, 9-methyl-3-oxa-9-azaspiro[5.5]undecane (III).

Pharmacology: The spiro ethers were screened for a variety of pharmacologic effects but no clear pattern of activity was observed. 9-*t*-Butyl-3-oxaspiro[5.5]undecane (4, Table III) caused a moderate decrease (30-60 mm. Hg) in blood pressure lasting more than 60 minutes when administered to anesthetized cats (I. P., 20 mg./kg.). In the same test *trans*-dodecahydrospiro[2*H*-indene-2,4'-(4*H*)-pyran] (5, Table III) produced a marked decrease (>61 mm. Hg) in blood pressure (I. V., 20 mg./kg.) which persisted for 12-13 minutes.

EXPERIMENTAL (4)

1-Methyl-4,4-bis-(β-hydroxyethyl)piperidine (I).

Reduction of 100 g. (0.37 mole) of diethyl-1-methylpiperidine-4,4-diacetate with 19 g. (0.5 mole) of lithium aluminum hydride afforded 51 g. (74%) of product. Due to the relative insolubility of I in ether it was necessary to extract the filter-cake several times with hot isopropyl alcohol in order to obtain the optimum yield. After recrystallization from methanol-acetone the material melted 83-84°.

1-Methyl-4,4-bis-(β-chloroethyl)piperidine (II).

A solution of 51 g. (0.27 mole) of 1-methyl-4,4-bis-(β-hydroxyethyl)piperidine in methylene dichloride (300 ml.) was added slowly to a stirred solution of thionyl chloride (48 ml.) in methylene dichloride (400 ml.). The reaction mixture was stirred and refluxed for 2-3 hours. The solvent and excess thionyl chloride were removed under reduced pressure. Fresh solvent (400 ml.) was added and again removed. The residue was diluted with ether (500 ml.) and the product was filtered off, washed with ether, and dried, m.p. 156-157°, yield, 69 g. (97%).

9-Methyl-3-oxa-9-azaspiro[5.5]undecane (III).

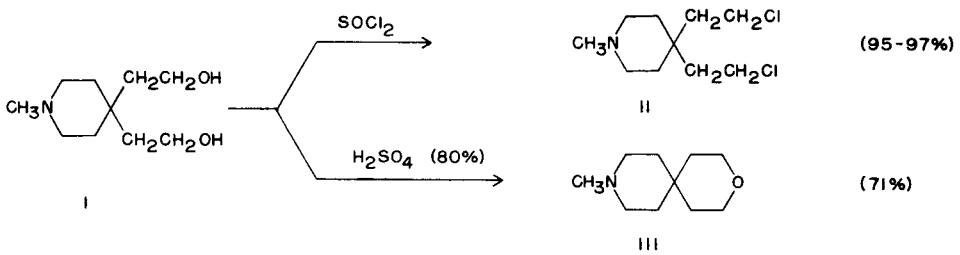
1-Methyl-4,4-bis-(β-hydroxyethyl)piperidine, 25 g. (0.134 mole), was added in portions to 100 ml. of 80% sulfuric acid. After the initial exotherm subsided the solution was heated (80-90°) for 3 hours on the steam-bath. After cooling it was poured onto 500 g. of ice and then made basic by the addition of 40% sodium hydroxide. The solution was extracted into benzene, washed (saline), and dried over sodium sulfate. After removing the benzene the residue was distilled under reduced pressure and the fraction boiling at 115-118°/12 mm. was collected. The yield was 16 g. (71%).

General procedure - (A) - for spiro ethers.

A solution of the glycol (1 part) and 48% hydrobromic acid (5 parts) was heated at 100° for 20 hours. After cooling and diluting with water the product was extracted into ether, the ether solution was washed with water, then with sodium bicarbonate and dried over sodium sulfate. After removing the solvent the product was obtained by vacuum distillation (75-90%).

(B) Dibromides.

A solution of 1 part of glycol or spiro ether in 5 parts of a 1:2 mixture of concentrated sulfuric acid and 48% hydrobromic acid was heated at 100° for 20 hours. The reaction mixture was worked up as in (A). The yield of distilled dibromide was 65-70%.

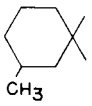
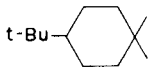
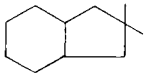
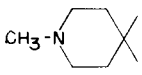


I II III

TABLE I

bis-(Hydroxyalkyl)-Derivatives

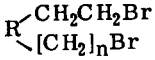
$$R\begin{matrix}\diagup CH_2CH_2OH \\ \diagdown [CH_2]_nOH\end{matrix}$$

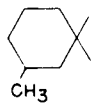
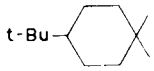
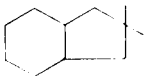
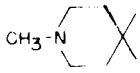
	R	B.p., M.p.*	n	Formula	%C Calcd.	%C Found	%H Calcd.	%H Found
1	 (a)	116-120°/0.15 mm	2	$C_{10}H_{20}O_2$	69.72	70.01	11.70	11.83
2		115-123°/0.15 mm	1	$C_9H_{18}O_2$	68.31	68.20	11.47	11.45
3		113-137°/0.1 mm	2	$C_{11}H_{22}O_2$	70.92	70.97	11.90	11.88
4		119-120°*	2	$C_{14}H_{28}O_2$	73.63	73.83	12.36	12.07
5		50-51°*	2	$C_{13}H_{24}O_2$	73.53	73.38	11.39	11.44
6		110-120°/0.1 mm	2	$C_9H_{18}O_2$	68.31	68.06	11.47	11.30
7		83-84°*	2	$C_{10}H_{21}NO_2$ (b)	64.12	64.38	11.30	11.26

(a) J. N. Ashley, R. F. Collins, M. Davis, and N. E. Siritt, *J. Chem. Soc.*, 3307 (1958). (b) Calcd. for $C_{10}H_{21}NO_2$: N, 7.48. Found: 7.39.

TABLE II

bis-(Bromoalkyl)-Derivatives

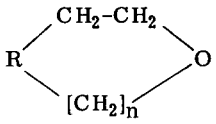


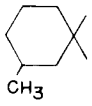
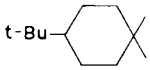
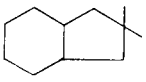
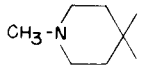
	R	B.p., M.p., °C	n	Formula	%C Calcd.	%C Found	%H Calcd.	%H Found	Yield %
1		116-120°/0.2 mm	2	$C_{10}H_{18}Br_2$	40.28	40.34	6.08	6.02	35
2		112-115°/0.5 mm	1	$C_9H_{16}Br_2$	38.05	38.29	5.68	5.71	76
3		128-131°/0.1 mm	2	$C_{11}H_{20}Br_2$	42.33	42.43	6.44	6.32	32
4		145-147°/0.1 mm (a)	2	$C_{14}H_{26}Br_2$	47.45	47.22	7.39	7.19	27
5		145-145°/0.1 mm (b)	2	$C_{13}H_{22}Br_2$	46.17	46.19	6.56	6.28	24
6		95-97°/0.1 mm	2	$C_9H_{16}Br_2$	38.05	38.41	5.69	5.68	47
7		156-157°	2	$C_{10}H_{20}Cl_3N$		(c)		(c)	95

(a) M.p., 64-65° [methanol]. (b) M.p., 47-48° [methanol]. (c) Analysis; Calcd: N, 5.38; Cl, 40.80. Found: N, 5.16; Cl, 40.55.

TABLE III

Spiro Ethers



	R	n	B.p., °C	Formula	%C Calcd.	%C Found	%H Calcd.	%H Found	Yield %
1		2	55-57°/0.5 mm	$C_{10}H_{18}O$	77.86	77.60	11.76	11.74	47
2		1	42-45°/5 mm	$C_9H_{16}O$	77.08	76.77	11.50	11.43	6
3		2	93-94°/10 mm	$C_{11}H_{20}O$	78.51	78.73	11.97	11.96	36
4		2	96-100°/0.1 mm	$C_{14}H_{26}O$	79.93	79.61	12.46	12.33	23
5		2	75-76°/0.1 mm	$C_{13}H_{22}O$	80.35	80.03	11.42	11.38	37
6		2	63-64°/10 mm	$C_9H_{16}O$	77.08	76.85	11.52	11.29	43
7		2	90-95°/3 mm	$C_{10}H_{19}NO$ (a)	70.95	70.78	11.32	11.14	71 (b)

(a) Analysis: Calcd.; N, 8.28. Found: 8.32. (b) Method B.

REFERENCES

(1) Present Address - Dept. of Pharmaceutical Chemistry, Howard University, Washington, D. C.

(2a) C. H. Grogan, C. F. Geschickter, and L. M. Rice, *J. Med. Chem.*, 7, 78 (1964). (b) L. M. Rice, C. F. Geschickter and C. H. Grogan, *ibid.*, 6, 388 (1963). (c) M. E. Freed, C. H. Grogan and L. M. Rice, *J. Heterocyclic Chem.*, 1, 125 (1964). (d) L. M. Rice, M. E. Freed and C. H. Grogan, *J. Org. Chem.*, 29, 2637 (1964).

(3) A. L. Vogel, *J. Chem. Soc.*, 1758 (1934).

(4) Melting points were taken on a Hoover-Thomas melting point apparatus and are corrected.

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