430. *Some Bisquaternary Salts.*

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A series of bisquaternary salts has been prepared (for pharmacological study) in which two heterocyclic nuclei are joined by a polymethylene chain attached to the quaternary nitrogen atoms.

Polymethylene bisammonium salts have been shown to have considerable activity in paralysing transmission in autonomic ganglia (Barlow and Ing, *Brit. J. Pharmacol.*, 1948, **3**, 298; Paton and Zaimis, *ibid.*, 1949, **4**, 381), and in particular hexamethylenebistrimethylammonium salts ("Hexamethonium" salts) have found application in the treatment of both hypertension and peptic ulceration. It has been reported (Collier and Taylor, *Nature*, 1949, **164**, 491; Taylor, *J.*, 1951, 1150) that when the ammonium groups are derived from heterocylic compounds and are separated by a chain of ten carbon atoms the salts possess high neuromuscular blocking activity. One such compound, hexamethylenebis-1-1'-methylpiperidinium di-iodide, has been described by von Braun (*Ber.*, 1910, **43**, 2860) and, when pharmacological examination of this compound gave promising results, we prepared salts in which the chain length and the heterocyclic component were varied. Several of these were considerably more active than "Hexamethonium" salts. The compounds from unsaturated heterocyclic compounds were less active than those from simple saturated analogues.

Three general methods of preparation were used. The *N*-methyl or *N*-ethyl saturated (Method A) or unsaturated heterocyclic base (Method B) was heated in alcohol with less than 0·5 mol. of polymethylene dihalide. In some cases it was advantageous to heat the base in acetone solution with the dibromide and an equivalent of sodium iodide, and to isolate the quaternary di-iodide. Alternatively, 2 mols. of the saturated ring-compound were condensed with the polymethylene dibromide, and the resulting diacid base treated with methyl or ethyl iodide (Method C). In the case of piperazine one of the nitrogen atoms was protected by a carbethoxy-group, which was ultimately removed by acid hydrolysis. In Method D, a diamidine was condensed with acetylacetone in pyridine, and the polymethylenebispyrimidine treated with methyl iodide. Condensation of hexamethylenediamine with tetramethylene dibromide yielded as isolable products a mixture of 1 : 6-dipyrrolidino-*n*-hexane and 6-pyrrolidino-*n*-hexylamine, which were separated by distillation and treated with methyl iodide (Method E); this avoids the use of the relatively inaccessible pyrrolidine, which is most conveniently prepared by the lithium aluminium hydride reduction of succinimide (cf. the reduction of phthalimide by Uffer and Schlittler, *Helv. Chim. Acta*, 1948, **31**, 1399).

Experimental

1 : 4-*Dimethylpiperidine*.—4-Methylpiperidine (58 ml.) was added with cooling to 98% formic acid (60 ml.). 40% Aqueous formaldehyde (60 ml.) was added, and the solution was heated on the steam-bath overnight. After the addition of excess of concentrated hydrochloric acid, the solution was evaporated to a paste. Excess of 50% potassium hydroxide solution was added, and the *base* distilled off, dried (KOH), and distilled, as a colourless oil, b. p. 125° (Found : N, 12·4. $C_7H_{15}N$ requires N, 12·1%).

1 : 6-*Dimorpholinohexane*.—1 : 6-Dibromohexane (24 g.), morpholine (102 g.), and dry benzene (100 ml.) were heated under reflux for 16 hours. The mixture was cooled and poured into excess of 2N-hydrochloric acid, and the aqueous layer was washed with benzene. The aqueous solution was strongly basified with sodium hydroxide and extracted with ether. The extract was dried ($MgSO_4$) and evaporated; distillation gave the *base* (13 g., 52%), prisms, m. p. 41°, b. p. 190°/11 mm. (Found : C, 65·3; H, 10·7; N, 10·7. $C_{14}H_{28}O_2N_2$ requires C, 65·6; H, 10·9; N, 10·9%).

Hexamethylenebis-1-4-*carbethoxypiperazine* was similarly obtained, and crystallised from light petroleum in colourless needles, m. p. 75° (Found : N, 13·9. $C_{20}H_{38}O_4N_4$ requires N, 14·1%).

Reaction of Hexamethylenediamine with Tetramethylene Dibromide.—Hexamethylenediamine (11·6 g., 0·1 mol.), potassium carbonate (28 g., 0·2 mol.), and dry ethanol (100 ml.) were heated under reflux. Tetramethylene dibromide (43·2 g., 0·2 mol.) was added dropwise during 1 hour,

and heating was continued a further 6 hours. The solvent was evaporated, and the residue was treated with 30% aqueous sodium hydroxide. The basic products were extracted into ether, which was dried ($MgSO_4$) and distilled, giving impure 6-pyrrolidino-*n*-hexylamine (2 g., 12%), b. p. 127—129°/12 mm. (Found: N, 15·9. Calc. for $C_{10}H_{22}N_2$: N, 16·5%), and 1 : 6-*dipyrrolidino*-n-*hexane* (3·4 g., 30%), b. p. 148—151°/12 mm. (Found: N, 12·45. $C_{14}H_{28}N_2$ requires N, 12·5%).

1-6′-*Dimethylamino*-n-*hexylpyrrolidine Dimethiodide.*—6-Pyrrolidino-*n*-hexylamine (3·4 g.) and methyl iodide (11·5 ml.) were added to a solution of sodium hydroxide (5·6 g.) in methanol (60 ml.), heated under reflux for 4 hours, and then evaporated to dryness. The residual *salt* was extracted with ether and with hot acetone, then crystallised from dry ethanol, and formed

	X{A·[CH_2]$_n$·A}X				Method of	Found, %		Reqd., %	
n	A	X	M. p.	Formula	prepn.	N	Hal	N	Hal
6	2-(1 : 4 : 6-Trimethylpyrimidyl)	I	240° *	$C_{20}H_{32}N_4I_2$	D	9·8	43·3	9·6	43·6
8	,,	,,	243 *	$C_{22}H_{36}N_4I_2$	D	9·3	42·2	9·2	41·7
10	,,	,,	198 *	$C_{24}H_{40}N_4I_2$	D	8·7	39·0	8·8	39·8
4 [a]	1 : 4-Dimethylglyoxalino	Picrate	187	$C_{26}H_{28}O_{14}N_{10}$	B	19·8	—	19·4	—
5 [a]	,,	,,	149	$C_{27}H_{30}O_{14}N_{10}$	B	19·4	—	19·4	—
6 [a]	,,	Br	227	$C_{16}H_{28}N_4Br_2$	B	12·7	37·0	12·8	36·7
4 [a]	1-Ethyl-2-methylbenziminazolino	,,	312	$C_{24}H_{32}N_4Br_2$	B	10·4	29·7	10·4	29·9
6 [a]	,,	,,	298	$C_{26}H_{36}N_4Br_2$	B	9·7	28·2	9·9	28·3
3 [a]	1-Methylbenzotriazolino	,,	194—195	$C_{17}H_{20}N_6Br_2$	B	17·4	32·6	17·1	32·6
4 [a]	,,	,,	231 *	$C_{18}H_{22}N_6Br_2$	B	17·2	33·3	17·4	33·2
5 [a]	,,	,,	213 *	$C_{19}H_{24}N_6Br_2$	B	16·6	31·9	16·9	32·2
6 [a]	,,	,,	228 *	$C_{20}H_{26}N_6Br_2$	B	16·7	32·0	16·5	31·4
10 [a]	,,	I	170 *	$C_{24}H_{34}N_6I_2$	B	12·7	38·9	12·7	38·5
5 [a]	2-Methylbenzotriazolino	Picrate	154	$C_{31}H_{28}O_{14}N_{12}$	B	21·2	[b]	21·2	—
6	Thiazolino	Br	226	$C_{12}H_{18}N_2S_2Br_2$	B	6·7	38·6	6·8	38·7
6	Benzothiazolino	,,	232	$C_{20}H_{22}N_2S_2Br_2$	B	5·6	31·1	5·5	31·2
1	1-Methylpiperidino	I	338 *	$C_{13}H_{28}N_2I_2$ [f]	C	5·7	53·5	5·9	53·5
2	,,	,,	275	$C_{14}H_{30}N_2I_2$	C	5·7	53·1	5·8	52·9
3	,,	,,	266	$C_{15}H_{32}N_2I_2$	A	5·6	51·2	5·7	51·4
4	,,	,,	265	$C_{16}H_{34}N_2I_2$	A	5·4	49·4	5·5	50·0
5	,,	Br	270 [c]	$C_{17}H_{36}N_2Br_2$ [f]	A	6·4	36·7	6·4	36·6
6	,,	,,	255 *	$C_{18}H_{38}N_2Br_2$ [f]	A	5·8	35·5	6·2	35·4
7	,,	I	235	$C_{19}H_{40}N_2I_2$	A	4·9	45·8	5·1	46·2
3	1-Ethylpiperidino	Br	282	$C_{17}H_{36}N_2Br_2$	A	6·4	37·1	6·5	37·3
10	,,	,,	238	$C_{24}H_{50}N_2Br_2$	A	5·4	30·8	5·3	30·4
5	1 : 2-Dimethylpiperidino	I	290	$C_{19}H_{40}N_2I_2$	A	5·0	46·0	5·1	46·2
6	,,	Br	265	$C_{20}H_{42}N_2Br_2$	A	5·9	33·7	5·9	34·0
5	1 : 3-Dimethylpiperidino	I	256	$C_{19}H_{40}N_2I_2$	A	5·1	46·1	5·1	46·2
6	,,	,,	245	$C_{20}H_{42}N_2I_2$	A	5·0	44·9	5·0	45·0
5	1 : 4-Dimethylpiperidino	,,	245	$C_{19}H_{40}N_2I_2$	A	5·2	46·0	5·1	46·2
6	,,	,,	255 [c]	$C_{20}H_{42}N_2I_2$ [f]	A	5·0	44·1	4·9	44·3
3	1-Methylpyrrolidino	,,	286 *	$C_{13}H_{28}N_2I_2$ [f]	A	5·8	53·6	5·9	53·4
4	,,	,,	276	$C_{14}H_{30}N_2I_2$	A	5·8	53·1	5·8	52·8
5	,,	,,	292	$C_{15}H_{32}N_2I_2$ [f]	A	5·5	50·8	5·5	50·5
6	,,	,,	179	$C_{16}H_{34}N_2I_2$	C	5·6	50·2	5·5	49·9
6	,,	Br	232	$C_{16}H_{34}N_2Br_2$	—	6·1	35·3	6·2	35·5
6	,,	Tartrate	196	$C_{24}H_{44}O_{12}N_2$ [f]	—	5·0	[d]	5·0	—
12	,,	I	188	$C_{22}H_{46}N_2I_2$	A	4·7	42·7	4·7	42·7
14	,,	,,	150	$C_{24}H_{50}N_2I_2$	A	4·5	41·3	4·5	41·0
6	1-Ethylpyrrolidino	Br	287	$C_{18}H_{38}N_2Br_2$	A	6·1	35·9	6·3	36·2
4	4-Methylmorpholino	,,	250	$C_{14}H_{30}O_2N_2Br_2$	A	6·5	36·7	6·5	36·6
5	,,	,,	240	$C_{15}H_{32}O_2N_2Br_2$	A	6·5	36·7	6·5	37·0
6	,,	I	217	$C_{16}H_{34}O_2N_2I_2$	C	4·8	47·5	5·2	47·0
7	,,	,,	204	$C_{17}H_{36}O_2N_2I_2$	A	5·0	46·1	5·0	45·8
7	,,	Br	236	$C_{17}H_{36}O_2N_2Br_2$	A	6·1	34·7	6·1	34·8
9	,,	I	197	$C_{19}H_{40}O_2N_2I_2$	A	5·0	42·7	4·7	42·3
12	,,	,,	173	$C_{22}H_{46}O_2N_2I_2$	A	4·4	40·7	4·5	40·7
6	4-Ethylmorpholino	,,	249 *	$C_{18}H_{38}O_2N_2I_2$	C	4·7	44·3	4·9	44·7
6	4-Carbethoxy-1-methylpiperazino	,,	213 *	$C_{22}H_{44}O_4N_4I_2$	C	8·1	37·1	8·2	37·2
6	1-Methylpiperazino	I,2HCl	200	$C_{16}H_{38}N_4Cl_2I_2$	—	9·1	[e]	8·9	—

* With decomp.

[a] It is not known which nitrogen atom is quaternary. [b] Found: C, 46·9; H 3·5. Required: C, 47·0; H, 3·6%. [c] After loss of water at a lower temperature. [d] Found: C, 51·2; H 8·2. Required: C, 51·3; H, 8·0%. [e] Found: Cl, 11·6; I, 40·5. Required: Cl, 10·8; I, 40·9%. [f] $+0·5H_2O$. [g] $+2H_2O$.

colourless needles (3 g., 30%), m. p. 199° (Found : N, 5·7; I, 53·2. $C_{14}H_{32}N_2I_2$ requires N, 5·8; I, 52·6%).

Polymethylenebisdiamidine Dihydrochlorides.—These have all been previously described [Easson and Pyman, *J.*, 1931, 2999; Sin'iti Kawai, Tatsuo Hosono, Yoshio Shikinami, and Shunychi Yonechi, *Sci. Papers Inst. Phys. Chem. Res.* (*Tokyo*), 1931, **16**, Nos. 306—9, 9—16 (*Chem. Abs.*, 1931, **25**, 5665)], but the following procedure gives improved yields (70—85%).

A solution of the polymethylene dicyanide (0·1 mol.) and dry ethanol (14 ml.) in dry ether (70 ml.) was cooled in ice and saturated with hydrogen chloride. The mixture was kept overnight, and the solid was collected and powdered under dry ether. The liquid was decanted and the residue stirred into ice-cooled saturated ethanolic ammonia (250 ml.). The mixture was kept at 40° for 22 hours, heated under reflux for 1 hour, then cooled, and filtered. Amidine hydrochloride sufficiently pure for the next stage was precipitated from the filtrate by the addition of dry ether.

Hexamethylenebis-2-(4 : 6-*dimethylpyrimidine*).—Suberodiamidine dihydrochloride (5·26 g.), piperidine (6 ml.), and acetylacetone (8 ml.) were heated in pyridine (60 ml.) under reflux for 3 hours. The clear solution was steam-distilled, and the residue cooled in ice. The colourless solid *base* was collected and crystallised from benzene–light petroleum, forming flattened needles (4·5 g., 70%), m. p. 81° (Found: C, 66·1; H, 8·85; N, 17·5. $C_{18}H_{26}N_4,1\frac{1}{2}H_2O$ requires C, 66·4; H, 9·0; N, 17·2%). Similarly prepared were *octamethylenebis*-2-(4 : 6-*dimethylpyrimidine*), b. p. 172°/0·2 mm. (Found : N, 16·8. $C_{20}H_{30}N_4$ requires N, 17·2%), and decamethylenebis-2-(4 : 6-dimethylpyrimidine), b. p. 170°/0·05 mm., which, though not obtained pure, yielded the desired quaternary salt.

Quaternary Salts.—The polymethylenebispyrimidines prepared as above were treated with methyl iodide in ethanol at 100°. Hexamethylenebis-1-4-carbethoxypiperazine was similarly converted into the quaternary salt, and the carbethoxy-groups were then removed by concentrated hydrochloric acid at 100° (6 hours; sealed tube). Dimorpholino- and dipiperidino-hexane were treated with methyl iodide in acetone, the reaction being vigorously exothermic. In all other cases excess of a tertiary base was heated at 100° (sealed tube) with a polymethylene dihalide in ethanol or acetone. It was often advantageous to add an equivalent amount of sodium iodide to the reaction mixture if the dibromide was being used.

The *salts* were generally crystallised from ethanol, in a few cases with the addition of either water or ether. They are listed in the Table.

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