[Contribution from the College of Pharmacy, University of Michigan]

Polycyclic Quaternary Ammonium Salts. I

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Ditertiary bases were prepared and alkylated to produce bisquaternary salts. By this method or by interaction of N-methylpolymethylenimines with polymethylene bromides, a number of cyclic quaternary ammonium salts were obtained. Many of these compounds contained 7-, 8- and 9-membered heterocyclic rings.

During the last few years there has been great interest in 1,6-hexamethylenebistrimethylammonium dichloride (hexamethonium) (I) and 1,10-decamethylenebistrimethylammonium dibromide (decamethonium) (II) because of the hypotensive activity of the former and the muscle-relaxing effect of the latter.[3,4]

$$(CH_3)_3\overset{+}{N}—(CH_2)_6—\overset{+}{N}(CH_3)_3\ 2Cl^-$$

I

$$(CH_3)_3\overset{+}{N}—(CH_2)_{10}—\overset{-}{N}(CH_3)_3\ 2Br^-$$

II

Recently Libman, *et al.*,[5] have described a number of bicyclic bisquaternary salts; several of these compounds were found to be highly active hypotensive agents.[6-8]

The object of this investigation was the preparation of compounds of types III and IV which contained polymethylenimino radicals. In some of

$$(CH_3)(C_2H_5)_2\overset{+}{N}—(CH_2)_2—\overset{-}{N}<(CH_2)_x(CH_3)\ 2A^-$$

III, $x = 6, 7$ or 8

$$(R)(CH_2)_x > N—(CH_2)_z—N<(CH_2)_y(R')\ \ 2A^-$$

IV, $x = 4, 5, 6$ or 7
$y = 4, 5, 6, 7$ or 8
$z = 2, 3, 4, 5, 6$ or 8
R and $R' = CH_3$, C_2H_5 or $CH_2{=}CHCH_2$

the compounds which were prepared, a methyl-substituted polymethylenimino group or a morpholino group was introduced in place of the unsubstituted polymethylenimino radical. We were especially interested in the synthesis of compounds in which the heterocyclic nucleus was represented by a 7-, 8- or 9-membered polymethylenimino group. The only compounds of this type which have been described hitherto in the literature are derivatives of hexamethylenimine prepared by Jerchel and Jung[9] and by Smith and Cavallito.[10]

The general method employed for the preparation of the bases (Table I), required for the synthesis of some of the salts of types III and IV (Table II), is

$$(CH_2)_x > NH \xrightarrow[2,\ NaOH]{1,\ ClCH_2CH_2OH}$$

$$\underset{V}{(CH_2)_x > NCH_2CH_2OH} \xrightarrow[2,\ NaOH]{1,\ SOCl_2}$$

$$(CH_2)_x > NCH_2CH_2Cl \xrightarrow[NaOH,C_2H_5OH]{(CH_2)_y > NH}$$

$$\underset{VI}{(CH_2)_x > NCH_2CH_2N < (CH_2)_y}$$

In some cases N-(β-hydroxyethyl)-morpholine was used in place of V, and in others N-(β-chloroethyl)-diethylamine was employed instead of VI.

Propylene-1-(N-piperidine)-2-(N′-heptamethylenimine), $(CH_2)_5{>}N–CH_2CH(CH_3)–N{<}(CH_2)_7$, was obtained from 2-methyl-2-(1-heptamethylenimino)-ethyl chloride and piperidine.

All of the salts listed in Table II which contain two carbon atoms between the two nitrogen atoms were synthesized by alkylation of the required bases listed in Table I. The dimethobromides and diallobromides were obtained by interaction of the ditertiary bases with the required bromides. When ethyl bromide was employed, only the monoquaternary salt was formed. Treatment of this salt with hydrogen bromide yielded the ethobromide hydrobromide; treatment with methyl or allyl bromide produced the unsymmetrical bisquaternary salt (Table II, 11, 17, 19). For example, N,N′-ethylenedipyrrolidine reacted with ethyl bromide to form the monoquaternary salt which was converted by hydrogen bromide into N,N′-ethylenedipyrrolidine ethobromide hydrobromide, $(C_2H_5)(CH_2)_4{>}\overset{+}{N}–(CH_2)_2–N{<}(CH_2)_4(H)\ 2Br^-$. In the same manner, N,N′-ethylenedipiperidine was converted into its ethobromide hydrobromide.

When ethylene-N-piperidine-N′-morpholine (Table I, 28) was treated with allyl bromide and ethanol, the allobromide hydrobromide was produced instead of the diallobromide. It is believed that the product was formed by alkylation of the piperidino nitrogen atom, followed by alcoholysis of the excess allyl bromide to give hydrogen bromide which then reacted with the morpholino nitrogen atom.

It was found that the monoethobromide of N,N′-ethylenedipyrrolidine reacted with tetramethylene bromide to form N,N‴-diethyl-N,N′-ethylene-N′,-N″-tetramethylene-N″,N‴-ethylenetetrapyrrolidinium tetrabromide (VII).

Compounds listed in Table II which contain more than two carbon atoms between the nitrogen atoms were prepared by the Eschweiler–Clarke method, and the resulting tertiary amines were condensed with a polymethylene bromide.

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[1] This paper represents part of a dissertation submitted by Eric B. Hotelling in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1953.

[2] The Wm. S. Merrell Company Fellow.

[3] W. D. M. Paton and E. J. Zaimas, *Nature*, **161**, 718 (1948); *Brit. J. Pharmacol.*, **4**, 381 (1949).

[4] R. B. Barlow and H. R. Ing, *Nature*, **161**, 719 (1948).

[5] D. D. Libman, D. L. Pain and R. Slack, *J. Chem. Soc.*, 2305 (1952).

[6] R. Wien and D. F. J. Mason, *Lancet*, **264**, 454 (1953).

[7] R. D. H. Maxwell and A. J. M. Campbell, *ibid.*, **264**, 455 (1953).

[8] F. H. Smirk, *ibid.*, **264**, 457 (1953).

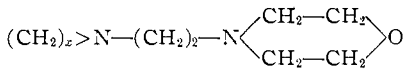
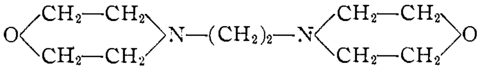
[9] D. Jerchel and G. Jung, *Chem. Ber.*, **85**, 1130 (1952).

[10] D. R. Smith and C. J. Cavallito, This Journal, **75**, 3033 (1953).

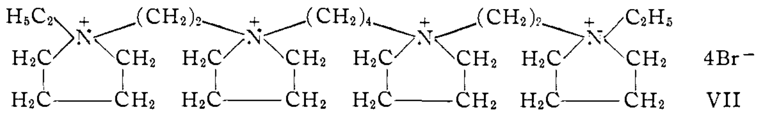
TABLE I

N,N,N',N'-TETRASUBSTITUTED ETHYLENEDIAMINES

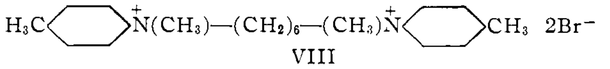
(Bases and Dihydrohalides)

	x	y	Salt	Yield, %	B.p., °C.	Mm.	M.p., °C.	Formula	Calcd. Nitrogen	Calcd. Halogen	Found Nitrogen	Found Halogen
(a) Ethylene·N-diethylamine-N'-polymethylenimines, $(C_2H_5)_2N—(CH_2)_2—N < (CH_2)_x$												
1	6		(Base)	50	122–126	14	.....					
2	6		Di-HCl	..	.....	..	222–224[a] d.	$C_{12}H_{28}N_2Cl_2$	10.33	26.15	10.20	25.96
3	6 (4-CH₃)		(Base)	47	136–141	15	.....					
4	6 (4-CH₃)		Di-HCl	..	.....	..	201–203[a] d.	$C_{13}H_{30}N_2Cl_2$	9.83	24.86	9.77	24.64
5	7		(Base)	55	129–134	11	.....					
6	7		Di-HCl	..	.....	..	194–196[a] d.	$C_{13}H_{30}N_2Cl_2$	9.83	24.86	9.89	24.74
7	8		(Base)	71	141–144	13	.....					
8	8		Di-HCl	..	.....	..	165–167[a]	$C_{14}H_{32}N_2Cl_2$	9.36	23.70	9.32	23.55
(b) N,N'-Ethylenedi-(polymethylenimines), $(CH_2)_x>N—(CH_2)_2—N<(CH_2)_y$												
9	4	4	(Base)	33	104–105	14	.....					
10	4	4	Di-HCl	..	.....	..	304–306 d.	$C_{10}H_{22}N_2Cl_2$	11.62	29.40	11.53	29.28
11	4	4	Di-HBr	..	.....	..	310–312 d.	$C_{10}H_{22}N_2Br_2$	8.49	48.42	8.52	48.31
12	4	5	(Base)	32	130–131	25	.....					
13	4	5	Di-HCl	6	.....	..	319–320 d.	$C_{11}H_{24}N_2Cl_2$	10.98	27.79	10.90	27.62
14	5	5	(Base)	64	143–146	30	.....					
15	5	5	Di-HCl[b]	..	.....[c]	..	332–333 d.	$C_{12}H_{26}N_2Cl_2$	10.41	26.34	10.55	26.21
16	5	5	Di-HBr[b]	..	.....	..	337–338 d.	$C_{12}H_{26}N_2Br_2$	7.82	44.63	7.77	44.67
17	5	6	(Base)	67	151–153	17	.....					
18	5	6	Di-HCl	..	.....	..	308–311 d.	$C_{13}H_{28}N_2Cl_2$	9.90	25.04	9.84	25.08
19	5	6	Di-HBr	..	.....	..	315–317 d.	$C_{13}H_{28}N_2Br_2$	7.53	42.95	7.38	43.21
20	5	6 (2-CH₃)	(Base)	53	177–181	25	.....					
21	5	6 (2-CH₃)	Di-HCl	..	.....	..	250–252[a] d.	$C_{14}H_{30}N_2Cl_2$	9.43	23.86	9.42	23.60
22	5	7	(Base)	60	204–208	73	.....					
23	5	7	Di-HCl	..	.....	..	278–280 d.	$C_{14}H_{30}N_2Cl_2$	9.43	23.86	9.39	23.91
24	6	6 (4-CH₃)	(Base)	44	162–165	11	.....					
25	6	6 (4-CH₃)	Di-HCl	..	.....	..	276–278	$C_{15}H_{32}N_2Cl_2$	9.00	22.78	8.98	22.72
26	8	6 (4-CH₃)	(Base)	35	182–186	10	.....					
27	8	6 (4-CH₃)	Di-HCl	..	.....	..	249–251	$C_{17}H_{36}N_3Cl_2$	8.26	20.89	8.23	20.89
(c) Ethylene·N-polymethylenimine-N'-morpholines,  $(CH_2)_x>N—(CH_2)_2—N<\begin{matrix}CH_2—CH_2\\CH_2—CH_2\end{matrix}>O$												
28	5		(Base)	82	149–152	25	.....					
29	5		Di-HCl	..	.....	..	302–303 d.	$C_{11}H_{24}ON_2Cl_2$	10.33	26.15	10.22	26.14
30	6		(Base)	47	145–148	11	....					
31	6		Di-HCl	..	....	..	290–291 d.	$C_{12}H_{26}ON_2Cl_2$	9.83	24.86	9.90	24.77
32	7		(Base)	41	153–156	10	.....					
33	7		Di-HCl	..	.....	..	272–273 d.	$C_{13}H_{28}ON_2Cl_2$	9.36	23.70	9.35	23.78
34	8		(Base)	41	172–175	14	.....					
35	8		Di-HCl	..	.....	..	247–249	$C_{14}H_{30}ON_2Cl_2$	8.95	22.64	8.88	22.61
(d) N,N'-Ethylenedimorpholine,  $O<\begin{matrix}CH_2—CH_2\\CH_2—CH_2\end{matrix}>N—(CH_2)_2—N<\begin{matrix}CH_2—CH_2\\CH_2—CH_2\end{matrix}>O$												
36			(Base)[d]	58	140–143	12	.....					
37			Di-HCl[d]	..	.....	..	322–324 d.	$C_{10}H_{22}O_2N_2Cl_2$	10.26	25.96	10.28	25.94

[a] Hygroscopic. [b] This salt was prepared by J. W. Brühl (*Ber.*, **4**, 738 (1871)), but the melting point was not reported. [c] J. W. Brühl (*Z. physik. Chem.*, **16**, 193 (1895)), b.p. 132.5° (14 mm.) and 261° (756.5 mm.). [d] L. Knorr and H. W. Brownsdon (*Ber.*, **35**, 4470 (1902)) stated that the base boiled at 153–154° (9 mm.) and that the dihydrochloride sublimed.



VII



VIII

In three instances the polymethylene bromide was replaced by 1,3-dibromo-2-propanol, *o*-xylylene bromide and *p*-xylylene bromide, respectively. Interaction of N-methylhexamethylenimine with these bromides yielded the dimethobromides of N,N'-(2-hydroxytrimethylene)-di-(hexamethylenimine), N,N'-*o*-xylylenedi-(hexamethylenimine) and N,N'-*p*-xylylenedi-(hexamethylenimine). The 2-hydroxytrimethylene compound was acetylated whereby the corresponding 2-acetoxytrimethylene derivative was produced.

N,N'-Hexamethylenedi-(γ-pipecoline)-dimetho-

TABLE II

ALKYL AND ALLYL BISQUATERNARY SALTS OF N,N,N′,N′-TETRASUBSTITUTED POLYMETHYLENEDIAMINES

The dibromides were all precipitated from a concentrated aqueous solution with isopropyl alcohol followed by ether or acetone. The dipicrates were dissolved in acetone and precipitated with water; when necessary, the mixture was concentrated.

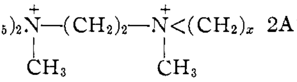
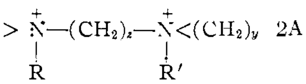
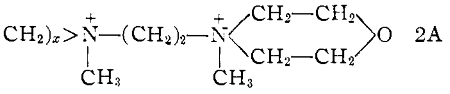
								Analyses, %			
								Calcd.		Found	
	x	y	z	A⁻	Yield, %	M.p., °C.[a]	Formula	Nitrogen	Bromine	Nitrogen	Bromine
(a) Salts of ethylene-N-diethylamine-N′-polymethylenimines,  $(C_2H_5)_2\overset{+}{\underset{CH_3}{N}}—(CH_2)_2—\overset{+}{\underset{CH_3}{N}}<(CH_2)_x\ 2A^-$											
1	6			Bromide	100	252–253	$C_{14}H_{32}N_2Br_2$	7.22	41.18	7.13	41.16
2	6			Picrate	...	232–234	$C_{26}H_{36}O_{14}N_8$	16.37		16.33	
3	6 (4-CH_3)			Bromide	57	247–248	$C_{15}H_{34}N_2Br_2$	6.97	39.74	6.98	39.65
4	6 (4-CH_3)			Picrate	...	216–218	$C_{27}H_{38}O_{14}N_8$	16.04		15.96	
5	7			Bromide	94	254–255	$C_{15}H_{34}N_2Br_2$	6.97	39.74	6.89	39.69
6	7			Picrate	...	213–214	$C_{27}H_{38}O_{14}N_8$	16.04		15.99	
7	8			Bromide	36	244–246	$C_{16}H_{36}N_2Br_2$	6.73	38.39	6.76	38.32
8	8			Picrate	...	222–224	$C_{28}H_{40}O_{14}N_8$	15.73		15.69	
(b) Salts of N,N′-polymethylenedi-(polymethylenimines),  $(CH_2)_x > \overset{+}{\underset{R}{N}}—(CH_2)_z—\overset{+}{\underset{R'}{N}}<(CH_2)_y\ 2A^{-b}$											
9	4	4	2	Bromide	94	287–288	$C_{12}H_{26}N_2Br_2$	7.82	44.63	7.71	44.70
10	4	4	2	Picrate	...	277–278	$C_{24}H_{30}O_{14}N_8$	17.13		17.01	
11	4	4	2	Bromide	...	258–260[c]	$C_{13}H_{28}N_2Br_2$	7.53	42.95	7.41	42.85
12	4	4	2	Picrate	...	256–258	$C_{25}H_{32}O_{14}N_8$	16.76		16.48	
13	4	5	2	Bromide	77	266–267[c]	$C_{13}H_{28}N_2Br_2$	7.53	42.95	7.50	43.14
14	4	5	2	Picrate	...	275–277	$C_{25}H_{32}O_{14}N_8$	16.76		16.67	
15	5	5	2	Bromide[d]	100	263–264	$C_{14}H_{30}N_2Br_2$	7.26	41.39	7.22	41.29
16	5	5	2	Picrate	...	269–270	$C_{26}H_{34}O_{14}N_8$	16.42		16.42	
17	5	5	2	Bromide	...	249–250	$C_{15}H_{32}N_2Br_2$	7.00	39.93	6.92	40.08
18	5	5	2	Picrate	...	235–238	$C_{27}H_{36}O_{14}N_8$	16.09		16.03	
19	5	5	2	Bromide	...	222–224	$C_{17}H_{34}N_2Br_2$	6.57	37.49	6.56	37.63
20	5	5	2	Picrate	...	181–182	$C_{29}H_{38}O_{14}N_8$	15.51		15.54	
21	5	5	2	Bromide	75	180–182	$C_{18}H_{34}N_2Br_2$	6.39	36.46	6.38	36.42
22	5	5	2	Picrate	...	177–178	$C_{30}H_{38}O_{14}N_8$	15.26		15.08	
23	6	5	2	Bromide	85	269–270	$C_{15}H_{32}N_2Br_2$	7.00	39.93	6.98	40.02
24	6	5	2	Picrate	...	258–260	$C_{27}H_{36}O_{14}N_8$	16.09		15.99	
25	6 (2-CH_3)	5	2	Bromide	61	239–240[c]	$C_{16}H_{34}N_2Br_2$	6.77	38.58	6.75	38.67
26	6 (2-CH_3)	5	2	Picrate	...	230–232	$C_{28}H_{38}O_{14}N_8$	15.77		15.71	
27	7	5	2	Bromide	73	266–267	$C_{16}H_{34}N_2Br_2$	6.77	38.58	6.58	38.64
28	7	5	2	Picrate	...	240–242	$C_{28}H_{38}O_{14}N_8$	15.77		15.77	
29	6 (4-CH_3)	6	2	Bromide	100	264–265	$C_{17}H_{36}N_2Br_2$	6.54	37.32	6.56	37.27
30	6 (4-CH_3)	6	2	Picrate	...	246–249	$C_{29}H_{40}O_{14}N_8$	15.47		15.30	
31	6 (4-CH_3)	8	2	Bromide	30	249–250	$C_{19}H_{40}N_2Br_2$	6.14	35.02	6.07	34.90
32	6 (4-CH_3)	8	2	Picrate	...	237–239	$C_{31}H_{44}O_{14}N_8$	14.89		14.86	
33	6	6	3	Bromide	100	251–252[c]	$C_{17}H_{36}N_2Br_2$	6.54	37.32	6.44	37.44
34	6	6	3	Picrate	...	250–252	$C_{29}H_{40}O_{14}N_8$	15.47		15.31	
35	7	7	3	Bromide	77	252–253[c]	$C_{19}H_{40}N_2Br_2$	6.14	35.02	6.06	34.92
36	7	7	3	Picrate	...	235–237	$C_{31}H_{44}O_{14}N_8$	14.89		14.84	
37	6	6	4	Bromide	80	262–264	$C_{18}H_{28}N_2Br_2$	6.34	36.13	6.32	36.05
38	6	6	4	Picrate	...	245–247	$C_{30}H_{42}O_{14}N_8$	15.18		14.98	
39	7	7	4	Bromide	80	257–258	$C_{20}H_{42}N_2Br_2$	5.96	33.98	5.90	33.99
40	7	7	4	Picrate	...	253–255	$C_{32}H_{46}O_{14}N_8$	14.62		14.57	
41	6	6	5	Bromide	85	266–267	$C_{19}H_{40}N_2Br_2$	6.14	35.02	6.05	34.91
42	6	6	5	Picrate	...	219–221	$C_{31}H_{44}O_{14}N_8$	14.89		14.95	
43	7	7	5	Bromide	80	253–254	$C_{21}H_{44}N_2Br_2$	5.79	33.00	5.81	33.13
44	7	7	5	Picrate	...	180–182	$C_{33}H_{48}O_{14}N_8$	14.36		14.23	
45	6	6	6	Bromide	98	272–273	$C_{20}H_{42}N_2Br_2$	5.96	33.98	6.02	33.98
46	6	6	6	Picrate	...	171–173	$C_{32}H_{46}O_{14}N_8$	14.62		14.70	
47	7	7	6	Bromide	54	246–248	$C_{22}H_{46}N_2Br_2$	5.62	32.07	5.60	31.98
48	7	7	6	Picrate	...	135–137	$C_{34}H_{50}O_{14}N_8$	14.11		13.98	
49	6	6	8	Bromide	80	264–265	$C_{22}H_{46}N_2Br_2$	5.62	32.07	5.63	32.02
50	6	6	8	Picrate	...	137–139	$C_{34}H_{50}O_{14}N_8$	14.11		14.15	
51	7	7	8	Bromide	77	231–233[c]	$C_{24}H_{50}N_2Br_2$	5.32	30.36	5.25	30.20
52	7	7	8	Picrate	...	151–152	$C_{36}H_{54}O_{14}N_8$	13.62		13.46	

TABLE II (*Continued*)

(c) Salts of ethylene-N-polymethylenimine-N′-morpholines,



$$(CH_2)_x{>}\overset{+}{N}(CH_3)—(CH_2)_2—\overset{+}{N}(CH_3){<}\begin{matrix}CH_2—CH_2\\CH_2—CH_2\end{matrix}{>}O \quad 2A$$

	x	*y*	*z*	A⁻	Yield, %	M.p., °C.[a]	Formula	Analyses, % Calcd. Nitrogen	Calcd. Bromide	Found Nitrogen	Found Bromide
53	5			Bromide	88	278–280	$C_{13}H_{28}ON_2Br_2$	7.22	41.19	7.24	41.16
54	5			Picrate	...	279–282	$C_{25}H_{32}O_{15}N_8$	16.37		16.21	
55	6			Bromide	25	249–250[c]	$C_{14}H_{30}ON_2Br_2$	6.97	39.74	6.89	39.64
56	6			Picrate	...	234–236	$C_{26}O_{34}O_{15}N_8$	16.04		15.88	
57	7			Bromide	56	222–223[c]	$C_{15}H_{32}ON_2Br_2$	6.73	38.40	6.70	38.26
58	7			Picrate	...	201–203	$C_{27}H_{36}O_{15}N_8$	15.73		15.51	
59	8			Bromide	81	207–209[c]	$C_{16}H_{34}ON_2Br_2$	6.51	37.14	6.48	36.99
60	8			Picrate	...	215–217	$C_{28}H_{38}O_{15}N_6$	15.43		15.41	

[a] All of the salts melted with decomposition except 20, 21, 44, 46, 48, 50, 52, 56, 58 and 60. [b] R and R′ = CH_3 except in the following instances: in compounds 11, 12, 17 and 18, R′ = C_2H_5; in compounds 19 and 20, R = C_2H_5, R′ = $CH_2{=}CHCH_2$; in compounds 21 and 22, R and R′ = $CH_2{=}CHCH_2$. [c] Hygroscopic. [d] The corresponding dimethiodide has been described by O. Aschan, *Ber.*, **32**, 988 (1899).

bromide (VIII) was prepared from N-methyl-γ-pipecoline and hexamethylene bromide.

We are indebted to the Wm. S. Merrell Company research laboratories for the evaluation of the quaternary salts (Table II) as hypotensive agents. The test compound was injected intravenously into anesthetized dogs and the blood pressure was recorded from the femoral artery. The most promising compounds are ethylene-N-piperidine-N′-2-methylhexamethylenimine dimethobromide[25] and ethylene-N-piperidine-N′-heptamethylenimine dimethobromide.[27] At a 3 mg./kg. dose level, these compounds produced a blood pressure decrease in the order of 50–60% which lasted for about 30 minutes.

Experimental

The procedures mentioned below illustrate the general methods used for the synthesis of the compounds listed in the tables. In addition, preparative procedures for compounds not mentioned in the tables are described.

N-(β-Chloroethyl)-hexamethylenimine,[11] N-(β-chloroethyl)-4-methylhexamethylenimine[11] and 2-methyl-2-(1-heptamethylenimino)-ethyl chloride,[12] were obtained by methods which have been described.

N,N′-Ethylenedipyrrolidine (Table I, 9).—A mixture of 355 g. (5.0 moles) of pyrrolidine and 300 cc. of isopropyl alcohol was placed in a 2-liter, 3-necked flask fitted with a stirrer, condenser and dropping funnel. The mixture was stirred, heated to the boiling point and 376 g. (2.0 moles) of ethylene bromide was added, dropwise, at such a rate that the mixture refluxed without the use of external heat. The solvent and excess pyrrolidine were removed by distillation until the temperature of the liquid in the distillation flask reached 110°. The flask was cooled, the precipitate was filtered, washed with isopropyl alcohol and then with ether. The product was dissolved in about 350 cc. of water, and 100 g. of sodium hydroxide was added. The oily precipitate was extracted with ether, the extract dried, the solvent removed and the product distilled; yield 109 g.

Ethylene-N-piperidine-N′-hexamethylenimine (Table I, 17).—A mixture of 29.5 g. (0.2 mole) of freshly distilled N-(β-chloroethyl)-piperidine,[13] 19.8 g. (0.2 mole) of hexamethylenimine,[14] 10.0 g. (0.25 mole) of sodium hydroxide and 50 cc. of isopropyl alcohol was shaken frequently and allowed to remain at room temperature for three weeks. After filtration of the solid material, 2.0 g. of sodium hydroxide was added to the filtrate. The mixture was filtered after 12 hours, the solvent removed from the filtrate and the product distilled; b.p. 157–161° (24 mm.), yield 25.0 g. (60%).

The dihydrochloride melted at 309–311° dec. and the dihydrobromide at 315–317° dec.

The same base (b.p. 151–153° (17 mm.)) was obtained in 67% yield by interaction of 13.4 g. of freshly distilled N-(β-chloroethyl)-hexamethylenimine, 7.1 g. of piperidine, 4.0 g. of sodium hydroxide and 25 cc. of isopropyl alcohol in the manner described above; mixed m.p. of the hydrochlorides 308–311° dec., mixed m.p. of the hydrobromides 315–316° dec.

Propylene-1-(N-piperidine)-2-(N′-heptamethylenimine).—2-Methyl-2-(1-heptamethylenimino)-ethyl chloride hydrochloride[12] (11.0 g.) was treated with concd. sodium hydroxide solution, the liberated base extracted with ether and the solvent removed from the dried extract. To the residue there was added 4.2 g. of piperidine, 2.5 g. of sodium hydroxide and 25 cc. of isopropyl alcohol. The subsequent procedures were the same as those described above. The base boiled at 135–137° (4 mm.), yield 5.9 g. (51%).

The hygroscopic dihydrochloride precipitated when an ethereal solution of the base was treated with hydrogen chloride; m.p. 194–196°.

Anal. Calcd. for $C_{15}H_{32}N_2Cl_2$: N, 9.00; Cl, 22.78. Found: N, 9.09; Cl, 22.60.

Ethylene-N-piperidine-N′-heptamethylenimine Dimethobromide (Table II, 27).—A solution of 7.5 g. of the required base in 25 cc. of isopropyl alcohol was placed in a citrate bottle, cooled below 0° and 5.8 g. of cold, anhydrous methyl bromide added. After 2 days at room temperature, the precipitate was filtered and washed with isopropyl alcohol; yield 10.1 g. (73%). The salt was dissolved in 20 cc. of water, the solution treated with Norite, filtered and 50 cc. of isopropyl alcohol, followed by 100 cc. of acetone, added to the filtrate; yield 9.1 g. The product can be recrystallized from methanol.

The dipicrate (Table II, 28) was obtained by treatment of 1.0 g. of the dimethobromide, dissolved in a small amount of water, with a saturated aqueous solution of picric acid The precipitate was washed with water, dissolved in 25 cc. of acetone, 50 cc. of water added and the solution evaporated until crystallization began; the mixture was then cooled.

N,N′-Ethylenedipyrrolidine Ethobromide Hydrobromide.—A mixture of 16.8 g. of N,N′-ethylenedipyrrolidine, 21.8 g. of ethyl bromide and 50 cc. of isopropyl alcohol, after 2 weeks at ordinary temperature, was evaporated almost to dryness and the oily residue, the monoethobromide, was triturated with ether. The product was dissolved in acetone and solution treated with hydrogen bromide. The crystalline salt was recrystallized from absolute ethanol; m.p. 250–252° dec.

Anal. Calcd. for $C_{12}H_{26}N_2Br_2$: N, 7.82; Br, 44.63. Found: N, 7.66; Br, 44.47.

N,N′-Ethylenedipyrrolidine Methobromide Ethobromide (Table II, 11).—The monoethobromide, obtained in the experiment described above, was dissolved in isopropyl alcohol, and excess methyl bromide was added. The pre-

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[11] G. R. Toy, Dissertation, University of Michigan, 1951.

[12] Eu-Phang Tsao, Dissertation, University of Michigan, 1952.

[13] S. Gabriel and J. Colman, *Ber.*, **40**, 424 (1907).

[14] L. Ruzicka, M. Kobelt, O. Häfliger and V. Prelog, *Helv. Chim. Acta*, **32**, 544 (1949).

cipitate was dissolved in a small amount of water and the product precipitated by the addition of isopropyl alcohol and then acetone.

N,N′-Ethylenedipiperidine Ethobromide Hydrobromide.—The precipitate, which had deposited after 3 weeks from a solution of 19.6 g. of N,N′-ethylenedipiperidine, 21.8 g. of ethyl bromide and 50 cc. of ether, was dissolved in acetone and the solution treated with hydrogen bromide. The precipitate was recrystallized from absolute ethanol; m.p. 311–313° dec.

Anal. Calcd. for $C_{14}H_{30}N_2Br_2$: N, 7.26; Br, 41.39. Found: N, 7.19; Br, 41.55.

Ethylene-N-piperidine-N′-morpholine Allobromide Hydrobromide.—The precipitate (11.0 g.), formed after 12 hours from a mixture of 9.9 g. of ethylene-N-piperidine-N′-morpholine (Table I, 28), a threefold excess of allyl bromide and 50 cc. of absolute ethanol, was dissolved in water, the solution treated with charcoal (Norite), filtered and the product precipitated by the addition of isopropyl alcohol and then acetone; m.p. 219–221° dec.

Anal. Calcd. for $C_{14}H_{28}ON_2Br_2$: N, 7.00; Br, 39.94. Found: N, 6.88; Br, 40.07.

N,N‴-Diethyl-N,N′-ethylene-N′,N″-tetramethylene-N″,N‴-ethylenetetrapyrrolidinium Tetrabromide (VII).—A mixture of 8 g. of crude N,N′-ethylenedipyrrolidine monoethobromide, 32.4 g. (tenfold excess) of tetramethylene bromide and 50 cc. of isopropyl alcohol was distilled slowly until the temperature of the mixture reached 90°. The material was then refluxed for 1 hour. After the addition of ether, the very hygroscopic precipitate was filtered; yield 0.9 g. The product was recrystallized from isopropyl alcohol. The large prisms were separated by hand from a fibrous, very hygroscopic impurity, dissolved in methanol, the solution treated with Norite, filtered, the product precipitated with ether and then recrystallized from isopropyl alcohol; yield 0.4 g., m.p. 235–237° dec.

Anal. Calcd. for $C_{28}H_{58}N_4Br_4$: N, 7.27; Br, 41.52. Found: N, 7.21; Br, 41.44.

The tetrapicrate precipitated when picric acid was added to an aqueous solution of the tetrabromide; m.p. 175–179°.

Anal. Calcd. for $C_{52}H_{66}O_{28}N_{16}$: N, 16.44. Found: N, 16.33.

N,N′-(2-Hydroxytrimethylene)-di-(hexamethylenimine) Dimethobromide.—A mixture of 5.5 g. of 1,3-dibromo-2-propanol, 5.7 g. of N-methylhexamethylenimine[11] and 75 cc. of isopropyl alcohol was refluxed for 6 hours, cooled and 150 cc. of ether added. After the oily precipitate had become crystalline, it was filtered and dried at 110°; yield 10 g. The material was dissolved in 15 cc. of water, the solution treated with Norite and to the filtered solution there was added, successively, isopropyl alcohol, acetone and ether. The precipitated product melted at 234–236° dec. after it had been dried at 110°.

Anal. Calcd. for $C_{17}H_{36}ON_2Br_2$: N, 6.31; Br, 35.96. Found: N, 6.35; Br, 36.00.

The dipicrate melted at 268–270° dec.

Anal. Calcd. for $C_{29}H_{40}O_{15}N_8$: N, 15.14. Found: N, 15.23.

N,N′-(2-Acetoxytrimethylene)-di-(hexamethylenimine) Dimethobromide.—A mixture of 4.2 g. of the 2-hydroxytrimethylene compound, 10 g. of acetic anhydride and 1 cc. of pyridine was refluxed for 5 minutes. The gummy precipitate, obtained after the addition of ether to the cold solution, was dissolved in hot isopropyl alcohol. The product was precipitated by the addition of ether to the cold solution. The material was dissolved in a small amount of water, the solution treated with Norite, filtered and acetone, and then ether, added to the filtrate. The product was dried at 110°; yield 3.3 g., m.p. 202–204° dec.

Anal. Calcd. for $C_{19}H_{38}O_2N_2Br_2$: N, 5.76; Br, 32.86. Found: N, 5.81; Br, 32.88.

The dipicrate melted at 186–188°.

Anal. Calcd. for $C_{31}H_{42}O_{16}N_8$: N, 14.32. Found: N, 14.36.

N,N′-*o*-Xylylenedi-(hexamethylenimine) Dimethobromide.—A mixture of 5.7 g. of N-methylhexamethylenimine,[11] 6.6 g. of *o*-xylylene bromide and 75 cc. of isopropyl alcohol was refluxed for 6 hours, cooled, the precipitate filtered and dried at 110°. The material, dissolved in a minimum amount of water, was treated with Norite, filtered and the product precipitated from the filtrate by the addition of isopropyl alcohol and then ether. The hygroscopic product was dried at 110°; yield 11.1 g., m.p. 200–202° dec.

Anal. Calcd. for $C_{22}H_{38}N_2Br_2$: N, 5.72; Br, 32.59. Found: N, 5.62; Br, 32.35.

The dipicrate melted at 200–202°.

Anal. Calcd. for $C_{34}H_{42}O_{14}N_8$: N, 14.25. Found: N, 14.18.

N,N′-*p*-Xylylenedi-(hexamethylenimine) Dimethobromide.—N-Methylhexamethylenimine (5.7 g.) was added, slowly, to a refluxing solution of 6.6 g. of *p*-xylylene bromide in 75 cc. of isopropyl alcohol. A thick pasty precipitate formed almost immediately. The cooled mixture was filtered and the material dried at 110°. After treatment in the manner described above, the hygroscopic product weighed 9.8 g., m.p. 255–257° dec.

Anal. Calcd. for $C_{22}H_{38}N_2Br_2$: N, 5.72; Br, 32.59. Found: N, 5.55; Br, 32.44.

The dipicrate melted at 195–197°.

Anal. Calcd. for $C_{34}H_{42}O_{14}N_8$: N, 14.25. Found: N, 14.12.

N-Methyl-γ-pipecoline.—A solution of 10.0 g. of γ-picoline in 20 cc. of isopropyl alcohol in a citrate bottle was cooled in an ice-bath and a 1.2 molar amount of methyl bromide added. After 2 days at room temperature, the precipitated methobromide weighed 15.1 g. (75%). The salt was dissolved in 60 cc. of acetic acid, 0.5 g. of platinum oxide catalyst added and the material was hydrogenated at 60° under an initial pressure of 45 pounds. Hydrogenation was completed after 3 hours. The product (5.4 g.) boiled at 123–126° (757 mm.), over-all yield 44%.

The hydrochloride melted at 210–212°.

Anal. Calcd. for $C_7H_{16}NCl$: N, 9.36; Cl, 23.68. Found: N, 9.38; Cl, 23.72.

N,N′-Hexamethylenedi-(γ-pipecoline) Dimethobromide (VIII).—A mixture of 4.0 g. of N-methyl-γ-pipecoline, 4.4 g. of hexamethylene bromide and 25 cc. of isopropyl alcohol was refluxed for 8 hours and then cooled. The precipitate weighed 4.9 g. (58%), m.p. 265–266° dec.[15]

Anal. Calcd. for $C_{20}H_{42}N_2Br_2$: N, 5.96; Br, 33.98. Found: N, 5.91; Br, 33.92.

The dipicrate precipitated when picric acid was added to an aqueous solution of the dimethobromide; m.p. 131–133°.

Anal. Calcd. for $C_{32}H_{46}O_{14}N_8$: N, 14.62. Found: N, 14.65.

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(15) The corresponding dimethiodide has been reported (ref. 5).