[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Polycyclic Quaternary Ammonium Salts. II

BY F. F. BLICKE AND ERIC B. HOTELLING[1,2]

RECEIVED DECEMBER 12, 1953

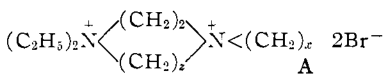
Bis-quaternary salts were prepared by the addition of ethylene or trimethylene bromide to a number of ditertiary bases. By this method a number of bicyclic spirobisquaternary salts and tricyclic dispirobisquaternary salts were obtained. Many of these compounds contained 7-, 8- and 9-membered heterocyclic rings.

In a previous publication[3] the synthesis of a number of ditertiary bases, represented by the general formulas I and II, was described. In some instances the polymethylenimino radical was replaced by a methyl-substituted polymethylenimino or a morpholino group.

During this investigation these bases were condensed with either ethylene or trimethylene bromide to produce bicyclic spirobisquaternary (A) or tricyclic dispirobisquaternary salts (B). This type

$$\underset{\text{I}}{(C_2H_5)_2N—(CH_2)_2—N<(CH_2)_x} + Br(CH_2)_z\,Br \longrightarrow$$

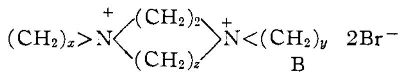
x = 6, 7 or 8 z = 2 or 3



A

$$\underset{\text{II}}{(CH_2)_x>N—(CH_2)_2—N<(CH_2)_y} + Br(CH_2)_z\,Br \longrightarrow$$

x = 4, 5, 6 or 7; y = 4, 5, 6, 7 or 8

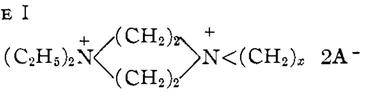


B

of condensation had been used previously by Brühl[4] and by Scholtz,[5] and a few compounds analogous to the products which we obtained have been synthesized by other investigators[6-9] by heating compounds such as N-(β-chloroethyl)-piperidine.

TABLE I

BICYCLIC SPIROBISQUATERNARY SALTS



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

	x	z	A⁻	M.p., °C.[a]	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Bromine, % Calcd.	Bromine, % Found
1	6	2	Bromide	296–298	16	$C_{14}H_{30}N_2Br_2$	7.26	7.21	41.39	41.33
2	6	2	Picrate	281–282		$C_{26}H_{34}O_{14}N_8$	16.42	16.48		
3	7	2	Bromide	296–298	14	$C_{15}H_{32}N_2Br_2$	7.00	6.85	39.93	39.98
4	7	2	Picrate	228–230		$C_{27}H_{36}O_{14}N_8$	16.09	15.90		
5	8	2	Bromide	280–281	8	$C_{16}H_{34}N_2Br_2$	6.77	6.78	38.58	38.49
6	8	2	Picrate	252–253		$C_{28}H_{38}O_{14}N_8$	15.77	15.66		
7	6	3	Bromide	282–284	29	$C_{15}H_{32}N_2Br_2$	7.00	6.96	39.93	39.71
8	6	3	Picrate	231–233		$C_{27}H_{36}O_{14}N_8$	16.09	16.02		
9	6 (4-CH$_3$)	3	Bromide	285–286	21	$C_{16}H_{34}N_2Br_2$	6.77	6.60	38.58	38.37
10	6 (4-CH$_3$)	3	Picrate	171–173		$C_{28}H_{38}O_{14}N_8$	15.77	15.65		
11	7	3	Bromide	282–284	23	$C_{16}H_{34}N_2Br_2$	6.77	6.76	38.58	38.39
12	7	3	Picrate	235–237		$C_{28}H_{38}O_{14}N_8$	15.77	15.56		
13	8	3	Bromide	272–273	21	$C_{17}H_{36}N_2Br_2$	6.54	6.44	37.32	37.23
14	8	3	Picrate	233–235		$C_{29}H_{40}O_{14}N_8$	15.47	15.51		

[a] All compounds except 10 melted with decomposition.

The quaternary compounds were screened for hypotensive activity in The Wm. S. Merrell Company research laboratories. They were administered intravenously to anesthetized dogs or cats and the blood pressure recorded from the femoral artery was used as the measure of activity. The most interesting compounds probably are N,N',N,-N'-diethyleneoctamethyleniminiummorpholinium dibromide (Table II, 37) and N,N',N,N'-diethylenedi-(4-methylhexamethyleniminium) dichloride. The latter substance (m.p. 330–332° dec.) was obtained by cyclization of β-(4-methylhexamethylenimino)-ethyl chloride and will be described in a forthcoming publication. In 1-2 mg./kg. doses, these compounds produced a blood pressure decrease of about 25% which lasted for about 4 minutes.

Experimental

The compounds obtained from bases of type I are reported in Table I; those obtained from II are to be found in Table II.

The general method employed for the synthesis of compounds listed in Tables I and II is illustrated by the first procedure described below.

N,N'-Ethylene-N,N'-trimethyleneoctamethyleniminiummorpholinium Dibromide (Table II, 45).—A mixture of 7.1 g. (0.03 mole) of ethylene-N-octamethylenimine-N'-morpholine,[3] 7.1 g. (0.035 mole) of trimethylene bromide and

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

[4] J. W. Brühl, *Ber.*, **4**, 738 (1871).

[5] M. Scholtz, *ibid.*, **35**, 3047 (1902).

[6] W. Marckwald and O. Frobenius, *ibid.*, **34**, 3544 (1901).

[7] J. P. Mason and H. W. Block, THIS JOURNAL **62**, 1443 (1940).

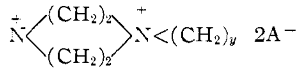
[8] G. R. Toy, Dissertation, University of Michigan, 1951.

[9] N. J. Doorenbos, Dissertation, University of Michigan, 1953.

TABLE II

TRICYCLIC DISPIROBISQUATERNARY SALTS

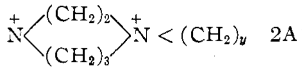
(a) N,N′,N,N′-Diethylenedi-(polymethyleniminium) salts, $(CH_2)_x >$



$$(CH_2)_x > \overset{+}{N}\begin{matrix}(CH_2)_2\\(CH_2)_2\end{matrix}\overset{+}{N}<(CH_2)_y\ \ 2A^-$$

	x	y	A⁻	M.p., °C.[a]	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Bromine, % Calcd.	Bromine, % Found
1	4	4	Bromide	342–344	33	$C_{12}H_{24}N_2Br_2$	7.87	7.80	44.88	44.97
2	4	4	Chloride	350–352		$C_{12}H_{24}N_2Cl_2$	10.49	10.45	Cl, 26.54	26.49
3	4	4	Chloroaurate	252–254		$C_{12}H_{24}N_2Au_2Cl_8$			Au, 45.1	45.3
4	4	4	Chloroplatinate	Indefinite		$C_{12}H_{24}N_2PtCl_6$			Pt, 32.3	32.6
5	4	5	Bromide	348–349	32	$C_{13}H_{26}N_2Br_2$	7.57	7.55	43.18	43.02
6	4	5	Picrate	303–304		$C_{25}H_{30}O_{14}N_8$	16.82	16.65		
7	5	5	Bromide[b]	346–347	28	$C_{14}H_{28}N_2Br_2$	7.30	7.11	41.61	41.80
8	5	5	Chloride[b]	Over 400		$C_{14}H_{28}N_2Cl_2$	9.49	9.36	Cl, 24.02	24.09
9	5	5	Chloroaurate[b]	284–286		$C_{14}H_{28}N_2Au_2Cl_8$			Au, 43.7	43.9
10	5	5	Chloroplatinate[b]	Indefinite		$C_{14}H_{28}N_2PtCl_6$			Pt, 30.9	31.0
11	5	6	Bromide	339–340	28	$C_{15}H_{30}N_2Br_2$	7.04	7.02	40.14	40.34
12	5	6	Picrate	285–287		$C_{27}H_{34}O_{14}N_8$	16.14	15.97		
13	5	6 (2-CH₃)	Bromide	309–310	25	$C_{16}H_{32}N_2Br_2$	6.80	6.61	38.77	39.01
14	5	6 (2-CH₃)	Picrate	256–257		$C_{28}H_{36}O_{14}N_8$	15.82	15.86		
15	5	7	Bromide	305–306	27	$C_{16}H_{32}N_2Br_2$	6.80	6.70	38.77	38.99
16	5	7	Picrate	280–281		$C_{28}H_{36}O_{14}N_8$	15.82	15.79		
17	6	6 (4-CH₃)	Bromide	320–321	28	$C_{17}H_{34}N_2Br_2$	6.57	6.51	37.49	37.62
18	6	6 (4-CH₃)	Picrate	288		$C_{29}H_{38}O_{14}N_8$	15.51	15.55		
19	8	6 (4-CH₃)	Bromide	289–291	33	$C_{19}H_{38}N_2Br_2$	6.17	6.17	35.17	35.33
20	8	6 (4-CH₃)	Picrate	275		$C_{31}H_{42}O_{14}N_8$	14.93	14.78		

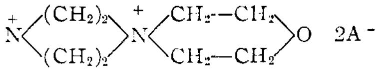
(b) N,N′-Ethylene-N,N′-trimethylenedi-(polymethyleniminium) salts, $(CH_2)_x >$



$$(CH_2)_x > \overset{+}{N}\begin{matrix}(CH_2)_2\\(CH_2)_3\end{matrix}\overset{+}{N}<(CH_2)_y\ \ 2A^-$$

	x	y	A⁻	M.p., °C.[a]	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Bromine, % Calcd.	Bromine, % Found
21	4	4	Bromide	313–314	55	$C_{13}H_{26}N_2Br_2$	7.57	7.50	43.18	43.11
22	4	4	Picrate	257–258		$C_{25}H_{30}O_{14}N_8$	16.82	16.78		
23	4	5	Bromide	325–326	46	$C_{14}H_{28}N_2Br_2$	7.30	7.19	41.61	41.70
24	4	5	Picrate	260–262		$C_{26}H_{32}O_{14}N_8$	16.47	16.38		
25	5	5	Bromide[c]	320–321	36	$C_{15}H_{30}N_2Br_2$	7.04	6.99	40.14	40.21
26	5	5	Picrate	255–256		$C_{27}H_{34}O_{14}N_8$	16.14	16.10		
27	5	6	Bromide	312–313	51	$C_{16}H_{32}N_2Br_2$	6.80	6.66	38.77	38.78
28	5	6	Picrate	259–261		$C_{28}H_{36}O_{14}N_8$	15.82	15.77		
29	6	6 (4-CH₃)	Bromide	300–301	30	$C_{18}H_{36}N_2Br_2$	6.36	6.23	36.29	36.22
30	6	6 (4-CH₃)	Picrate	256–258		$C_{30}H_{40}O_{14}N_8$	15.22	15.27		
31	8	6 (4-CH₃)	Bromide	268–269	33	$C_{20}H_{40}N_2Br_2$	5.98	5.89	34.12	34.32
32	8	6 (4-CH₃)	Picrate	214–217		$C_{32}H_{44}O_{14}N_8$	14.66	14.70		

(c) N,N′,N,N′-Diethylenepolymethyleniminiummorpholinium salts, $(CH_2)_x >$

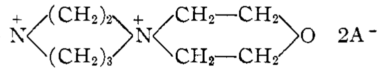


$$(CH_2)_x > \overset{+}{N}\begin{matrix}(CH_2)_2\\(CH_2)_2\end{matrix}\overset{+}{N}\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}O\ \ 2A^-$$

	x	y	A⁻	M.p., °C.[a]	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Bromine, % Calcd.	Bromine, % Found
33	5		Bromide	353–354	19	$C_{13}H_{26}ON_2Br_2$	7.26	7.13	41.39	41.21
34	5		Picrate	292–293		$C_{25}H_{30}O_{15}N_8$	16.42	16.38		
35	7		Bromide	291–292	20	$C_{15}H_{30}ON_2Br_2$	6.77	6.71	38.58	38.52
36	7		Picrate	274–275		$C_{27}H_{34}O_{15}N_8$	15.77	15.72		
37	8		Bromide	267–268	13	$C_{16}H_{32}ON_2Br_2$	6.54	6.45	37.33	37.51
38	8		Picrate	280–281		$C_{28}H_{36}O_{15}N_8$	15.47	15.30		

(d) N,N′-Ethylene-N,N′-trimethylenepolymethyleniminiummorpholinium salts,

$(CH_2)_x >$

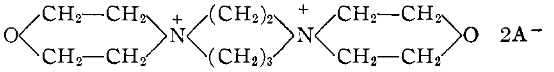


$$(CH_2)_x > \overset{+}{N}\begin{matrix}(CH_2)_2\\(CH_2)_3\end{matrix}\overset{+}{N}\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}O\ \ 2A^-$$

	x	y	A⁻	M.p., °C.[a]	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Bromine, % Calcd.	Bromine, % Found
39	5		Bromide	329–330	20	$C_{14}H_{28}ON_2Br_2$	7.00	6.96	39.94	40.10
40	5		Picrate	271–273		$C_{26}H_{32}O_{15}N_8$	16.09	15.99		
41	6		Bromide	306–308	30	$C_{15}H_{30}ON_2Br_2$	6.77	6.80	38.58	38.41
42	6		Picrate	244–246		$C_{27}H_{34}O_{15}N_8$	15.77	15.65		
43	7		Bromide	282–283	23	$C_{16}H_{32}ON_2Br_2$	6.54	6.56	37.33	37.19
44	7		Picrate	198–200		$C_{28}H_{36}O_{15}N_8$	15.47	15.34		
45	8		Bromide	279–280	12	$C_{17}H_{34}ON_2Br_2$	6.34	6.38	36.14	36.05
46	8		Picrate	182–184		$C_{29}H_{38}O_{15}N_8$	15.17	15.08		

TABLE II (*Continued*)

(e) N,N'-Ethylene-N,N'-trimethylenedimorpholinium salts,



$O\langle{}^{CH_2-CH_2}_{CH_2-CH_2}\rangle\overset{+}{N}\langle{}^{(CH_2)_2}_{(CH_2)_3}\rangle\overset{+}{N}\langle{}^{CH_2-CH_2}_{CH_2-CH_2}\rangle O\ \ 2A^-$

	x	y	A⁻	M.p., °C.[a]	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Bromine, % Calcd.	Bromine, % Found
47			Bromide	326–327	14	$C_{13}H_{26}O_2N_2Br_2$	6.97	6.86	39.75	39.66
48			Picrate	277–278		$C_{25}H_{30}O_{16}N_8$	16.04	15.93		

[a] All compounds melted with decomposition except 42, 44 and 46. Compounds 18 and 20 were explosive. [b] The bromide and chloroplatinate have been prepared (ref. 4) but the melting points were not reported. O. Aschan (*Ber.*, **32**, 988 (1899)) obtained the iodide. The chloride has been prepared (ref. 6), but the melting point was not mentioned. It was stated (ref. 6) that the chloroaurate melted at 273–274° dec. [c] Ref. 5, m.p. over 300°.

75 cc. of isopropyl alcohol was refluxed for 24 hours. The precipitate was filtered and washed with isopropyl alcohol; yield 1.5 g. (12%). The salt was dissolved in a few cc. of water, the solution treated with Norite, filtered and the product precipitated with isopropyl alcohol; m.p. 279–280° dec.

The dipicrate precipitated when picric acid was added to an aqueous solution of the dibromide; m.p. 182–184°.

N,N',N,N'-Diethylenedipyrrolidinium Dibromide (Table II, 1).—In addition to the use of the general method described above, this compound was obtained directly from pyrrolidine and ethylene bromide.

A mixture of 35.5 g. (0.5 mole) of pyrrolidine, 20.0 g. (0.5 mole) of sodium hydroxide and 60 cc. of water was stirred, and 94.0 g. (0.5 mole) of ethylene bromide was added, dropwise, at such a rate that the material refluxed. The mixture was stirred and refluxed for 6 hours. After the product had precipitated from the cooled mixture, it was filtered and washed with alcohol; yield 24.5 g. (28%). It was dissolved in a small amount of water, the solution treated with Norite, filtered and the product precipitated with isopropyl alcohol; yield 22.9 g., m.p. 342–344°, mixed m.p. with material obtained by the use of the general method 342–344°.

In order to convert the dibromide into the dichloride, 5.0 g. of the former substance, dissolved in 50 cc. of water, was shaken with 4.8 g. of silver oxide for 3 hours. The filtered solution was neutralized with hydrochloric acid. The solution was concentrated to a small volume, cooled, and the product precipitated by the addition of isopropyl alcohol and then acetone; yield 2.7 g. A portion of the product was converted into the chloraurate and chloroplatinate.

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

2-(1-Hydroxypropyl)-amides of 1-Hydroxy-6-amino- and 1-Hydroxy-7-aminobenzo(f)quinoline-2-carboxylic Acids

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The two basic amides mentioned in the title were obtained by interaction of the corresponding ethyl esters of the 2-carboxylic acids with 2-aminopropanol. The required acids were prepared by a series of reactions from acenaphthene.

The two basic amides described in this paper were prepared by interaction of the ethyl esters of the required 2-carboxylic acids with 2-aminopropanol. They were synthesized in order that they might be tested for oxytocic activity.

To obtain ethyl 1-hydroxy-6-aminobenzo(f)-quinoline-2-carboxylate (V), acenaphthene was oxidized to naphthalic anhydride[3] which was nitrated to produce 3-nitrophthalic anhydride.[4] Mercuration of the anhydride yielded a mixture of anhydro-3-nitro-8-hydroxymercuri-1-naphthoic acid and anhydro-6-nitro-8-hydroxymercuri-1-naphthoic acid.[5] When the mixture was heated with hydrochloric acid, a mixture of 6-nitro-1-naphthoic and 3-nitro-1-naphthoic acids was produced.[5] When the mixture was dissolved in acetic acid and the solution was cooled, most of the 3-nitro acid precipitated. The 3-nitro acid was converted into 3-nitro-1-naphthylamine[6] by the use of sodium azide and sulfuric acid. After acetylation of the amino group and reduction of the nitro group, 3-amino-1-acetylaminonaphthalene (I) was obtained.

Condensation of I with diethyl ethoxymethylenemalonate (II)[7] yielded 1-acetylamino-3-naphthylaminoethylenemalonate (III) which, when heated, cyclized to ethyl 1-hydroxy-6-acetylaminobenzo(f)-quinoline 2-carboxylate (IV, IV'). Treatment with hydrochloric acid eliminated the acetyl group whereby the ester, ethyl 1-hydroxy-6-aminobenzo-(f)quinoline-2-carboxylate (V) was obtained. The structure of the ester V was established by removal of the amino group which converted it into a compound of known structure, ethyl 1-hydroxybenzo-(f)quinoline-2-carboxylate.[8,9]

The ethyl ester V reacted with 2-aminopropanol to form the desired 2-(1-hydroxy)-propylamide (VI).

Ethyl 1-hydroxy-7-aminobenzo(f)quinoline-2-carboxylate was obtained by the preparation of the following series of intermediates: 2-*p*-toluenesulfon-

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(1) This paper represents part of a dissertation submitted by J. E. Gearien in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1949.

(2) Parke, Davis and Company Fellow.

(3) C. Graebe and F. Gfeller, *Ber.*, **25**, 652 (1892).

(4) C. Graebe and N. Briones, *Ann.*, **327**, 84 (1903).

(5) G. J. Leuck, R. P. Perkins and F. C. Whitmore, THIS JOURNAL, **51**, 183 (1929).

(6) This compound had been obtained by V. Vesely and K. Dvorak (*Bull. soc. chim.*, **33**, 327 (1923)) by a different process. See also ref. 5.

(7) R. C. Fuson, W. E. Parkham and L. J. Reed, *J. Org. Chem.*, **11**, 194 (1946).

(8) A. C. Mueller and C. S. Hamilton, THIS JOURNAL, **65**, 1017 (1943).

(9) R. E. Foster, R. D. Lipscomb, T. J. Thompson and C. S. Hamilton, *ibid.*, **68**, 1327 (1946).