sample of the trithioörthoformate of trimethylenedithiol; m.p. 80–82°.

Anal. Calcd. for $C_{11}H_{20}S_6$: C, 38.4; H, 5.83; S, 55.8; mol. wt., 344. Found: C, 38.77; H, 5.66; S, 56.7; mol. wt., 342.

The yield of purified acetate, m.p. 221–222°, was 58% in this case but variations from 55 to 75% were noted depending on the amount of contaminant.

Methyl 3(α)-Formoxy-11,12-diketocholanate-12-ethylenethioketal (XXVIII).—A suspension of 2.0 g. of the diketocholanate XX in 9 ml. of methanol was cooled and saturated with dry hydrogen chloride. Then one ml. of ethylene dithiol was added and the hydrogen chloride stream was continued for 1.5 hours. Nitrogen was passed through the solution for one hour and the mixture worked up as above. The yellow oil that was left was formylated in 90% formic acid. Dilution with water threw down the product which was purified by crystallization from dilute acetone and then ligroin; m.p. 128.5–130.5°.

Anal. Calcd. for $C_{28}H_{42}O_5S$: S, 12.27. Found: S, 12.10.

Methyl 3(α)-Carboethoxyoxy-11,12-diketocholanate-12-trimethylenethioketal (XXVII).—Ten grams of the mercaptol XXIV was dissolved in pyridine and then treated with an equal weight of ethyl chlorocarbonate. The ester was isolated in the usual way and then purified by recrystallization from acetone; m.p. 161–163.5°, $[\alpha]^{25}D$ −8°.

Anal. Calcd. for $C_{31}H_{48}O_6S_2$: C, 64.10; H, 8.33. Found: C, 64.20; H, 8.24.

Desulfuration Experiments

Methyl 3(α)-Acetoxy-11-ketocholanate (XVII).—Two grams of the pure thioketal acetate XXVI was suspended in 100 ml. of methanol which contained 10 g. of wet Raney nickel catalyst. The mixture was shaken mechanically for six hours. After the catalyst was removed the filtrate was evaporated to dryness and the residue was recrystallized from dilute acetone to furnish 1.54 g. of the desired substance (yield, 95%); m.p. 131–133°. One further crystallization raised the m.p. to 133–134° $[\alpha]^{25}D$ +70° (Turner, *et al.*,[5] reported m.p. 134–134.5°, $[\alpha]D$ +68 ± 2°).

Anal. Calcd. for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48. Found: C, 72.89; H, 9.40.

When the reaction was carried out in refluxing methanol for one hour the yield was 90% of recrystallized ester. When carried out as described above but for only 15 minutes the reaction mixture gave the desired 11-keto ester XVII, m.p. 131–132.4° in 86% yield.

The yield of once recrystallized methyl 3(α)-acetoxy-11-ketocholanate (m.p. 130°) from thioketal acetate, m.p. 216–218°, was 90%. Since the yield of mercaptol was 82% and the acetate XXVI was 88%, the over-all yield of the required ester XVII from methyl 3(α)-formoxy-11,12-diketocholanate was 65%.

Methyl 3(α)-Formoxy-11-ketocholanate (XVIII). A. From Methyl 3(α)-Acetoxy-11-ketocholanate.—A mixture of 1.08 g. of methyl 3(α)-acetoxy-11-ketocholanate, 10 ml. of methanol and 6 ml. of 5 *N* potassium hydroxide was refluxed for one-half hour. The methanol was removed *in vacuo* and the residue was dissolved in water and carefully acidified to *p*H 3. The crystalline acid so obtained weighed 810 mg. and melted at 222–224° after recrystallization from dilute acetone.

The acid was esterified in methanol containing hydrogen chloride. The crude methyl ester melted at 99–102° (Turner[5] reported m.p. 102–103°.) Formylation was accomplished in our usual fashion. The formate was purified by crystallization from acetone; m.p. 142–143.5°, $[\alpha]^{25}D$ + 73.4°.

Anal. Calcd. for $C_{28}H_{40}O_5$: C, 72.18; H, 9.32. Found: C, 71.92; H, 9.53.

B. From Methyl 3(α)-Hydroxy-11,12-diketocholanate-12-trimethylenethioketal (XXIV).—The solvated mercaptol XXIV (2.0 g.) was refluxed in 50 ml. of methanol in which there was suspended 5.0 g. of moist Raney nickel catalyst. After 4 hours the solvent was removed leaving a residue which solidified on cooling. The latter was warmed with 15 ml. of 90% formic acid for one-half hour. The diluted reaction mixture yielded an oil which solidified when triturated with methanol; wt. 1.25 g. After three recrystallizations from acetone the sulfur-free ester melted at 139.5–140.5° and did not depress the m.p. of the sample prepared as described above.

Methyl 3(α)-Carboethoxyoxy-11-ketocholanate.—Three grams of the crude ester XXVII and 10 g. of Raney nickel catalyst were boiled in methanol overnight. The mixture was worked up in the usual way to furnish 1.50 g. of the substance. After recrystallization from acetone and then methanol the desired compound melted at 146–147.5°.

Anal. Calcd. for $C_{28}H_{44}O_6$: C, 70.55; H, 9.31. Found: C, 70.37; H, 9.11.

RENSSELAER, NEW YORK

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

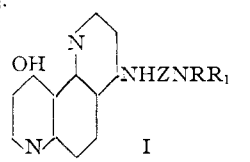
The Synthesis of Bis-quaternary Salts of Some 1,7-Phenanthroline Derivatives

BY ALEXANDER R. SURREY, ARTHUR J. OLIVET AND JAMES O. HOPPE

RECEIVED APRIL 9, 1954

The reaction of 4-chloro-10-hydroxy-1,7-phenanthroline with a variety of primary–tertiary diamines is described. The resulting 4-substituted-amino-10-hydroxy-1,7-phenanthrolines were quaternized with methyl bromide or iodide to give bis-quaternary salts which have been examined for their neuromuscular blocking activity.

As part of a general investigation in these laboratories of potential neuromuscular blocking agents we have prepared a series of bis-quaternary salts (Table IV) of some 1,7-phenanthroline derivatives having the general formula I where Z is $(CH_2)_n$ or $(CH_2)_nO(CH_2)_3$.



I

These 4-substituted-amino-10-hydroxy-1,7-phenanthrolines (Table III) were prepared from 4-chloro-10-hydroxy-1,7-phenanthroline[1] by reaction with the appropriate primary-tertiary diamine in isopropyl alcohol in the presence of hydrogen chloride. On the basis of our previous work in which it was demonstrated that the 1-ring nitrogen is probably involved in hydrogen bonding with the 10-hydroxyl group, we have assumed that quaternization of these bases (I) occurs at the 7-position in the phenanthroline ring and at the terminal tertiary nitrogen in the side chain.

The primary–tertiary diamines employed in the present work were of two types $NH_2(CH_2)_nNR_1R_2$ and $NH_2(CH_2)_3O(CH_2)_nNR_1R_2$. The compounds of the first type have been reported previously. The first two members of this series, where n = 2 and 3, are commercially available. Where n = 4, the diamine 4-diethylaminobutylamine was pre-

(1) A. R. Surrey and R. A. Cutler, THIS JOURNAL, **76**, 1109 (1954).

pared from 1-bromo-3-chloropentane by reaction with diethylamine followed by treatment with sodium cyanide and reduction of the resulting 4-diethylaminobutyronitrile with Raney nickel in methanolic ammonia solution.[2] A different sequence of reactions was employed for the preparation of the compounds where $n = 5$[3] and 6.[4] Starting with the appropriate dichlorobutane or dichloropentane the cyano group was introduced first followed by reaction with diethylamine and then reduction.

The oxygen interrupted side chains, the second type (Table II), were prepared essentially by the method of Whitmore.[5] The tertiary aminoalcohol was allowed to react with acrylonitrile in the presence of a basic catalyst and the resulting amino nitrile (Table II) was reduced catalytically with Raney nickel as described above in the presence of a large excess of ammonia. The yields of primary amine in this last step were usually 75–80%.

N-(2-Chlorobenzyl)-N-methylethanolamine was prepared by methylation of N-chlorobenzylethanolamine[6] with formaldehyde and formic acid. The remaining benzylalkylethanolamines (Table I) were prepared from the appropriate benzaldehyde by reductive alkylation in aqueous alcohol with either ethylamine or methylamine using Raney nickel as the catalyst. The resulting secondary amines were allowed to react with ethylene chlorohydrin to give the ethanolamine derivatives.

The reaction of the primary–tertiary diamines with 4-chloro-10-hydroxy-1,7-phenanthroline was very rapid. Usually the dihydrochloride of the product separated in 1–2 hours. In some instances it was necessary to concentrate the reaction mixture or to add acetone to precipitate the dihydrochloride salt. The bases (Table III) were obtained by dissolving the hydrochlorides in water and adding ammonium hydroxide. Some of the solid bases were found to be quite soluble in water which may account for the poor yields obtained in a few instances. Many of the bases retained moisture even after recrystallization.

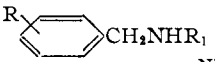
In each instance, the base was dried *in vacuo* 10–15° below its melting point before it was quaternized. Quaternization with methyl bromide was carried out by adding an excess of the alkyl halide to a solution of the base in hot acetonitrile and the mixture was allowed to stand until the solid product separated. In a few cases, methyl bromide was bubbled into a refluxing acetonitrile solution until solid appeared. The yields of product obtained by this procedure were good and usually no further purification was necessary. This was advantageous since it was found that recrystallization of some of the salts was accompanied by decomposition. Attempts to prepare monomethobromide salts were unsuccessful, only the bis-salts were isolated. Quaternization with methyl and ethyl iodide was carried out in refluxing acetonitrile. Most of the bis-quaternary salts retained varying amounts of water which could not be completely removed by drying even at elevated temperatures (100–110°) in a vacuum oven.

Pharmacology.—Tests were made for evidence of neuromuscular blocking activity in mice by the inclined screen technique and in the sciatic nerve–gastrocnemius muscle preparation in the cat under sodium pentobarbital anesthesia. The compounds were administered in solution by subcutaneous injection in the mice and by intravenous injection in the cat. A progressive increase in activity was observed in both the mouse and the cat as the number of carbons in the side chain was increased from 2 to 6 carbons (compds. 1–5, Table IV). The maximum activity observed with the 6-carbon homolog (compd. 5) was similar to that of *d*-tubocurarine in the mouse and approximately one-third as great in the cat. The change in activity in respect to length of the side chain was less marked in the cat than in the mouse. The increase in chain length was also associated with an increase in toxicity in the mouse. Introduction of an oxygen atom in the side chain did not appear to change the activity (see compds. 5 and 10). Optimum activity in the mouse with the oxygen interrupted side chain was associated with the presence of a piperidyl or ethyl group on the terminal nitrogen atom, whereas in the cat the trimethylammonium compound, compd. 11, showed the greatest activity. Replacement of an ethyl group on the terminal nitrogen by a benzyl or alkoxybenzyl group resulted in approximately a 30% or greater reduction in activity as measured in the mouse.

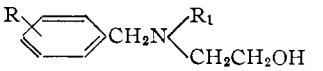
Experimental[7]

N-Benzylalkylamines (Table I).—Three moles of an aqueous solution of ethylamine or methylamine was added with

TABLE I

Benzylalkylamines, 

R	R_1	B.p., °C.	Mm.	$n^{25}D$	Formula	Nitrogen, % Calcd.	Found
H	Me	.....	..	....	$C_8H_{11}N$[a]	..	..
H	Et	86–88	15	1.5109	$C_9H_{13}N$[b]	..	..
2-CH_3O	Me	121–122	20	....	$C_9H_{13}NO$[c]	..	..
2-CH_3O	Et	147–149	40	1.5208	$C_{10}H_{15}NO$	8.48	8.13
2,3-Di-CH_3O	Me	95–98	0.5	1.5225	$C_{10}H_{15}NO_2$	7.74	7.28[d]
2,3-Di-CH_3O	Et	115–117	2.0	1.5188	$C_{11}H_{17}NO_2$	7.17	6.97
2-Cl	Me	.....	..	....	.....	..	..

Benzylalkylethanolamines, 

H	Me	136–138	16	1.5245	$C_{10}H_{15}NO$	8.48	8.34
H	Et	106–108	1.5	1.5181	$C_{11}H_{17}NO$	7.81	7.76
2-CH_3O	Me	102–105	0.2	1.5312	$C_{11}H_{17}NO_2$	7.34	7.34
2-CH_3O	Et	107–110	0.6	1.5220	$C_{12}H_{19}NO_2$	6.69	6.73
2,3-Di-CH_3O	Me	144–148	1.5	1.5261	$C_{12}H_{19}NO_3$	6.22	6.20
2,3-Di-CH_3O	Et	141–144	0.7	1.5211	$C_{13}H_{21}NO_3$	5.85	5.93
2-Cl	Me	116–118	0.8	1.5394	$C_{10}H_{14}ClNO$	7.01	6.97

[a] Sumner Chemical Co. [b] R. C. Young and R. Robinson, *J. Chem. Soc.*, 275 (1933). [c] N. H. Cromwell and H. Hoeksema, THIS JOURNAL, 67, 1658 (1945). [d] Sufficiently pure for next step.

(2) W. Huber, THIS JOURNAL, **66**, 876 (1944).

(3) H. Normand and G. Voreaux, *Compt. rend.*, **231**, 703 (1950); see also M. Frankel, H. S. Mosher and F. C. Whitmore, THIS JOURNAL, **72**, 81 (1950).

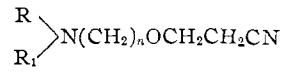
(4) J. Cason, L. Wallcave and C. N. Whiteside, *J. Org. Chem.*, **14**, 40 (1949); D. S. Breslow and C. R. Hauser, THIS JOURNAL, **67**, 786 (1945).

(5) F. C. Whitmore, H. S. Mosher, R. A. Adams, R. B. Taylor, E. C. Chapin, C. Weisel and W. Yanko, *ibid.*, **66**, 725 (1944).

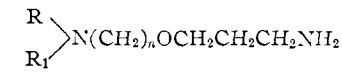
(6) A. R. Surrey, *ibid.*, **76**, 2214 (1954).

(7) Melting points are uncorrected.

TABLE II



Substituted-aminoalkoxypropionitriles



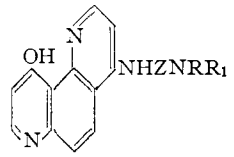
Substituted-aminoalkoxypropylamines

R	R_1	n	B.p. °C.	Mm.	$n^{25}D$	Nitrogen, % Calcd.	Found	B.p. °C.	Mm.	$n^{25}D$	Formula	Nitrogen, %[a] Calcd.	Found
Et	Et	3	132–136[b]	12	1.4426	...	...	110–112	9	1.4470	$C_{10}H_{24}N_2O$[b]	15.04	14.80
Et	Et	2	128–130[b]	16	1.4400	...	...	105–108	14	1.4460	$C_9H_{22}N_2O$[b]	16.08	15.95
Me	Me	2	115–116	14	1.4348	19.71	19.71	86–88	12	1.4411	$C_7H_{18}N_2O$	19.17	18.75
Bu	Bu	2	133–141	0.75	1.4432	12.43	12.38	103–105	0.65	1.4471	$C_{13}H_{30}N_2O$	12.17	11.97
Me	$C_6H_5CH_2$	2	147–149	.5	1.5061	12.83	12.54	138–140	.6	1.5080	$C_{13}H_{22}N_2O$	12.60	12.49
Et	$C_6H_5CH_2$	2	147–149	.5	1.5002	12.06	11.69	128–131	.7	1.5045	$C_{14}H_{24}N_2O$	11.85	10.79[c]
Me	2-CH_3O-$C_6H_4CH_2$	2	160–164	.9	1.5142	11.28	11.44	148–151	.4	1.5170	$C_{14}H_{24}N_2O_2$	11.10	10.98
Et	2-CH_3O-$C_6H_4CH_2$	2	145–147	.1	1.5008	10.67	11.08	143–145	.2	1.5098	$C_{15}H_{26}N_2O_2$	10.52	10.59
Me	2,3-Di-CH_3O-$C_6H_3CH_2$	2	166–170	.2	1.5137	10.07	9.75	153–156	.3	1.5151	$C_{15}H_{26}N_2O_3$	9.92	9.84
Et	2,3-Di-CH_3O-$C_6H_3CH_2$	2	158–161	.05	1.5083	9.58	9.69	150–153	1.0	1.5112	$C_{16}H_{28}N_2O_3$	9.45	9.47
Me	2-Cl-$C_6H_4CH_2$	2	165–166	.7	1.5198	11.09	11.08	152–153	0.8	1.5212	$C_{13}H_{21}ClN_2O$	10.91	10.86
	C_5H_{10}(piperidyl)	2	150–152	13	1.4662	15.37	15.00	133–134	12	1.4719	$C_{10}H_{22}N_2O$	15.04	14.92

[a] Basic nitrogen, titrated with acetous perchloric acid in anhydrous media. [b] F. C. Whitmore, H. S. Mosher, R. A. Adams, R. B. Taylor, E. C. Chapin, C. Weisel and W. Yanko, THIS JOURNAL, 66, 725 (1944). [c] Sufficiently pure for next step.

TABLE III

4-SUBSTITUTED-AMINO-10-HYDROXY-1,7-PHENANTHROLINES



Cpd.	R	R_1	n	Yield, %[a]	M.p., °C.[b]	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
					Z = $(CH_2)_n$							
1	Et	Et	2	95	130–132[c]	$C_{18}H_{22}N_4O$	69.63	69.67	7.15	7.16	18.05	18.28
2	Et	Et	3	96	116–117[d]	$C_{19}H_{24}N_4O$	...	...	..	..	17.28	16.91
3	Et	Et	4	57	100–102[e]	$C_{20}H_{26}N_4O$	70.99	70.72	7.93	8.00	16.56	16.11
4	Et	Et	5	75	117–118[f]	$C_{21}H_{28}N_4O$	71.56	71.52	8.01	7.95	15.90	15.81
5	Et	Et	6	93	118–120[c]	$C_{22}H_{30}N_4O$	72.10	71.80	8.25	8.40	15.29	15.30
6	Et	$HOCH_2CH_2$	3	41	109–111[g]	$C_{19}H_{24}N_4O_2$	...	...	..	..	16.48	16.80
7	Bu	Bu	4	51	86–89[e]	$C_{24}H_{34}N_4O$	73.08	73.18	8.69	8.68	14.20	14.10
8	Me	$C_6H_5CH_2$	5	79	153–154[c]	$C_{25}H_{28}N_4O$	74.96	75.12	7.05	6.86	13.99	13.85
					Z = $(CH_2)_nO(CH_2)_3$							
9	Et	Et	3	38	107–109[e]	$C_{22}H_{30}N_4O_2$	69.08	69.06	7.90	7.88	14.64	14.56
10	Et	Et	2	75	95–96[h]	$C_{21}H_{28}N_4O_2$	...	...	...	..	15.25	15.51
11	Me	Me	2	68	128–130[e]	$C_{19}H_{24}N_4O_2$	...	...	..	..	16.45	16.18
12	Me	$C_6H_5CH_2$	2	45	113–115[e]	$C_{25}H_{28}N_4O_2$	72.10	71.80	6.78	6.55	13.46	13.45
13	Et	$C_6H_5CH_2$	2	54	104–105[e]	$C_{26}H_{30}N_4O_2$	72.36	72.20	7.01	6.85	12.98	12.88
14	Me	2-$CH_3OC_6H_4CH_2$	2	65	105–106[i]	$C_{26}H_{30}N_4O_3$	69.93	70.17	6.77	6.99	12.55	12.37
15	Me	2,3-Di-$CH_3OC_6H_3CH_2$	2	25	108–110[e]	$C_{27}H_{32}N_4O_4$	...	...	..	..	11.76	11.57
16	C_5H_{10} (piperidyl)		2	53	143–144[c]	$C_{23}H_{28}N_4O_2$	69.43	69.08	7.42	7.63	14.72	14.52
17	Bu	Bu	2	34	102–103[e]	$C_{25}H_{36}N_4O_2$	...	...	..	..	13.19	13.14
18	Et	2-$CH_3OC_6H_4CH_2$	2	31	127–129[e]	$C_{27}H_{32}N_4O_3$	...	...	..	..	11.76	11.57
19	Et	2,3-Di-$CH_3OC_6H_3CH_2$	2	24	86–89[i]	$C_{28}H_{34}N_4O_4$	...	...	..	..	11.42	10.92
20	Me	2-$ClC_6H_4CH_2$	2	80	89–90[e]	$C_{25}H_{27}ClN_4O_2$	66.57	66.40	6.04	5.23	12.42	12.25

[a] Yield before recrystallization. [b] Melting points are uncorrected. [c] Recrystallized from acetone. [d] Skellysolve C. [e] Acetonitrile. [f] Ethylene dichloride. [g] Benzene. [h] Benzene–Skellysolve B. [i] Ethyl acetate.

ice-cooling to one mole of the benzaldehyde dissolved in ethanol and the resulting Schiff base was reduced directly with Raney nickel at 60° and a hydrogen pressure of 1000 p.s.i. The catalyst was filtered off and the alcohol removed by distillation. Solid sodium carbonate was added to the aqueous residue, the resulting oil was taken up in benzene and the product was distilled. Yields were usually between 60–65%.

N-Benzyl-N-alkylethanolamines (Table I).—Two moles of the above benzylalkylamine and 1 mole of ethylene chlorohydrin were dissolved in 3–4 volumes of dry toluene and refluxed with stirring for 4 hours. The solid benzylalkylamine hydrochloride which had separated was filtered off and washed with toluene. The solvent was removed from the filtrate by distillation and the product was obtained from the residue by distillation at reduced pressure; yields were 70–75%.

In some cases where the benzylalkylamine hydrochloride did not separate as a solid, 35% aqueous sodium hydroxide was added and the organic layer was separated and worked up as described above.

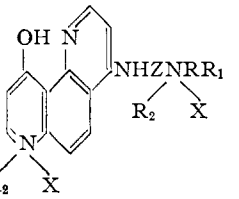
Substituted-aminoalkoxypropionitriles (Table II).—These compounds were prepared from the appropriate aminoalcohol and acrylonitrile according to the procedure of Whitmore.[5] Yields were usually about 70%.

Substituted-aminoalkoxypropylamines (Table II).—These compounds were prepared by the reduction of the above nitriles with Raney nickel according to the method of Whitmore,[5] except that 6–7 moles of methanolic ammonia was used as solvent to increase the yield of primary amine. Yields were usually 75–80%.

N-(2-Chlorobenzyl)-N-methylethanolamine.—A mixture of 33.1 g. of formic acid, 50 g. of N-(2-chlorobenzyl)-ethanolamine and 24 ml. of 40% aqueous formaldehyde solution was heated on a steam-bath for 24 hours. After cooling, the mixture was neutralized with solid sodium carbonate and then made strongly basic with 35% sodium hydroxide

TABLE IV

DIQUATERNARY SALTS OF 4-SUBSTITUTED-AMINO-10-HYDROXY-1,7-PHENANTHROLINES



Cpd.[k]	R_2X	Yield, %[a]	M.p., °C.[b]	Formula	H_2O, % Found[c]	Analyses, %[d] Halogen Calcd.	Halogen Found	Nitrogen Calcd.	Nitrogen Found	Curarimimetic act., mg./kg. Mouse s.c. ED_{50}	Cat i.v. AED_{50}	Toxicity, mg./kg. Mouse s.c ALD_{50}
1	MeBr	70	218–222	$C_{20}H_{28}Br_2N_4O$[e]	4.78	Br 31.93	32.45	11.30	10.98	33 ± 2	0.8	..
2	MeBr	69	259–263	$C_{21}H_{30}Br_2N_4O$[f]	3.79	31.07	30.40	10.89	10.90	11 ± 0.8	<.5	20
3	MeBr	82	242–245	$C_{22}H_{32}Br_2N_4O$	2.95	30.25	30.18	10.61	10.32	3.1 ± .2	.65	4
4	MeBr	84	276–277	$C_{23}H_{34}Br_2N_4O$	0.75	29.47	29.30	10.33	10.10	1.15 ± .06	.24	1.3
5	MeBr	74	268–270	$C_{24}H_{36}Br_2N_4O$	..	28.82	29.10	[g]	..	0.4 ± .04	.3	0.8
6	MeI	60	258–260	$C_{21}H_{30}I_2N_4O_2$	...	I 40.56	39.83	8.97	9.11	12.5 ± .6	..	28
7	MeI	88	204–206	$C_{26}H_{40}I_2N_4O$	4.08	37.42	37.30	8.26	8.03	7.8 ± 1.8	.6	..
8	MeI	88	228–230	$C_{27}H_{44}I_2N_4O$	2.18	37.08	36.80	8.18	8.18	3.3 ± 0.5	1.0	5.3
9	MeBr	67	236–238	$C_{24}H_{36}Br_2N_4O_2$	2.05	Br 27.97	27.30	9.80	9.92	0.3 ± .03	0.37	..
9a	EtI	99	202–205	$C_{26}H_{40}I_2N_4O_2$	..	I 36.52	36.36	8.07	8.05	0.66 ± .04	.26	1.1
10	MeBr	55	249–253	$C_{22}H_{34}Br_2N_4O_2$	..	Br 28.66	28.13	10.05	10.31	0.6	.26	1.5
11	MeI	100	263–266	$C_{21}H_{30}I_2N_4O_2$	..	I 40.56	40.00	8.97	8.73	3.2 ± 0.9	.06	7.0
12	MeI	88	200–202	$C_{27}H_{34}I_2N_4O_2$[h]	0.35	36.04	35.20	7.95	7.86	2.2 ± .4	.90	4.7
13	MeI	76	218–223	$C_{28}H_{36}I_2N_4O_2$	0.56	35.54	34.58	7.84	7.95	1.8 ± .1	..	..
14	MeI	61	168–171	$C_{28}H_{36}I_2N_4O_3$[i]	1.82	34.76	34.20	7.69	7.49	.....	..	3.1
15	MeI	50	177–178	$C_{29}H_{38}I_2N_4O_4$	2.45	33.37	33.23	7.37	7.49	4.3 ± 1.0	1.0	..
16	MeI	96	195–198	$C_{24}H_{34}I_2N_4O_2$	3.24	38.20	38.10	8.43	8.25	0.22 ± 0.02	0.35	1.1
	d-Tubocurarine									0.4 ± 0.04	0.12	0.72 ± 0.03

[a] Yields before recrystallization. [b] Melting points are uncorrected. [c] Moisture analyses by Karl Fischer method. [d] Analyses calculated and reported on dry basis. [e] Recrystallized from 95% ethanol. [f] Triturated with hot isopropyl alcohol. [g] Calcd.: C, 51.70; H, 6.30. Found: C, 51.66; H, 6.31. [h] Recrystallized from methanol. [i] Recrystallized from ethanol. [k] Z is the same as in the correspondingly numbered compounds in Table III.

solution. The product was taken up in benzene and fractionally distilled, 32 g. (56%), b.p. 116–118° at 0.8 mm.

5-(N-Benzyl-N-methylamino)-valeronitrile.—A solution of 28.3 g. of 4-chlorovaleronitrile and 58 g. of benzylmethylamine in 100 ml. of xylene was refluxed for 3 hours. The benzylmethylamine hydrochloride which separated was filtered off and the xylene removed from the filtrate by distillation *in vacuo*. The product, 27.5 g. (56%), distilled at 126–129° at 0.3 mm., $n^{25}D$ 1.5077.

Anal. Calcd. for $C_{13}H_{18}N_2$: N, 13.86. Found: N, 13.14.

5-(N-Benzyl-N-methylamino)-pentylamine.—This was prepared from the above crude nitrile by reduction with Raney nickel in methanolic ammonia solution; yield 70%, b.p. 107–109° at 0.5 mm., $n^{25}D$ 1.5100.

Anal. Calcd. for $C_{13}H_{22}N_2$: N, 13.58. Found: N, 13.31.

4-Substituted-amino-10-hydroxy-1,7-phenanthrolines (Table III).—The following example illustrates the general method of preparation of these compounds.

A mixture of 10 g. (0.0435 mole) of 4-chloro-10-hydroxy-1,7-phenanthroline, 10 g. of phenol, 13.8 g. of 5-diethylaminopentylamine (0.087 mole), 10 ml. of 5.97 *N* alcoholic hydrogen chloride (0.0597 mole) and 60 ml. of isopropyl alcohol was refluxed with stirring for about 3 hours. After 45 minutes a complete solution was obtained and at the end of 2 hours solid began to appear in the reaction mixture. The reaction mixture was cooled and an equal volume of acetone was added to ensure complete separation of the product. The yellow solid was filtered off and washed well with acetone. This solid was then dissolved in water, and the solution was made strongly basic with ammonium hydroxide and the base was extracted with chloroform. The solvent was removed *in vacuo* to give 11.5 g. (75%) of 4-(5-diethylaminopentylamino)-10-hydroxy-1,7-phenanthroline melting at 110–113°. After recrystallization from ethylene dichloride and drying at 60° (20 mm.) over calcium chloride for 24 hours, the product (10 g.) melted at 117–118°.

Bis-quaternary Salts of 4-Substituted-amino-10-hydroxy-1,7-phenanthrolines (Table IV).—The following examples illustrate the procedures employed for quaternization of the above bases.

Method A.—4-(2-Diethylaminoethylamino)-10-hydroxy-1,7-phenanthroline (3.1 g.) was dissolved in 100 ml. of hot acetonitrile and 1.9 g. of methyl bromide gas was introduced. After about 30 minutes solid began to separate. At the end of 24 hours the product was filtered off, 3.5 g. (70%), m.p. 215–220°. After two recrystallizations from 95% ethanol and drying at 110–115° (30 mm.) for 24 hours, the 4-(2-diethylaminoethylamino)-10-hydroxy-1,7-phenanthroline dimethobromide melted at 218–222°.

Method B.—Methyl bromide gas was introduced continuously into a solution of 1.9 g. of 4-(5-diethylaminopentylamino)-10-hydroxy-1,7-phenanthroline in 100 ml. of refluxing acetonitrile for 10 minutes. After about 5 minutes solid began to separate. The reaction mixture was allowed to stir and cool for 1 hour, and the product was filtered off and dried at 80° (20 mm.) for 24 hours over calcium chloride. The yield of 4-(5-diethylaminopentylamino)-10-hydroxy-1,7-phenanthroline dimethobromide was 2.5 g. (84%), m.p. 276–277°.

Method C.—A solution of 3 g. of 4-[3-(2-dimethylaminoethoxy)-propylamino]-10-hydroxy-1,7-phenanthroline and 6 ml. of methyl iodide in 150 ml. of acetonitrile was refluxed with stirring for 1 hour. The product which separated was filtered off at room temperature, washed with ethanol and dried at 60° (10 mm.) over calcium chloride for 24 hours. A theoretical yield of 4-[3-(2-dimethylaminoethoxy)-propylamino]-10-hydroxy-1,7-phenanthroline dimethiodide was obtained, m.p. 263–266°.

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