[CONTRIBUTION FROM THE INSTITUTE FOR CANCER RESEARCH]

Nitrogen Mustard Analogs of Antimalarial Drugs[1]

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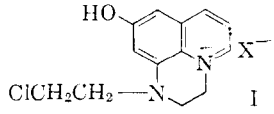
The hydrochlorides of thirty nitrogen mustard derivatives in the quinoline and acridine series of antimalarial drugs have been synthesized for studies of their antitumor potentialities. Pamoates of several of the mustards have also been prepared. Some of the diol intermediates were made by independent syntheses.

Introduction

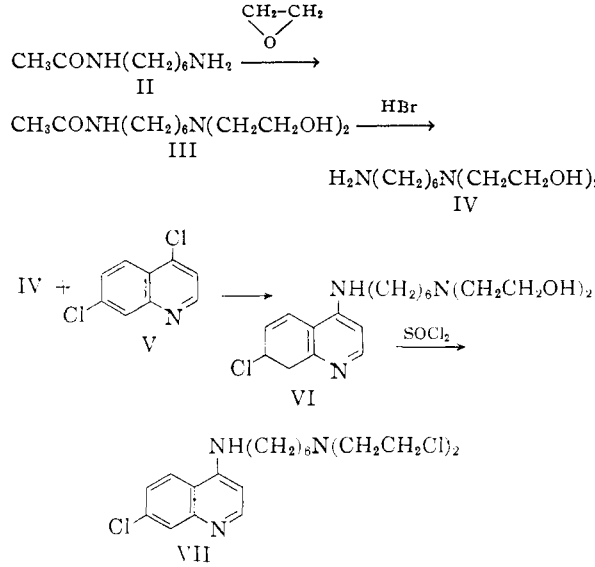
The nitrogen mustard group has been incorporated into many organic molecules possessing varying types of physiological activity.[2-4] We decided to utilize the substituted quinoline nuclei of several antimalarial drugs as carriers of the bis-(2-chloroethyl)-amino group. Pharmacologic data[5] on the toxicity and tissue distribution of the antimalarials suggested that such carriers might lead to some preferential localization of the alkylating activity in certain tissues; in addition, several of the antimalarials themselves show bone marrow depressant activity.[6] The majority of the antimalarial mustards have displayed pronounced antitumor activities in tests employing mouse ascites tumors.[7] Further information on this point will be reported elsewhere by Creech, *et al.*; pharmacologic studies are being conducted by Leon H. Schmidt and investigations of the effects of these mustards on rat leukemia and in patients are being made by Ralph Jones, Jr.

Attempts were made to place the bis-(2-chloroethyl)-amino group directly into the 4- and 8-positions of representative quinoline nuclei. Even with the use of reactive 4-bromoquinolines, the yields were low. The diol skeleton could be introduced into the 8-position of 6-methoxyquinoline, but subsequent chlorination led to cyclization to a pyridoquinoxalinium skeleton (I) accompanied by hydrolysis of the ether. Although it was unstable, the 8-(monochloroethyl)-amino derivative of 6-methoxyquinoline was isolated successfully.

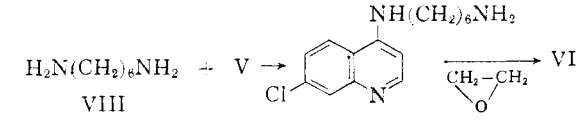


I

Since the di- and monofunctional compounds obtained by direct introduction of the substituent into the quinoline nucleus were found to be ineffective against ascites tumors,[7] synthetic efforts were concentrated on compounds in which the mustard group was placed at the end of an "antimalarial" side chain as in the types synthesized by Jones, Price and Sen.[8] Many of the compounds possible from eleven nuclei and six side-chains have been made. Two methods were employed for the synthesis of the intermediate diols. The procedure used for most of the compounds was to preform the entire side chain before incorporation into the quinoline nucleus, as exemplified by the reactions



The diol intermediates of several of the compounds carrying the two- and six-carbon side-chains were also obtained by attaching the primary aminoalkylamino chain first and hydroxyethylating the primary amine group, as shown by VIII, IX and VI.



The general scheme of synthesis has remained fairly constant, with variations being made only in the temperatures and times of condensation and chlorination, and in the modes of isolation; data are recorded in Tables I and II. The majority of the diol intermediates were ultimately crystallized or yielded crystalline salts; the rest were molecularly distilled.

Of the several methods of chlorination used to produce the mustards,[8-10] we had greatest success

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TABLE I

DIOLS

Side-chains = $-NH(CH_2)_nN(CH_2CH_2OH)_2$ and $-NHCH(CH_3)(CH_2)_3N(CH_2CH_2OH)_2$

No.	Side-chain	Other substituents	Condensation Time, hr.	Condensation Temp., °C.	M.p., °C.	Yield, %	Analyses, %[a] Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
					Quinolines							
1	2-Ethyl (n = 2)		10	100	150[b]	62	65.43	7.69	15.26	65.16	7.71	15.41
2	2-Propyl (n = 3)		48	100	155[b]	67			14.52			14.80
3	2-Butyl (n = 4)		6	115	150[b]	34	67.30	8.31	13.86	66.81	8.21	13.52
4	2-Methylbutyl		12	130	187–188[c]	30	Cl	18.17	10.76	Cl	17.91	10.65
5	4-Propyl		4	145	250[b]	40	66.41	7.95	14.52	66.75	8.25	13.77
6	4-Methylbutyl		3	150	138–139.5	85	68.11	8.57	13.24	67.75	9.32	13.32
7	4-Propyl	2-Methyl	7	130	185[b]	51	67.20	8.24	13.86	66.84	8.30	13.69
8	4-Methylbutyl	2-Methyl	3	160	207–211[d]	60	P 11.75[d]		7.96	P 11.65[d]		7.59
9	4-Hexyl (n = 6)	2-Methyl	(4	125)[e]	102–104	79	69.52	9.05	12.15	69.60	8.67	12.21
10	4-Ethyl	2-Phenyl	6	150	131.5–132.5	65	71.77	7.18	11.95	72.11	7.30	11.49
11	4-Propyl	2-Phenyl	5	135	250[b]	48	72.31	7.45	11.49	71.96	7.35	11.71
12	4-Methylbutyl	2-Phenyl	4	180	195[f]	54	I 39.09[f]		6.47	I 38.34[f]		6.54
13	4-Propyl	2-p-Chlorophenyl	7	150	250[b]	60	66.00	6.50	10.50	66.18	6.07	10.17
14	4-Methylbutyl	2-p-Chlorophenyl	(a) 4	(a) 165	206–208[f]	20	I 37.12[f]		6.15	I 37.13[f]		5.91
			(b) 1	(b) 195								
15	4-Propyl	3-Methyl	6	155	158.5–159.5[f]	36	I 45.40[f]		7.51	I 45.68[f]		7.72
16	4-Ethyl	5-Chloro	4	115	135.2–136.2	90	58.16	6.52	13.56	58.22	6.60	13.28
17	4-Propyl	5-Chloro	6	130	265[b]	32	59.34	6.80	12.97	59.42	6.72	13.09
18	4-Methylbutyl	5-Chloro	10	100	110[g]	65	49.83	6.73	9.68	49.90	6.98	10.17
19	4-Hexyl	5-Chloro	2	125	74–75	46	62.37	7.71	11.49	62.66	7.76	11.54
20	4-Ethyl	6-Methoxy	5	130	129–130	95	62.93	7.61	13.75	63.54	7.59	13.19
21	4-Propyl	6-Methoxy	5	135	201–203[d]	96	P 12.02[d]		8.15	P 12.04[d]		7.76
22	4-Hexyl	6-Methoxy	(7	135)[e]	136.5–138	83	66.46	8.65	11.63	66.00	8.63	11.23
23	4-Ethyl	7-Chloro	4	120	135–136	97	58.16	6.52	13.56	57.70	6.40	13.54
24	4-Propyl	7-Chloro	5	100	136.5–137	59	59.34	6.85	12.98	59.40	6.97	12.89
25	4-Butyl	7-Chloro	8	125	155–157	82	60.40	7.12	12.42	60.47	6.94	12.35
26	4-Amyl (n = 5)	7-Chloro	5	135	129.2–130	76	61.45	7.40	11.91	61.67	7.57	11.87
27	4-Heptyl (n = 7)	7-Chloro	Proc. B		110–113	40	63.23	7.96	11.06	62.65	7.75	11.01
28	4-Ethyl	2-Methyl-7-chloro	3	140	149.5–150.5	65	59.34	6.85	12.98	60.20	6.88	13.06
29	4-Propyl	2-Methyl-7-chloro	2	150	137–138	50	60.40	7.13	12.41	60.66	7.44	11.80
30	4-Hexyl	2-Methyl-7-chloro	Proc. B		157–158.5	55	63.23	7.97	11.05	63.31	8.04	11.21
31	4-Ethyl	3-Methyl-7-chloro	(7	128)[h]	97–97.8	68	59.34	6.85	12.98	59.45	6.77	12.88
32	4-Propyl	3-Methyl-7-chloro	10	135	200[b]	40	60.40	7.13	12.41	60.03	7.45	12.37
33	4-Methylbutyl	3-Methyl-7-chloro	(18	150)[h]	155[b]	49	62.36	7.71	11.50	62.50	7.93	11.79
34	4-Hexyl	3-Methyl-7-chloro	4	120	164–168[d]	84	P 10.75[d]		7.29	P 10.63[d]		7.19
35	4-Propyl	3-Methyl-6-methoxy	14	135	180[b]	52	64.66	8.14	12.59	63.51	8.33	12.06
					Acridines							
36	9-Ethyl	2-Methoxy-6-chloro	4	110	168–169.5[i]	45	59.04	6.45	10.30	58.73	6.45	10.45
37	9-Hexyl	2-Methoxy-6-chloro	3	120	190	54	55.55	6.60	Cl 20.50	54.83	6.75	Cl 19.87
					Isoquinoline							
38	1-Propyl		3	150	160[b]	56	66.41	8.01	14.52	66.47	8.02	14.76

[a] Values are either single analyses or averages of checks. [b] Pot temperature of molecular distillation (Hickman still); pressure 0.01–0.1 μ. [c] Isolated as the dihydrochloride. [d] Isolated as the diphosphate. [e] Also prepared by procedure B. [f] Isolated as the dihydriodide. [g] Isolated as the dihydrochloride·$^1/_2H_2O$. [h] Starting material 4-bromo-7-chloro-3-methylquinoline. [i] Monohydrate.

with the one involving standing for several days with a large excess of thionyl chloride. The products were all isolated as dihydrochlorides; these ranged widely in solubility characteristics and ease of purification. It was found that the melting range was not a satisfactory index of purity; products in which the replacement of hydroxyl by chlorine was far from complete often gave melting points identical with those of analytically pure products.

The sparingly soluble salts of pamoic acid, methylene bis-(2-hydroxy-3-naphthoic acid), were made of some of the mustards to take advantage of certain improved pharmacological properties, such as greater antitumor effectiveness and lower toxicity.[7] When these salts could be induced to separate in a crystalline form, individuals of good analytical purity were obtained; amorphous preparations tended to be much less pure.

TABLE II

MUSTARDS DERIVED FROM DIOLS IN TABLE I

Table I ref.	Chlorination conditions: At 0°, hours	At 24°, hours	Additional heating: °C.	Hr.	Solvation	M.p., °C.	Yield, %	Analyses, %[a]: Calcd. C	H	N	Cl	Found C	H	N	Cl
1	72	72	..	..	.....	143–145	77	46.76	5.50	10.91	36.82	46.73	5.76	10.62	35.14
2	72	48	35	1	.....	217–218.5	72	48.14	5.81	10.53	35.53	47.91	5.94	10.31	35.50
3	72	24	35	1	.....	218.5–220	82	49.41	6.10	10.17	34.32	49.47	6.38	10.32	33.57
4	72	..	..	..	.....	208.5–209.5	42	50.60	6.37	9.84	33.17	50.40	6.53	9.58	32.82
5	72	..	..	..	.....	<100[b]	82	48.14	5.81	10.53	35.53	48.26	5.90	11.14	34.67
7	72	24	40	1	.....	219–220.5	73	49.14	6.10	10.17	34.32	49.00	6.31	10.26	34.03
9	36	24	..	..	.....	202–205	70	52.76	6.87	9.22	31.15	52.92	6.89	9.39	31.07
10	72	20	..	..	1 H_2O	215–218	59	52.63	5.68	8.76	29.59	52.42	5.71	9.01	28.89
11	48	15	..	..	.....	225–227	68	55.59	5.73	8.84	29.84	55.90	5.87	9.15	29.55
12	72	4	..	..	.....	197–201	65			8.35	28.18			8.19	27.46
13	72	..	..	..	.....	241–243	32	51.84	5.14	8.25	34.78	51.83	5.34	8.16	33.54
15	72	24	..	..	.....	145	67	49.41	6.10	10.17	34.32	49.20	6.47	9.94	32.41
16	72	24	..	..	$1\frac{3}{4}H_2O$[c]	134–139 d.	95	39.93	5.25	9.31	39.30	40.22	5.41	9.67	39.22
17	72	..	..	..	.....	188–189	29	44.31	5.11	9.69	40.88	44.23	5.16	9.95	40.50
18	20	24	..	..	$1\frac{1}{3}H_2O$[c]	144–146 d.	69	44.50	5.95	8.65	36.49	44.05	6.05	8.26	36.53
19	72	24	40	0.5	.....	186–187	96	47.97	5.93	8.83	37.27	47.75	6.05	8.61	36.96
20	48	24	..	..	$\frac{1}{2}H_2O$	196–198	59	45.31	5.70	9.89	33.44	45.18	5.85	9.96	32.27
21	72	15	..	..	1 H_2O	140–142.5	55	45.65	6.08	9.38	31.71	45.65	6.19	9.68	31.63
23	60	1	..	..	1 H_2O	210–212	75	41.16	5.06	9.60	40.51	41.46	5.29	9.84	40.73
24	72	..	..	..	.....	190–192	56	44.31	5.11	9.69	40.88	43.87	5.18	10.02	41.09
25	72	..	..	..	.....	188.5–189.5	72	45.61	5.40	9.39	39.60	45.75	5.89	9.22	38.37
28	70	15	..	..	.....	254	65	44.32	5.12	9.68	40.89	44.46	5.31	10.39	39.63
29	48	30	..	..	$\frac{1}{2}H_2O$	214–215	93	44.71	5.52	9.20	38.82	44.99	5.80	9.98	38.19
30	72	8	..	..	.....	190–192	47	49.05	6.17	8.57	36.21	49.21	6.41	8.62	35.05
31	30	30	..	..	2 H_2O	210–212	90	40.91	5.59	8.95	37.75	40.63	5.49	9.22	37.43
32	48	..	..	..	.....	211–212	75	45.62	5.40	9.39	39.60	45.55	5.69	8.97	38.20
35	72	..	..	..	.....	205.5–206.5	56	48.77	6.14	9.48	32.00	48.98	6.58	9.71	30.98
36	30[d]	30	40	3	1 H_2O	217–220	51	46.40	5.06	8.11	34.25	46.35	5.26	8.29	33.09
37	..	20	..	..	1 H_2O	153–155	54	50.25	5.92	7.32	30.90	50.43	6.07	7.26	29.81
38	72	15	40	1.5	.....	220–222	80	48.18	5.81	10.53	35.53	48.12	5.96	9.93	34.95

[a] Values are either single analyses or averages of checks. All five analytical laboratories, to whom many of these compounds were sent, reported unusually great difficulties with the total halogen analyses because of the lability of the aliphatic and ionic chlorines. [b] Amorphous, hygroscopic. [c] This value arrived at through a Karl Fischer water determination done through the courtesy of the Analytical Department of Parke, Davis & Co. [d] Allowed to warm during initial mixing of reactants; if the usual procedure of cooling is employed the diol does not dissolve and the reaction does not proceed to completion.

TABLE III

PAMOATES

Table I ref.	Side-chain	Other substituents	M.p., °C.	Yield, %	Analyses, %[a]: Calcd. C	H	N	Cl	Found C	H	N	Cl
7	4-Propyl	2-Methyl	213–216	32	65.91	5.36	5.77	9.76	65.76	5.48	6.06	9.51
11	4-Propyl	2-Phenyl	220	75	68.40	5.23	5.32	8.98	68.07	5.41	5.54	9.05
13	4-Propyl	2-(4-Chlorophenyl)[b]	213–215	73	65.50	4.89	5.09	12.89	63.75	5.71	5.57	12.45
								Redried:	65.24	4.86	5.24	11.78
16	4-Ethyl	5-Chloro[b]	196–198	88	62.09	4.66	5.72	14.47	60.75	5.01	5.89	14.18
								Redried:	61.85	4.65		
17	4-Propyl	5-Chloro	212–216	47	62.53	4.84	5.61	14.20	61.04	5.17	5.72	13.11
18	4-Methylbutyl	5-Chloro	175–178	74	63.34	5.19	5.40	13.69	62.65	5.43	5.63	13.61
25	4-Butyl	7-Chloro	195–198	85	62.96	5.02	5.51	13.94	62.94	5.21	5.62	14.05
32	4-Propyl	3-Methyl-7-chloro	193–195	72	62.99	4.98	5.50	13.92	62.79	5.17	5.87	13.40
..	(4-Methylbutyl	2-Methyl-7-chloro)[c]	207–211	78	63.76	5.35	5.31	13.45	63.68	5.42	5.50	13.62

[a] Values are either single analyses or averages of checks. [b] Apparently a monohydrate which loses water but also HCl on more drastic drying. [c] Corresponding diol and mustard dihydrochloride reported by Jones, *et al.*[8]

Departure was made from the antimalarial type of compound to include some 2-substituted quinolines and a 1-substituted isoquinoline, as well as the direct chlorination products of one of the side-chains.

Part A of the Experimental procedure describes the preparation of intermediates and compounds in which the 2-chloroethylamine has been attached directly to the quinoline nucleus; part B describes the side-chain mustards.

Experimental[11]

Part A. 8-Bis-(2-hydroxyethyl)-amino-6-methoxyquinoline.—To a stirred suspension of 8.7 g. of 8-amino-6-meth-

(11) All melting points were determined in a capillary tube and are uncorrected.

oxyquinoline[12] in 80 ml. of 2 *N* acetic acid was added 18 ml. of ethylene oxide. After the loosely stoppered mixture had been stirred for about 6 hours, it became homogeneous and was allowed to remain at room temperature overnight. Excess sodium bicarbonate was added and the product was extracted with ethyl acetate, washed, dried and concentrated. The solvent was replaced with benzene, the solution was treated with carbon, and pentane was added to turbidity. After overnight cooling, the crystals were separated; the yield of product, m.p. 72–77.5°, was 10.5 g. (80%). Crystallization and vacuum sublimation gave an analytical sample melting at 79.5–81°.

Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.0; H, 6.91; N, 10.7. Found: C, 64.1; H, 6.92; N, 10.9.

1-(2-Chloroethyl)-9-hydroxy-1,2-dihydro-3-H-pyrido-[1,2,3-de]quinoxalinium Nitrate.—A solution of 2.65 g. of 8-bis-(2-hydroxyethyl)-amino-6-methoxyquinoline in benzene was concentrated to 40 ml. and 5 ml. of phosphorus oxychloride was added. After stirring and concentrating over a period of 15 minutes, 50 ml. of 6 *N* hydrochloric acid was added, the remaining benzene was distilled and the solution was refluxed for 3.5 hours, concentrated *in vacuo*, cooled, and partially neutralized with solid sodium bicarbonate (*p*H about 2). A little water was added to make the mixture almost homogeneous and excess saturated sodium nitrate solution was added. After cooling, the product was removed by filtration and washed with cold dilute sodium nitrate, yielding 2.5 g. (76%). Two precipitations from filtered aqueous solutions by the addition of sodium nitrate solution, and washing with cold water, gave 1.1 g. of analytically pure, bright orange-red product, m.p. 177–179°.

Anal. Calcd. for $C_{13}H_{14}N_3O_4Cl$ (demethylation as well as chlorination having occurred): C, 50.1; H, 4.57; N, 13.5; Cl, 11.4. Found: C, 50.1; H, 4.70; N, 13.2; Cl, 11.1; methoxyl, none.

8-(2-Hydroxyethyl)-amino-6-methoxyquinoline was obtained as a by-product in an earlier attempted synthesis of the bis-substituted amine above. A mixture of 17.4 g. of 8-amino-6-methoxyquinoline, 8.8 g. of ethylene oxide and 25 ml. of toluene was heated in a sealed glass vessel for 55 hours at 110°. After cooling at −12° the mixture was filtered and the precipitate washed with a little benzene and with petroleum ether. It weighed 7.9 g. (36%) and was recrystallized from 100 ml. of 30% ethanol with Norit treatment to give 5.6 g., m.p. 92.5–94.5°. An analytical sample obtained by further recrystallization and vacuum sublimation melted at 93.2–94°.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: N, 12.83. Found: N, 13.46, 13.28.

8-(2-Chloroethyl)-amino-6-methoxyquinoline.—To 0.92 ml. of phosphorus oxychloride, cooled in a test-tube, was added 2.18 g. of the above hydroxy compound in 2.2 ml. of dioxane. After heating at 100° for one hour, the mixture was added to benzene and ice, the aqueous layer was separated and the organic layer dried and concentrated *in vacuo*. The residue was crystallized from hexane to give 0.75 g. (31%) of large, light yellow crystals which melted at about 30° and decomposed to a highly colored compound unless kept cold.

Anal. Calcd. for $C_{12}H_{13}N_2ClO$: C, 60.89; H, 5.54; N, 11.83. Found: C, 60.93, 60.74; H, 5.49, 5.29; N, 12.17, 12.07.

4-Bromo-7-chloroquinoline originally was isolated during an unsuccessful attempt to prepare 4-bis-(2-bromoethyl)-amino-7-chloroquinoline by hydrobromic acid cleavage of 7-chloro-4-morpholinoquinoline; it is more efficiently synthesized as given below. (7-Chloro-4-morpholinoquinoline, not previously reported, can be prepared in high yield from the condensation of two moles of morpholine with one of 4,7-dichloroquinoline at 135° for several hours. An analytical sample melted at 138–139°. Calcd. for $C_{13}H_{13}N_2OCl$: C, 62.75; H, 5.28; N, 11.26. Found: C, 63.23; H, 5.16; N, 10.95.) A solution of 7.14 g. of 4,7-dichloroquinoline in 65 ml. of freshly distilled hydrobromic acid was refluxed for 50 minutes; half the volume was distilled in an additional 15 minutes. The solution was cooled, made alkaline and extracted with benzene. The residue from concentration of the benzene solution was recrystallized from petroleum ether to yield 6.7 g. (77%), m.p. 100–102° Further recrystallization and vacuum sublimation gave an analytical sample melting at 104–105°.

Anal. Calcd. for C_9H_5NBrCl: C, 44.58; H, 2.08; N, 5.77. Found: C, 44.42; H, 1.98; N, 6.12.

7-Chloro-4-iodoquinoline was synthesized in 75% yield by a similar procedure except that the heating time was only 20 minutes in all. An analytical sample melted at 125–126°.

Anal. Calcd. for C_9H_5NClI: C, 37.21; H, 1.87; N, 4.87. Found: C, 36.97; H, 1.98; N, 4.82.

4-Bromo-7-chloro-3-methylquinoline.—The presence of the 3-methyl group caused steric hindrance and necessitated forcing conditions for complete replacement of the 4-chloro atom. A solution of 40 g. of 4,7-dichloro-3-methylquinoline[12] in 600 ml. of freshly distilled hydrobromic acid was distilled slowly through a 50-cm. Widmer column; about 25 ml. of distillate, b.p. 110°, was removed over a period of about 15 hours; the distillation temperature then gradually rose to 126° and an additional 200 ml. of distillate was removed. The cooled residue was worked up as above to give 40 g. of crude product, m.p. 80–82°. An analytical sample, m.p. 81.2–82.3°, was prepared by recrystallization and vacuum sublimation.

Anal. Calcd. for $C_{10}H_7NBrCl$: C, 46.82; H, 2.73; N, 5.45; halogen as Cl, 27.65. Found: C, 47.30, 47.21; H, 2.82, 2.69; N, 5.49, 5.48; halogen as Cl, 27.65, 27.68.

7-Chloro-4-bis-(2-hydroxyethyl)-aminoquinoline.—A mixture of 24 g. each of diethanolamine and of 4-bromo-7-chloroquinoline and 9.4 g. of phenol was stirred and heated at 135–140° for an hour and then taken up in 750 ml. of *N* acetic acid. The phenol was removed by extraction with benzene, after which the solution was made strongly alkaline and extracted with four 150-ml. portions of ethyl acetate. The combined organic layer was washed with water and with 85 ml. of 0.1 *N* acetic acid; these washings were discarded. The next extract with 150 ml. of 0.5 *N* acetic acid was made basic, extracted three times with ethyl acetate, dried and concentrated to a residue of 12.4 g. of crude oily product. This was crystallized several times from ethyl acetate, finally yielding 2.5 g. (9%) of pure product, m.p. 126–127.5°.

Anal. Calcd. for $C_{13}H_{15}N_2O_2Cl$: C, 58.5; H, 5.7; N, 10.5; Cl, 13.3. Found: C, 58.5; H, 5.8; N, 10.5; Cl, 13.6.

A nitric acid salt also was prepared by addition of sodium nitrate to a solution of the base in acetic acid and crystallizing from water, m.p. 122–125°. *Anal.* Calcd. for $C_{13}H_{15}N_2O_2Cl\cdot HNO_3$: C, 47.3; H, 4.9; N, 12.7. Found: C, 46.9; H, 5.17; N, 12.7.

7-Chloro-4-bis-(2-chloroethyl)-aminoquinoline.—A solution of 2.5 g. of the above diol in purified and dried chloroform was concentrated to about 275 ml. and 2.5 ml. of thionyl chloride was added with swirling. The solution was concentrated to 80 ml. by distillation over a period of an hour, cooled, and several volumes of dry ether were added. The precipitated heavy oil was separated and extracted with several portions of acetone. An unidentified crystalline residue remained. The acetone solution was concentrated to 50 ml., wet ether was added, and the product separated after prolonged cooling. It weighed 1.3 g. (39%), m.p. 98–102°; after recrystallization from isopropyl alcohol–ether it melted at 101–103°.

Anal. Calcd. for $C_{13}H_{13}N_2Cl_3\cdot HCl\cdot H_2O$: C, 43.7; H, 4.4; N, 7.8; Cl, 39.7. Found: C, 44.0; H, 4.7; N, 7.9; Cl, 39.4.

Part B. Representative Procedures Related to Table I.—This includes (I) synthesis of the 2, 4, 5, and 6-methylene side chains, (II) synthesis of diol intermediates by procedure A or **B**, and (III) isolation of crystalline salts, when the diol itself is an oil. All the 4-chloroquinoline nuclei were available or had been reported previously with the exception of the compound described next.

4-Chloro-2-(4-chlorophenyl)-quinoline.—A mixture of 35 g. of 4-hydroxy-2-(4-chlorophenyl)-quinoline[13] and 72 ml. of phosphorus oxychloride was refluxed for two hours, cooled and poured on ice. The cold mixture was made

(12) Generously supplied by Sterling-Winthrop Research Institute.

(13) R. C. Fuson and D. M. Burness, THIS JOURNAL, **68**, 1270 (1946).

strongly alkaline and extracted with benzene–ether. Concentration and addition of petroleum ether gave a first crop of 26 g. (69%), m.p. 128–129.5°, and a second crop of 7.9 g. (21%), m.p. 126–127°. A sample crystallized from *n*-heptane melted at 129–130°.

Anal. Calcd. for $C_{15}H_9NCl_2$: Cl, 25.87. Found: Cl, 25.30.

Synthesis of Side Chains. 2-[Bis-(2-hydroxyethyl)-amino]-ethylamine Dihydrochloride and Free Base.—To a cold solution of 151 g. of monoacetylethylenediamine[14] in 1.2 l. of methanol was added 163 g. (2.5 molar equivalents) of ethylene oxide. After standing at approximately 20° overnight, the solution was warmed in a 65–70° bath under an ice condenser for 6 hours. The solvent was removed and the residue distilled *in vacuo;* the crude product weighed 278 g. (98.7%), boiled at 168–175° (50 μ) and was apparently contaminated with 9–10% ethylene oxide polymers as shown by its nitrogen analysis. To 288 g. of the above crude distillate was added 260 ml. (2.0 molar equivalents) of concentrated hydrochloric acid and 100 ml. of water, and the solution was heated in an open wide-mouthed erlenmeyer flask for 6 hours on the steam-cone. After four hours, 25 ml. of 5 *M* hydrochloric acid was added; a total of 150 g. was lost by evaporation. After addition of 600 ml. of ethanol, the mixture was seeded and cooled overnight. A combination of the 245 g. first crop and an additional 35 g. obtained from the filtrate by dilution with acetone was dissolved in 110 ml. of 1 *N* hydrochloric acid and the solution added dropwise to 600 ml. of stirred, seeded ethanol. After adding 100 ml. of acetone and cooling overnight, a first crop of 204 g. was removed, m.p. 116–118°. A second crop of 35 g. of material (71% total) melting a degree lower was obtained from the filtrate.

The free base was obtained in near-quantitative yield by adding a warm concentrated aqueous solution of the salt to an ethanolic solution of the calculated amount of sodium hydroxide, diluting with acetone to precipitate 90% of the sodium chloride formed, filtering, concentrating, and distilling the residue *in vacuo*. The boiling point was 110° (20 μ), n^{20}_{daylight} 1.4943.

Anal. Calcd. for $C_6H_{16}N_2O_2$: C, 48.59; H, 10.88; N, 18.88. Found: C, 48.15; H, 10.87; N, 19.10.

4-[Bis-(2-hydroxyethyl)-amino]-butyronitrile.—A mixture of 92 g. (0.89 mole) of γ-chlorobutyronitrile and 105 g. (1.0 mole) of diethanolamine was stirred and heated at 100–110° for 3 hours with a brief rise to 190° due to the exothermic reaction. The mixture was dissolved in 250 ml. of ethanol and a solution of one equivalent of sodium hydroxide in 600 ml. of ethanol was added with stirring. After filtration of the precipitated sodium chloride (81% of the theoretical) the filtrate was concentrated *in vacuo* and the residue distilled; the product weighed 101.5 g. (67%) and boiled at 163–167° (0.3 mm.), at 143–145° (20 μ) on redistillation, $n^{27}D$ 1.48112.

Anal. Calcd. for $C_8H_{16}N_2O_2$: C, 55.80; H, 9.36; N, 16.27. Found: C, 55.22; H, 9.43; N, 16.05.

The picrate was separated from ethanol and recrystallization from absolute ethanol gave the product, m.p. 102.2–102.8°.

Anal. Calcd. for $C_{14}H_{18}O_9N_6$: C, 41.90; H, 4.77; N, 17.45. Found: C, 42.06; H, 4.78; N, 17.26.

4-[Bis-(2-hydroxyethyl)-amino]-butylamine.—Reduction of the above nitrile in ethanol solution with hydrogen and Raney W-2 catalyst at 100° and 1800 p.s.i. gave a hydrogen uptake of 90% of the theoretical over a period of 5 hours; the product was distilled *in vacuo* and obtained in 58% yield, b.p. 137–138° (40 μ), $n^{25}D$ 1.49554.

Anal. Calcd. for $C_8H_{20}O_2N_2$: C, 54.51; H, 11.44; N, 15.90. Found: C, 54.28; H, 11.00; N, 15.31.

5-[Bis-(2-hydroxyethyl)-amino]-pentylamine.—Monoacetylation of pentamethylenediamine was carried out similarly to that of ethylenediamine[14]; the compound boiled at 105–110° (20 μ). Reaction with a 2.9 molar ratio of ethylene oxide in methanol under conditions identical with those for the corresponding monoacetylethylenediamine gave an 89% yield of product, b.p. 184–190° (60 μ). Hydrolysis with two equivalents of hydrobromic acid at 100° gave an 89% yield of crude dihydrobromide. This was crystallized from absolute ethanol plus absolute ether, m.p. 107–108.5°.

Anal. Calcd. for $C_9H_{22}N_2O_2 \cdot 2HBr$: C, 30.70; H, 6.87; N, 7.96. Found: C, 31.06; H, 6.86; N, 7.77.

The free base was obtained in the same manner as was the "ethyl" side chain from its salt, b.p. 130° (1 μ). This compound also was prepared through the nitrile by a procedure identical with that for the corresponding butyl compound. The condensation was carried out at 135–145° for four hours; the 5-[bis-(2-hydroxyethyl)-amino]-valeronitrile was obtained in 59% yield, b.p. 165–168° (0.4 mm.), n^{19}_{daylight} 1.4835. It was reduced catalytically under the same conditions used for the corresponding butyronitrile; the yield was 75%, b.p. 131–135° (60 μ), n^{19}_{daylight} 1.4920.

6-[Bis-(2-hydroxyethyl)-amino]-hexylamine Dihydrobromide and Free Base.—Monoacetylation of hexamethylene diamine was carried out as was that of ethylenediamine; the compound boiled at 125–130° (30 μ). Reaction with a 2.5 molar ratio of ethylene oxide in methanol under conditions identical with those for the corresponding monoacetylethylenediamine gave a 96% yield of product, b.p. 195–200° (0.1 mm.). A mixture of 139 g. of the above distillate and 198 g. of freshly distilled 48% hydrobromic acid was heated at an internal temperature of 95–102° in an open flask for 7 hours; about 50 g. of solvent was lost by evaporation. After dilution with 100 ml. of ethanol and 1.1 l. of acetone and overnight cooling, the semi-crystalline product was removed by filtration. It was taken up in 300 ml. of ethanol, diluted with 300 ml. of acetone and cooled overnight to give 96 g. (46%) of side chain dihydrobromide, m.p. 100–105°. A sample purified for analysis by crystallization from ethanol melted at 119–120°.

Anal. Calcd. for $C_{10}H_{24}N_2O_2 \cdot 2HBr$: N, 7.65; Br, 43.66. Found: N, 7.53, 7.78; Br, 43.39, 43.27.

The free base can be obtained in near-quantitative yield as described above; it boils at 126° (20 μ) and has a refractive index of 1.4887.[6]

Synthesis of Diol Intermediates. 4-[2-Bis-(2-hydroxyethyl)-aminoethylamino]-6-methoxyquinoline (20 in Table I). Procedure A.—A mixture of 10.0 g. (0.052 mole) of 4-chloro-6-methoxyquinoline[15] and 12.0 g. (0.081 mole; 1.5–2.0 equivalents of side chain were typically used per mole of nucleus) of 2-[bis-(2-hydroxyethyl)-amino]-ethylamine was stirred and heated to an internal temperature of 128–132° for 5 hours (a small test portion was completely soluble in dilute acetic acid at the end of 4 hours, indicating near completion of the reaction). The mixture was dissolved in dilute acetic acid and the product was precipitated with alkali. After separation and drying, it weighed 15.0 g. (95%), m.p. 128–130°. Recrystallization from alcohol–benzene and vacuum sublimation raised the melting point to 129–130°.

7-Chloro-4-[6-bis-(2-hydroxyethyl)-aminohexylamino]-2-methylquinoline (30 in Table I). Procedure B.—A mixture of 8.5 g. of 4,7-dichloro-2-methylquinoline[12] and 35 ml. of hexamethylenediamine was stirred and heated to an internal temperature of 140–160° for 2 hours. A positive difference between the temperature of the mixture and that of the bath indicated the occurrence of reaction and a test portion showed complete solubility in dilute acetic acid. The mixture was poured into 300 ml. of 0.1 *N* sodium hydroxide; the precipitated solid weighed 12.5 g. Crystallization from benzene–petroleum ether using decolorizing carbon gave 9.1 g. (78%), m.p. 110–114°. A sample purified for analysis by vacuum sublimation melted at 116.5–117.5°. *Anal.* Calcd. for $C_{16}H_{32}N_3Cl$ [4-(6-aminohexylamino)-7-chloro-2-methylquinoline]: C, 65.86; H, 7.60; N, 14.40. Found: C, 66.09; H, 7.72; N, 14.17. To a filtered solution of 8.5 g. of this compound in 100 ml. of methanol was added 3.65 ml. (2.5 equivalents) of ethylene oxide. After standing in a stoppered flask overnight at 21°, the mixture was refluxed gently under an ice condenser for 4 hours. Following concentration *in vacuo* to half the volume, the product crystallized and the mixture was diluted to 150 ml. to give the theoretical yield of crude product (11.0 g.). Crystallization from alcohol in 71% recovery gave a product melting at 155–157.5°. An analytical sample was obtained by vacuum sublimation; the data are recorded in Table I.

4-(6-Aminohexylamino)-2-methylquinoline was obtained in essentially the manner described above from the reaction of 5.0 g. of 4-chloroquinaldine and 40 ml. of hexamethylene diamine at 145° for 3 hours. The yield of crystalline prod-

(14) S. R. Aspinall, THIS JOURNAL, **63**, 852 (1941).

(15) Generously supplied by S. B. Penick & Co.

uct from benzene–petroleum ether was 4.7 g. (65%), m.p. 101–103°. An analytical sample, m.p. 106–107°, was obtained by repeated vacuum sublimations.

Anal. Calcd. for $C_{16}H_{23}N_3$: C, 74.68; H, 9.03; N, 16.32. Found: C, 74.66; H, 9.15; N, 16.14.

Reaction with ethylene oxide under the conditions described above gave the corresponding diol, compound 9 in Table I, in 53% yield.

4-(6-Aminohexylamino)-7-chloroquinoline was obtained in 90% yield from the reaction of 40 g. of 4,7-dichloroquinoline[12] and 165 g. of hexamethylenediamine at 140° for two hours, and recrystallizing the crude product from benzene. An analytical sample, m.p. 135.8–136.8°, was obtained by distillation (195–205° (20 μ)) and vacuum sublimation.

Anal. Calcd. for $C_{15}H_{20}N_3Cl$: C, 64.86; H, 7.25; N, 15.15. Found: C, 64.89; H, 6.81; N, 14.98.

Reaction with ethylene oxide gave the pure corresponding diol[8] in 54% yield.

4-(2-Aminoethylamino)-7-chloro-3-methylquinoline was obtained in 85% yield from the reaction of 10.6 g. of 4,7-dichloro-3-methylquinoline[12] and 25 ml. of ethylenediamine under gentle reflux for 3 hours. Since the product forms an unstable hydrate in the presence of water, it was isolated by vacuum distillation after extraction from the basic mixture, b.p. 155–165° (25 μ). An analytical sample, m.p. 79–80.5°, was obtained by vacuum sublimation.

Anal. Calcd. for $C_{12}H_{14}N_3Cl$: C, 61.15; H, 6.00; N, 17.82. Found: C, 60.78; H, 6.07; N, 17.96.

An attempt to convert this compound to the diol with ethylene oxide in the usual manner failed.

4-(2-Aminoethylamino)-7-chloroquinoline[16] was obtained in 95% yield, m.p. 137–139°, from the reaction of 30 g. of 4,7-dichloroquinoline[12] and 90 ml. of ethylenediamine at 85° for 4 hours. Conversion to compound 23 in Table I was accomplished only in very poor yield.

4-(6-Aminohexylamino)-5-chloroquinoline was prepared in 79% yield from the reaction of 4,5-dichloroquinoline[12] with a ten-molar excess of hexamethylenediamine at 120° for one hour; after recrystallization and repeated vacuum sublimation it melted at 82.5–84.5°.

Anal. Calcd. for $C_{15}H_{20}N_3Cl$: C, 64.86; H, 7.25; N, 15.15. Found: C, 64.89, 65.00; H, 7.35, 7.29; N, 15.01, 14.80.

Reaction with ethylene oxide in methanol gave the corresponding diol, compound 19, in low yield.

4-(7-Aminoheptylamino)-7-chloroquinoline was obtained as a molecularly distilled oil in 35% yield from the condensation of 4,7-dichloroquinoline[12] with an eight-molar excess of heptamethylenediamine.

Anal. Calcd. for $C_{16}H_{22}N_3Cl$: C, 65.85; H, 7.60; N, 14.40; Cl, 12.15. Found: C, 65.77; H, 7.67; N, 14.26; Cl, 12.27.

Reaction with ethylene oxide in methanol gave the corresponding diol, compound 27, in 40% yield.

4-[4-Bis-(2-hydroxyethyl)-amino-1-methylbutylamino]-2-methylquinoline Diphosphate (8 in Table I).—The oily base was obtained by chloroform extraction after the acetic acid solution had been made basic, followed by washing, drying, and concentration *in vacuo*. It weighed 9.0 g. (96% from 5.0 g. of 4-chloroquinaldine); it was dissolved in a mixture containing 28 ml. of water, 14 ml. of methanol and 6.27 g. of 85% phosphoric acid, and isopropyl alcohol was added until turbidity persisted on swirling. After crystallization (cold) was complete, the product was removed by filtration; it weighed 10.4 g. (60%); the analyses are reported in Table I.

4-(3-Bis-(2-hydroxyethyl)-aminopropylamino]-3-methylquinoline Dihydriodide (5 in Table I).—The oily base was extracted with chloroform after the carboned acetic acid solution was made basic. The organic extracts were washed, dried, and concentrated and the residue was distilled in a small Hickman molecular still (vacuum of 0.1 μ; pot temperature 160–170°) giving 4.6 g. (44% from 6.15 g. of 4-chloro-3-methylquinoline[17]) of a light yellow oil. This was dissolved in 50 ml. of 4% acetic acid and 15 g. of potassium iodide was added; the precipitated salt weighed 9.25 g. Crystallization from ethanol gave 6.6 g. (78%, 36% over-all), m.p. 155–157°. The analytical sample melted at 158.5–159.5°; analyses are recorded in Table I.

5-Chloro-4-[4-(2-hydroxyethyl)-amino-1-methylbutylamino]-quinoline Dihydrochloride (18 in Table I).—The oily base was extracted with chloroform after the solution in dilute acetic acid had been extracted with benzene to remove any unreacted nucleus and had been made basic. The organic extracts were washed, dried and concentrated. The residue was treated with 2.5 molar equivalents of concentrated hydrochloric acid dissolved in absolute alcohol and the solution treated with several volumes of acetone to precipitate the salt. After filtration and drying, the product (19 g.) was recrystallized from alcohol containing 2 ml. of hydrochloric acid and acetone to give white, slowly precipitating crystals which weighed 14 g. (65% from 20 g. of 4,5-dichloroquinoline[12]) when dried to constant weight at 50° under aspirator vacuum (several hours). Analytical data are reported in Table I.

Procedures Related to Table II.—The chlorination of the dihydroxy compounds listed in Table I was carried out in a large excess of thionyl chloride utilized as a solvent and usually allowed to proceed near 0° for several days followed by another period at room temperature (4–40 hr.). If the chlorination does not go to completion, the product, although indistinguishable from a completely chlorinated product except by analytical or biological means, is usually not obtained in a better condition than that with an impurity of 3–5%. For this reason, mustards related to some of the diols in Table I do not appear in Table II since the correct chlorination conditions had not yet been found with the limited amount of material available for study.

7-Chloro-4-[2-bis-(2-chloroethyl)-aminoethylamino]-3-methylquinoline Dihydrochloride Dihydrate (31 in Table II).—To 150 ml. of cold thionyl chloride (Eastman Kodak Co. white label) was carefully added 18.6 g. of 7-chloro-4-[2-bis-(2-hydroxyethyl)-aminoethylamino]-3-methylquinoline (compound 31 in Table I). The mixture became slightly warm and then slowly became homogeneous; it was allowed to stand first at 0° for 30 hours and then at 24° for 30 hours. Excess thionyl chloride was removed *in vacuo* and about 100 ml. of dry ethanol was added to the residue, which dissolved on gentle heating. The mixture was again concentrated *in vacuo*, about 50 ml. more of ethanol was added, and the product crystallized. Excess acetone was added and the mixture cooled and filtered; the product weighed 25.1 g. (104%), m.p. 210–213°. This was taken up in 60 ml. of a 1:2:3 mixture of concentrated hydrochloric acid–water–ethanol, treated with Darco and made up to 150 ml. with ethanol. Cooling and filtration gave 25.2 g. of a mixture of hydrated and anhydrous product (visually distinguishable). Another crystallization from the same mixture gave 24.2 g. of compound 31, which softened and melted at about 95°, resolidified with gas evolution and remelted at 210–212°.

4-[3-Bis-(2-chloroethyl)-aminopropylamino]-2-phenylquinoline Pamoate (11 in Table III).—A solution of 6.2 g. (0.013 mole) of 4-[3-bis-(2-chloroethyl)-aminopropylamino]-2-phenylquinoline dihydrochloride (compound 11 in Table II) in 550 ml. of absolute ethanol was prepared by warming and to it was added rapidly with vigorous stirring 65.2 ml. of an ethanolic solution 0.20 *M* with respect to pamoic acid[18] and 0.40 *M* with respect to ethanolamine. A flocculent precipitate which formed initially was removed quickly by suction filtration; it weighed 150 mg. and was discarded. The filtrate was seeded and stirred for two hours at room temperature and the product was removed by filtration; it weighed 7.8 g. (75%) and melted at 220° with softening at 200°.

2-Bis-(2-chloroethyl)-aminoethylamine Dihydrochloride.—To 75 ml. of cold thionyl chloride was added 10 g. of 2-bis-(2-hydroxyethyl)-aminoethylamine. The mixture was allowed to stand for 8 days at 0° and then overnight at room temperature and excess thionyl chloride was removed *in vacuo*. The residue was taken up in ethanol and concentrated *in vacuo* twice, and finally crystallized from ethanol to yield 5.5 g. (31%) of crude product. Further recrystallization gave an analytical sample melting at 137–138.5°.

Anal. Calcd. for $C_6H_{14}N_2Cl_2 \cdot 2HCl$: C, 27.93; H, 6.25; N, 10.85; Cl, 54.96. Found: C, 27.90; H, 6.29; N, 10.77; Cl, 53.79.

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(16) D. E. Pearson, *et al.*, THIS JOURNAL, **68**, 1225 (1946).

(17) E. A. Steck, *et al.*, *ibid.*, **68**, 129 (1946).

(18) Methylene bis-(2-hydroxy-3-naphthoic acid).