mercaptopurine in *dilute* ($3–5 \times 10^{-5}M$) solutions in 0.01N sodium hydroxide was followed spectrophotometrically. A stock solution was prepared by dissolving 13.4 mg. of 6-mercaptopurine in 25 ml. of water containing 2 drops of 10N sodium hydroxide. A 50-*lambda* aliquot of this stock solution was added to 5 ml. of 0.01N sodium hydroxide (pH 11.9). The solution was covered to prevent evaporation and the ultraviolet absorption spectra was determined at intervals as indicated in Fig. 9. Curve A (0 time) shows the ultraviolet spectra of 6-mercaptopurine in 0.01N sodium hydroxide. Curve B (19 hr.) shows the spectra resulting from the partial oxidation of 6-mercaptopurine, while curve C(40 hr.) demonstrates that almost complete conversion to purine-6-sulfinate has occurred. Using the final absorption at 280 mμ (curve C), the amount of sulfinate present was calculated to be equivalent to 98% of the original mercaptan. Acidification of the 0.01N sodium hydroxide solution at the end of 40 hr. afforded hypoxanthine (curve D, maximum at 247 mμ) equivalent to 90% of the original 6-mercaptopurine. A small amount of unoxidized 6-mercaptopurine still appeared to be present as indicated by the small maximum at 325 mμ. Over the same period of time, conversion of 6-mercaptopurine to its sulfinate derivative also was found to occur at pH 9.4 (bicarbonate-carbonate buffer) to about the same extent as in the case of the more basic pH. In contrast however, 6-mercaptopurine treated with N sodium hydroxide (same conditions of concentration and time) demonstrated a reduction of only 30% in the original quantity of mercaptan.

Electrophoretic experiments. All studies were made using an E. C. electrophoresis apparatus.[44] Whatman 3MM paper was employed. Carbonate-bicarbonate buffer, pH 9.4 was prepared by dilution of a mixture of 200 ml. of a 0.2M sodium carbonate solution and 800 ml. of a 0.2M sodium bicarbonate solution to 4 liters with water.

Spectrophotometric studies. Ultraviolet absorption data were determined with a Cary recording spectrophotometer, model 11, using buffers and techniques previously described.[45,46] Solutions of the disulfides (II) for spectrophotometric determinations were prepared in alcohol-water mixtures (85:15) in which II were found to have greater stability than in water alone. Aliquots of these stock solutions were then measured at various pH values.

Acknowledgment. The authors are indebted to Drs. G. B. Brown and C. C. Stock for helpful discussions and continued interest.

NEW YORK 21, N. Y.

(44) Manufactured by E. C. Apparatus Co., Swarthmore, Pa.

(45) J. J. Fox and D. Shugar, *Bull. soc. chim. Belges*, **61**, 44 (1952).

(46) D. Shugar and J. J. Fox, *Biochem. Biophys. Acta*, 9, 199 (1952).

[CONTRIBUTION FROM THE INSTITUTE FOR CANCER RESEARCH]

Mono- and Difunctional Analogs of Some Quinoline and Acridine Nitrogen Mustards[1]

RICHARD M. PECK, ROBERT K. PRESTON, AND HUGH J. CREECH

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The pronounced antitumor activity displayed by two ethyl-2-chloroethylaminoalkylamino derivatives of acridine led to the synthesis of fifteen quinoline and acridine analogs of this type for studies of their structure-activity relationships compared with those of the corresponding bis(2-chloroethyl) forms. Sixteen other alkylating agents which incorporated a variety of modifications both in the side chain and in the quinoline or acridine nucleus were also prepared.

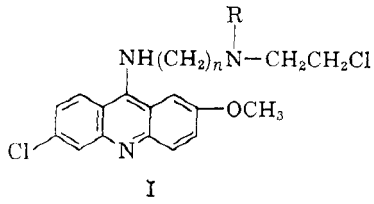
The initial phase[2] of this program was concerned primarily with the synthesis of bis(2-chloroethyl)-aminoalkyl derivatives of 4-aminoquinoline and 9-aminoacridine which usually contained methyl, chloro, or methoxy groups as additional nuclear substituents. In tests,[3] in which the prolongation of survival time of mice bearing ascites tumors served as a criterion of antitumor activity, it was found that the hydrochlorides of the propyl-, methylbutyl-, and hexylamino derivatives were highly active at molar dosages that approximated those required for nitrogen mustard itself. This is in striking contrast to the alkyl-type nitrogen mustards of benzimidazole and certain aryl-type nitrogen mustards which were effective only at molar levels that were at least ten times greater than those needed for nitrogen mustard.[3]

The current series of bis(2-chloroethyl) derivatives of quinoline and acridine includes several nuclear variants and a variety of compounds modified in the side chain. Among the latter are a bis(2-bromoethyl) analog, two hydrazines, an N-oxide, and some aryl-type nitrogen mustards and ethyleneimines. Several mono 2-chloroethylamino derivatives were also prepared. Four derivatives of acridine (I), in which R was CH_3CH_2— and n was 2 or 3, and in which R was CH_3— or CH_3CH_2-CH_2— and n was 3, displayed outstanding activity against ascites tumors at molar levels that were only slightly greater than those required for the corresponding "bis" structures. Only moderate activity was apparent when R was $(CH_3)_2CH$—:

(1) Supported in part by research grant CY-2975 from the National Cancer Institute, United States Public Health Service.

(2) R. M. Peck, R. K. Preston, and H. J. Creech, *J. Am. Chem. Soc.*, **81**, 3984 (1959).

(3) H. J. Creech, E. Breuninger, R. F. Hankwitz, Jr., G. Polsky, and M. L. Wilson, *Cancer Research*, **20** (No. 7, part 2) 471 (1960).



I

all analogs in which R was H— were inactive. This sharp specificity of the structure-activity relationships was made more evident by the lack of antitumor activity in the 6-methoxy- and 7-chloroquinolines substituted in the 4-position by side chains in which R was CH_3CH_2— and n was 2 or 3; analogs in which R was H— again were inactive. Several mono- and bis(2-chloroethyl) aminoalkylamines, "side chain mustards," were also prepared for comparative antitumor tests.

A series of "one-armed" mustards of the aryl type was prepared by Bergel *et al.*[4] and by Skinner *et al.*[5]; these displayed no, or only slight, antitumor activity.

The general scheme of synthesis was similar to that used previously and involved the condensation of the 2-hydroxyethylaminoalkyl- or arylamines with 4-chloroquinolines and 9-chloroacridines. Conversion to the 2-chloroethyl derivatives was accomplished with thionyl chloride or phosphorus oxychloride. The ethyleneimine derivatives were prepared from the corresponding ethyl sulfuric acids of quinoline and acridine.

EXPERIMENTAL[6]

Part A. Side chains. Of the 2-hydroxyethylaminoalkyl- or arylamines used in the preparation of the 2-chloroethyl compounds to be presented in this report, $H_2NCH_2CH_2NHCH_2CH_2OH$ is available commercially and the syntheses of $H_2N(CH_2)_3NHCH_2CH_2OH$ and $H_2N(CH_2)_3N(C_2H_5)CH_2CH_2OH$ have been described.[7] The preparation of six other compounds of this type is reported below.

N'-Methyl-N'-2-hydroxyethyl-1,3-propanediamine. In an analogous procedure,[7] cyanoethylmethylethanolamine was prepared (exothermic) from acrylonitrile and methylethanolamine, b.p. 85°/0.1 mm. (95%). Reduction with hydrogen in the presence of ammonia gave 66% of product. An analytical sample boiled at 124–127°/15 mm., n_{daylight}^{26} = 1.4743.

Anal. Calcd. for $C_6H_{16}N_2O$: C, 54.51; H, 12.19; N, 21.20. Found: C, 54.95; H, 12.56; N, 21.55.

N'-Isopropyl-N'-2-hydroxyethyl-1,3-propanediamine dihydrochloride. This compound was synthesized in an identical manner; no exothermic reaction was noted. The boiling point of the intermediate nitrile (81% yield) was about 90°/50 μ. Catalytic reduction gave a 75% yield of a fraction boiling at 136–140°/15 mm., n_{daylight}^{26} = 1.4700. The dihydrochloride, m.p. 113.5–115°, was prepared.

Anal. Calcd. for $C_8H_{20}N_2O{\cdot}2HCl$: C, 41.20; H, 9.51; N, 12.02; Cl, 30.41. Found: C, 40.19, 39.99; H, 9.31, 9.17; N, 11.59, 11.75; Cl, 30.07, 29.93.

N'-Propyl-N'-2-hydroxyethyl-1,3-propanediamine. The preparation was identical with the preceding one. The intermediate nitrile boiled at 80–83°/50 μ; the yield was 93%. The reduction product gave a yield of 50% of refractionated material boiling at 128–130°/10 mm., n_{daylight}^{26} = 1.4701.

Anal. Calcd. for $C_8H_{20}N_2O$: C, 59.95; H, 12.58; N, 17.49. Found: C, 60.34; H, 12.49; N, 17.74.

N'-Ethyl-N'-2-hydroxyethylethylenediamine dihydrochloride. To a flask containing 130 g. of warm ethylethanolamine was added with vigorous stirring over a 45-min. period 100 g. of 2-bromoethylamine hydrobromide. Heat was evolved and the temperature rose to about 100°. After cooling, 80 g. of 50% sodium hydroxide solution was added and the mixture was diluted with ethanol to about 500 ml. The mixture was filtered, stripped of solvent on the steam cone (aspirator), and refiltered. Volatile material boiling up to 120° (about 40 g.) was distilled at 15 mm. pressure. Refractionation gave 28 g. (43%) of product,[8] b.p. 110–114°/15 mm. The dihydrochloride, m.p. 128–129° was prepared.

Anal. Calcd. for $C_6H_{16}N_2O{\cdot}2HCl$: C, 35.13; H, 8.85; N, 13.66; Cl, 34.57. Found: C, 35.02, 34.75; H, 8.70, 8.51; N, 13.99, 14.09; Cl, 34.23, 34.56.

N',N'-Bis(2-hydroxyethyl)hydrazine. To 37.5 g. (0.5 mole) of monoacetylhydrazine in methanol was added 50 ml. of ethylene oxide. After standing overnight, an additional 10 ml. of ethylene oxide was added and the mixture was heated for 4 hr. in a 70° water bath under an ice condenser. The solvent was removed and the product was distilled twice, yielding 56 g. (69%) b.p. 140–145°/30–50 μ. This material was heated on the steam cone in a stoppered flask with 1 equivalent of concd. hydrochloric acid for 5 hr. and the volatile material was removed at water pump vacuum. Following a rough titration of the hydrochloric acid and acetic acid content of the distillate, one-fifth volume of 3% aqueous hydrochloric acid was added and the mixture was again heated for 5 hr. on the steam cone and stripped *in vacuo*. After this procedure had been repeated a third time, approximately 70% of the theoretical amount of acetic acid had been accounted for. To the final residue was added one equivalent of concentrated sodium hydroxide; it was again stripped of volatile material, diluted with ethanol, and filtered to remove sodium chloride. The filtrate was concentrated and distilled twice giving a central cut of product[9] boiling at 79–83°/20 μ (65% yield), n_{daylight}^{26} = 1.4937.

Anal. Calcd. for $C_4H_{12}N_2O_2$: C, 39.97; H, 10.07; N, 23.32. Found: C, 39.85; H, 9.35; N, 22.35.

p-Bis(2-hydroxyethyl)aminophenylacetonitrile. To 100 g. of *p*-aminophenylacetonitrile[10] hydrochloride in 1 l. of 2*N* acetic acid containing 1 equivalent of sodium acetate was added 200 ml. of ethylene oxide. Cooling for several hours was necessary to keep the temperature below 40°; after standing overnight at room temperature the mixture was treated with decolorizing carbon and concentrated *in vacuo*. The residue was neutralized with sodium bicarbonate, giving a reddish, macrocrystalline product. Two high-vacuum distillations in a modified von Braun flask gave 84 g., b.p. 184°/30 μ. Crystallization from dilute alcohol gave 80 g. (61%) of product, m.p. 87.0–88.5°. A vacuum-sublimed sample melting at 88.0–89.0° was analyzed.

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.52; H, 7.33; N, 12.73. Found: C, 65.17; H, 7.50; N, 12.72.

N-[p(2-Aminoethyl)phenyl]diethanolamine. Catalytic reduction (Raney Nickel) at 115° and 500–2000 p.s.i. of a mixture of 120 g. of the nitrile with 25 ml. of aqueous ammonia gave on filtration, concentration, vacuum distillation (b.p. 170–180°/50 μ) and crystallization from 50%

(4) F. Bergel and J. A. Stock, *J. Chem. Soc.*, 90 (1959).

(5) W. A. Skinner, H. F. Gram, and B. R. Baker, *J. Org. Chem.*, **25**, 777 (1960).

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

(7) A. R. Surrey and H. F. Hammer, *J. Am. Chem. Soc.*, **72**, 1814 (1950).

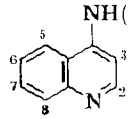
(8) Synthesized by a different procedure by S. Archer and C. M. Suter, *J. Am. Chem. Soc.*, **74**, 4296 (1952).

(9) Preparation of this compound (b.p. 187°/25 mm.) by direct hydroxyethylation of hydrazine has been reported; A. K. Plisov, *Khem. Zhurnal*, **3**, No. 1, 125 (1928).

(10) Eastman Kodak Practical grade; purified nitrile gave a cleaner reaction and higher (88%) yield.

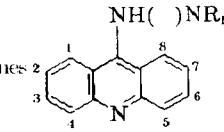
TABLE I

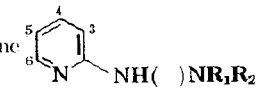
ALKYLATING AGENTS AND PRECURSORS

I. Quinolines 

( )	Other Substituents	R_1R_2	Salt	Prep.	Yield, %	M.P.	Calcd.[a] C	H	N	Cl	Found C	H	N	Cl
A. BIFUNCTIONAL														
—	7-Cl	$-(CH_2CH_2Cl)_2$	$HCl\cdot{}^1/_2H_2O$	$POCl_3$	23	220–222	42.88	4.43	11.55	38.95	43.37	4.51	11.98	38.82
—	7-Cl	$-(CH_2CH_2OH)_2$	—	Cond.	92	198–200	55.42	5.72	14.92		55.64	5.69	14.35	
$-(CH_2)_2-$	6-Br-2-C_6H_5	$-(CH_2CH_2Cl)_2$	$2HCl\cdot H_2O$	$SOCl_2$	59	228–230	45.18	4.70	7.53	31.77[b]	45.59	4.77	7.11	32.15[b]
$-(CH_2)_2-$	6-Br-2-C_6H_5	$-(CH_2CH_2OH)_2$	2HCl	Cond.	60	268.8–269.2	50.12	5.21	8.35	21.15[b]	50.02	5.48	8.21	20.63[b]
$-(CH_2)_3-$	6-Br-2-C_6H_5	$-(CH_2CH_2Cl)_2$	$2HCl\cdot{}^1/_2H_2O$	$SOCl_2$	76	207–209	46.93	4.83	7.46	31.49[b]	46.67	5.06	7.30	31.27[b]
$-(CH_2)_3-$	6-Br-2-C_6H_5	$-(CH_2CH_2OH)_2$	H_2O	Cond.	83	92–94	57.14	6.10	9.10	Br = 17.28	57.47	6.25	9.57	Br = 17.40
$-(CH_2CO)-$	7-Cl	$-(CH_2CH_2OH)_2$	—	Text			55.64	5.60	12.98		55.98	5.63	13.43	
$-(CH_2)_2-$	7-Cl;*N*-oxide	$-(CH_2CH_2Cl)_2$	2HCl	Text	25	85–105	41.34	4.63	9.64	40.70	40.83	4.67	9.70	40.39
$-CH(CH_3)(CH_2)_3-$	7-Cl	$-(CH_2CH_2Br)_2$[c]	3HBr	$SOBr_2$	54	188–189	30.15	3.65	5.85	24.52[b]	30.07	3.82	5.78	24.68[b]
$-(CH_2)_2-C_6H_4-$	7-Cl	$-(CH_2CH_2Cl)_2$	HCl	$POCl_3$	76[d]	205–208 dec.	54.93	5.05	9.15	30.89	54.84	5.33	8.94	31.01
$-(CH_2)_2-C_6H_4-$	7-Cl	$-(CH_2CH_2Cl)_2$	2HCl	$POCl_3$	10[d]	210–215 dec.	50.85	4.88	8.48	35.80	51.03	5.09	8.33	35.26
$-(CH_2)_2-C_6H_4-$	7-Cl	$-(CH_2CH_2OH)_2-$	—	Cond.	92	203.5–205	65.36	6.27	10.89		65.60	6.38	10.83	
B. MONOFUNCTIONAL														
$-(CH_2)_2-$	7-Cl	—H	$-CH_2CH_2Cl$[e]	2HCl	$SOCl_2$	25	254 dec.	43.72	4.80	11.77	39.71	43.85	5.20	11.49	38.83
$-(CH_2)_2-$	7-Cl	$-C_2H_5$	$-CH_2CH_2Cl$	2HCl	$SOCl_2$	43	233–235 dec.	46.77	5.50	10.91	36.82	47.09	5.53	10.43	35.84
$-(CH_2)_2-$	7-Cl	$-C_2H_5$	$-CH_2CH_2OH$	H_2O	Cond.	88	78–80	57.77	7.09	13.48		58.38	7.93	13.59	
$-(CH_2)_2-$	6-OCH_3	—H	$-CH_2CH_2Cl$	2HCl	$SOCl_2$	98	266–268 dec.	47.68	5.72	11.91	30.16	47.55	6.08	11.94	29.64
$-(CH_2)_2-$	6-OCH_3	—H	$-CH_2CH_2OH$	$2HCl\cdot{}^1/_2H_2O$	Cond.	73	238.5–239.0	47.73	6.58	11.93	20.13	47.06	6.68	11.75	20.58
$-(CH_2)_3-$	7-Cl	—H	$-CH_2CH_2Cl$[f]	$2HCl\cdot{}^1/_2H_2O$	$SOCl_2$	69	220–221.5	44.23	5.30	11.05	37.31	44.79	5.16	11.10	37.23
$-(CH_2)_3-$	7-Cl	$-C_2H_5$	$-CH_2CH_2Cl$[f]	$2HCl\cdot H_2O$	$SOCl_2$	48	195–197	46.06	6.04	10.07	34.00	46.12	6.37	9.84	34.77
$-(CH_2)_3-$	7-Cl	$-CH_3$	$-CH_2CH_2Cl$	$2HCl\cdot H_2O$	$SOCl_2$	79	145–147 dec.	44.69	5.75	10.42	35.18	44.58	5.90	10.42	35.40
$-(CH_2)_3-$	7-Cl	$-CH_3$	$-CH_2CH_2OH$	—	Cond.	71	119–120	61.32	6.86	14.30		60.85	7.29	14.33	
$-(CH_2)_3-$	6-OCH_3	—H	$-CH_2CH_2Cl$	2HCl	$SOCl_2$	94	238–240 dec.	49.12	6.05	11.46	29.01	48.85	6.14	11.10	29.14
$-(CH_2)_3-$	6-OCH_3	—H	$-CH_2CH_2OH$	2HCl	Cond.	50	223–224	51.73	6.66	12.07	20.36	51.62	6.61	11.50	20.32
$-(CH_2)_3-$	6-OCH_3	$-C_2H_5$	$-CH_2CH_2Cl$	2HCl	$SOCl_2$	67	112–114	49.46	6.84	10.18	25.77	48.86	6.88	10.19	25.86
$-(CH_2)_3-$	6-OCH_3	$-C_2H_5$	$-CH_2CH_2OH$	2HCl	Cond.	58	177–179	54.25	7.23	11.18	18.84	54.10	7.25	11.02	18.85

TABLE I (*Continued*)

II. Acridines 

III. Pyridine 

( )	Other Substituents	R_1	R_2	Salt	Prep.	Yield, %	M.P.	Calcd. C	Calcd. H	Calcd. N	Calcd. Cl	Found C	Found H	Found N	Found Cl
A. MONOFUNCTIONAL															
$-(CH_2)_2-$	6-Cl-2-OCH_3	—H	$-CH_2CH_2Cl$[g]	$2HCl{\cdot}1\frac{1}{2}H_2O$	$SOCl_2$	96	249–251 dec.	46.57	5.21	9.05	30.56	46.28	5.65	8.71	30.50
$-(CH_2)_2-$	6-Cl-2-OCH_3	$-C_2H_5$	$-CH_2CH_2Cl$	$2HCl{\cdot}\frac{3}{4}H_2O$	$SOCl_2$	74	245–247 dec.	50.18	5.58	8.78	29.63	50.60	5.83	8.66	28.49
$-(CH_2)_2-$	6-Cl-2-OCH_3	$-C_2H_5$	$-CH_2CH_2OH$	—	Cond.[h]	52	152.5–153.5	64.25	6.47	11.24		63.84	6.44	11.17	
$-(CH_2)_3-$	6-Cl-2-OCH_3	—H	$-CH_2CH_2Cl$[i]	2HCl	$SOCl_2$	70	274–276 dec.	50.60	5.14	9.31	31.40	51.30	5.58	9.40	28.52
$-(CH_2)_3-$	6-Cl-2-OCH_3	$-CH_3$	$-CH_2CH_2Cl$	$2HCl{\cdot}2\frac{1}{2}H_2O$	$SOCl_2$	76	235–238	47.08	5.93	8.24	27.80	47.57	5.98	8.41	27.45
$-(CH_2)_3-$	6-Cl-2-OCH_3	$-CH_3$	$-CH_2CH_2OH$	—	Cond.[h]	19	135–136.5	64.25	6.47	11.24		63.92	6.51	11.21	
$-(CH_2)_3-$	6-Cl-2-OCH_3	$-C_2H_5$	$-CH_2CH_2Cl$[j]	2HCl	$SOCl_2$	73	237.5–238.5	52.61	5.68	8.77	29.61	52.63	5.84	8.52	29.59
$-(CH_2)_3-$	6-Cl-2-OCH_3	$-CH(CH_3)_2$	$-CH_2CH_2Cl$	$2HCl{\cdot}2\frac{1}{2}H_2O$	$SOCl_2$	82	244–246 dec.	49.08	6.37	7.81	26.34	49.53	6.60	7.91	26.46
$-(CH_2)_3-$	6-Cl-2-OCH_3	$-CH(CH_3)_2$	$-CH_2CH_2OH$	—	Cond.[h]	25	133.5–135	65.74	7.02	10.46		65.29	7.24	10.68	
$-(CH_2)_3-$	6-Cl-2-OCH_3	$-CH_2CH_2CH_3$	$-CH_2CH_2Cl$	$2HCl{\cdot}1\frac{1}{2}H_2O$	$SOCl_2$	58	212–214 dec.	52.60	6.02	8.37	28.24	52.89	6.25	8.46	28.15
$-(CH_2)_3-$	6-Cl-2-OCH_3	$-CH_2CH_2CH_3$	$-CH_2CH_2OH$	—	Cond.[h]	59	106–107.5	65.80	7.03	10.46		65.69	7.06	10.53	
B. BIFUNCTIONAL															
		R_1R_2													
$-(CH_2)_2-C_6H_4-$	6-Cl-2-OCH_3	$-(CH_2CH_2Cl)_2$		$HCl{\cdot}H_2O$	$POCl_3$	40	167–170	47.70	4.67	9.28	31.30	48.12	4.74	9.16	29.77
	6-Cl-2-OCH_3	$-(CH_2CH_2OH)_2$		—	Cond.	72	147.5–150	59.74	5.57	11.62		59.46	5.56	10.98	
$-(CH_2)_2-C_6H_4-$	6-Cl-2-OCH_3	$-(CH_2CH_2Cl)_2$		$HCl{\cdot}\frac{3}{4}H_2O$	$POCl_3$	81	218–221	56.50	5.20	7.60	25.65	56.69	5.31	7.65	25.14
	6-Cl-2-OCH_3	$-(CH_2CH_2OH)_2$		—	Cond.[h]	77	193–195	67.01	6.06	9.02		67.10	6.20	8.80	
$-(CH_2)_3-$	—	$-(CH_2CH_2Cl)_2$[k]		2HCl	$SOCl_2$	60	144–146	41.28	6.06	12.04	40.62	40.02	6.15	11.85	40.75

[a] Values are either single analyses or averages of checks. As in the preceding paper,[2] several cases of analytical difficulties with the determination of total halogen were reported by the analytical laboratory. [b] Total halogen; calculated as chlorine. [c] The corresponding diol was synthesized by R. Jones, C. C. Price, and A. K. Sen, *J. Org. Chem.*, **22**, 783 (1957). [d] Isolated from the same experiment; total yield, 86%. [e] The corresponding alcohol was synthesized by E. A. Steck, L. L. Hallock, and C. M. Suter, *J. Am. Chem. Soc.*, **70**, 4065 (1948). [f] The corresponding alcohol was synthesized by A. R. Surrey and H. F. Hammer, *J. Am. Chem., Soc.*, **72**, 1814 (1950). [g] The corresponding alcohol was synthesized by J. T. Sheehan and E. A. Steck, *J. Am. Chem. Soc.*, **74**, 4969 (1952). [h] With methylcellosolve at reflux temperature. [i] The corresponding alcohol was synthesized by A. R. Surrey, C. M. Suter, and J. S. Buck, *J. Am. Chem. Soc.*, **74**, 4103 (1952). [j] For the corresponding alcohol, see Ref. (12). [k] The corresponding alcohol was isolated only as an oily molecular distillate.

TABLE II

"SIDE-CHAIN MUSTARDS"

R

$H_2N(CH_2)_nNCH_2CH_2Cl\cdot2HCl$

n	R	Moles $SOCl_2$ / Moles Precursor	Reaction Temp.	Reaction Time (hr.)	M.P.	Yield, %	Calcd.[a] C	Calcd.[a] H	Calcd.[a] N	Calcd.[a] Cl	Found C	Found H	Found N	Found Cl
2	—H[b]	7	79	4	173–175	58	24.57	6.70	14.33	54.40	24.44	6.82	14.18	54.49
2	$-C_2H_5$	5	60	1	139–140	25	32.23	7.66	12.53	47.58	32.23	7.96	12.39	47.63
3	—H	400	79	9	231–232	37	28.66	7.22	13.37	50.76	28.61	7.13	13.62	50.15
3	$-C_2H_5$	10[c]	40	3	133–135	32	35.38	8.06	11.79	44.77	35.48	8.16	11.52	44.27
3	$-CH(CH_3)_2$	4	45	6	140–141	44	38.18	8.41	11.13	42.27	38.43	8.40	11.37	42.03
4	$-CH_2CH_2Cl$	100	79	3	181–182	67	33.58	7.05	9.79	49.57	33.86	7.07	9.77	49.23

[a] Values are either single analyses or averages of checks. [b] Previously obtained in a modified procedure by E. Wilson and M. Tishler, *J. Am. Chem. Soc.*, **73**, 3635 (1951). [c] Using the free amine instead of the dihydrochloride.

ethanol, 102.5 g. (84%) of the diamine, m.p. 86–87°. An analytical sample obtained by vacuum sublimation melted at 87.0–87.8°.

Anal. Calcd. for $C_{12}H_{20}N_2O_2$: C, 64.27; H, 8.99; N, 12.49. Found: C, 64.44, 64.24; H, 9.03, 9.27; N, 12.52, 12.47.

Part B. Compounds in Table I. The 2-chloroethyl compounds in Table I for the most part were made from the corresponding hydroxy compound with thionyl chloride, as described in the previous paper.[2] A few were chlorinated by 10 min. refluxing with phosphorus oxychloride and decomposed with ice. The crude product was heated with 6*N* hydrochloric acid before recrystallization. The hydroxy precursors were made by the condensation of 1.1–2.0 moles of side chain with the appropriately substituted chloro nucleus; with certain acridine nuclei, Methyl Cellosolve was used as a solvent, in which case the monohydrochloride was usually isolated from the reaction mixture. An example is given below.

2-{[2-(6-Chloro-2-methoxy-9-acridinyl)ethyl]ethylamino}ethanol. A solution of 10 g. of 6,9-dichloro-2-methoxyacridine and 7.5 g. of *N'*-ethyl-*N'*-2-hydroxyethylethylenediamine in 50 ml. of Methyl Cellosolve was refluxed for 3 hr., let stand overnight, and diluted with an equal volume of acetone. The precipitate was filtered, washed, and dried; it weighed 11.9 g. (80% of the theoretical yield of monohydrochloride). About 20% of this crude material was unchanged substituted acridine which was insoluble in dilute acetic acid; the free base precipitated from solution following addition of alkali and was recrystallized successively from alcohol and from benzene with 81% recovery (overall yield from nucleus 52%) m.p. 152.5–153.8°. Analytical data are presented in Table I.

Part C. Compounds prepared other than by condensation and chlorination. N-(7-Chloro-4-quinolyl)glycyl diethanolamine. A mixture of 22 g. (0.0805 mole) of *N*-(7-chloro-4-quinolyl)glycine hydrochloride,[11] 300 ml. of absolute ethanol, and 2 ml. of concd. hydrochloric acid was refluxed for 5 hr. during which time the salt dissolved and the esterification proceeded. The mixture was stripped of solvent to remove water; 200 ml. of absolute ethanol and 1 ml. of acid were replaced,[12] and the mixture was refluxed for another 3 hr.

The solvent was again removed, and 25 g. of diethanolamine was added. The mixture was heated at an internal temperature of 120–127° for 3 hr. Stirring with water caused crystallization of the product, which was filtered and purified by precipitation from dilute acetic acid solution. The yield was 21.4 g. (82% overall) m.p. 171–172.5°. Several recrystallizations from ethanol raised the melting point to 177.5–179.0°. See Table I for analytical data.

2-(7-Chloro-4-quinolylamino)ethylsulfuric acid. A mixture of 31 g. of 7-chloro-4-(2-hydroxyethyl)aminoquinoline sulfate and 50 ml. of concd. sulfuric acid was warmed at 60–70° until solution was complete. After 2 hr., a sample was found to be completely soluble in dilute alkali; the mixture was diluted with water, filtered, taken up in dilute sodium hydroxide, filtered from insoluble material, and acidified with acetic acid. The product after filtration and drying

(11) The free amino acid has been reported by E. O. Titus *et al.*, *J. Org. Chem.*, **13**, 39 (1948). Our synthesis was by essentially the same method; however, we obtained the hemi-hydrate from water, m.p. 288–291° dec. The hydrochloride, obtained by treating this compound with concentrated acid, filtering, and washing with acetone melted at 275–278°.

(12) Hydrolysis of the resulting ester is a very facile reaction as shown in an initial effort to isolate the ester by dilution and neutralization in the cold. The ester precipitated as a crystalline solid but redissolved rapidly even in an ice bath. Using greater care, the ester was isolated, recrystallized from ethanol and vacuum sublimed, m.p. 210.5–212°.

Anal. Calcd. for $C_{13}H_{13}ClN_2O_2$: C, 58.98; H, 4.95; N, 10.58. Found: C, 59.70, 59.41; H, 5.21, 5.17; N, 10.75, 10.68.

weighed 14.7 g. (42.5%) m.p. 250°. An analytical sample was obtained by ethanol crystallization.

Anal. Calcd. for $C_{11}H_{11}ClN_2O_4S$: C, 43.63; H, 3.66; N, 9.26; S, 10.59. Found: C, 43.16; H, 3.75; N, 9.03; S, 11.15.

N-(7-Chloro-4-quinolyl)ethyleneimine. A slurry of 14.7 g. of quinolylaminoethylsulfuric acid in 25 ml. of water was stirred during the addition of 50 ml. of 40% sodium hydroxide. The mixture was heated with stirring in an open beaker; when the temperature reached about 140°, a visible reaction occurred, after which a sample showed solubility in dilute acetic acid. Following separation and washing by decantation, the oily product solidified. After leaching with dilute acetic acid, filtering and precipitating, the product again became oily and was separated by decantation, leached several times with warm benzene, and carboned in the organic layer. Concentration and addition of hexane, yielded 3.8 g. (38%) of crude crystalline product, m.p. 87–91°. After several precipitations from dilute acetic acid–ethanol mixtures and one crystallization from hexane, 1.05 g., m.p. 95–96° remained. A previously obtained vacuum sublimed analytical sample melted at 94.0–95.5°.

Anal. Calcd. for $C_{11}H_9ClN_2$: C, 64.55; H, 4.43; N, 13.69; Cl, 17.33. Found: C, 64.76; H, 4.30; N, 13.08; Cl, 17.26.

2-(6-Chloro-2-methoxy-9-acridinyl)ethylsulfuric acid. This compound was prepared from 6-chloro-2-methoxy-9-(2-hydroxyethylamino)acridine[13] and concentrated sulfuric acid at room temperature in essentially the same manner as the 7-chloro-4-quinolyl compound above. The yield after reprecipitation from dilute sodium hydroxide and alcohol with acetic acid was 93%, m.p. 300–305° dec.

Anal. Calcd. for $C_{16}H_{15}ClN_2O_5S\frac{1}{2}H_2O$: C, 49.04; H, 4.12; N, 7.15; S, 8.19. Found: C, 49.13; H, 4.09; N, 7.05; S, 8.20.

N-(6-Chloro-2-methoxy-9-acridinyl)ethylenimine. A mixture of 5.5 g. of the sulfuric acid ester and 25 ml. of 50% sodium hydroxide was stirred and heated in a beaker at 150° for about 1 hr., cooled, diluted, filtered and washed. The crude material was taken up in about 20 ml. of glacial acetic acid, diluted, and filtered (about 1.5 g. was insoluble). The soluble material was precipitated with alkali; it weighed 3.2 g. The precipitation from dilute acetic acid was repeated in the presence of an equal volume of alcohol, giving 0.6 g. (15%), m.p. 185–188°. Two sublimations at 180°/0.1 μ gave 0.4 g. (10%) of product, m.p. 184–187°.

Anal. Calcd. for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.28, 67.00; H, 4.73, 4.59; N, 9.79, 9.65.

7-Chloro-4-[2-bis(2-chloroethyl)-N-oxyaminoethylamino]-quinoline dihydrochloride. A solution of 20 g. of 7-chloro-4-{[2-bis(2-chloroethyl)aminoethylamino]} quinoline dihydrochloride monohydrate[2] in 400 ml. of glacial acetic acid was cooled to room temperature and 26 ml. of 40% peracetic acid was added. The temperature rose slowly to 35°, was kept there for an hour and then brought to 45° for 15 min. and momentarily to 60°. After cooling, 2 ml. of hydrochloric acid and 250 ml. of acetone were added, the mixture was diluted to 1 l. with dry ether and cooled for 1 week. The crystalline precipitate was filtered and washed; it weighed 16.3 g. This was dissolved in water; acetone and ether were added to give two crops of product. The first contained more than two molecules of hydrogen chloride; the second weighed 5.1 g. (26% of the theoretical). See Table I.

Part D. Aliphatic 2-chloroethyl compounds (Mustards derived from side chains). These compounds were prepared by the addition of the hydroxyethyl precursor, as its dihydrochloride, to an excess of stirred thionyl chloride. The mixture was warmed to complete the reaction, excess thionyl chloride was removed under water pump vacuum, and the residue was recrystallized twice from absolute ethanol containing a trace of concentrated hydrochloric acid. The products were obtained as hygroscopic, sharp-melting crystalline dihydrochlorides (See Table II).

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(13) J. H. Burckhalter *et al.*, *J. Am. Chem. Soc.*, **65**, 2012 (1943).

[CONTRIBUTION FROM THE CHEMICAL THERAPEUTICS RESEARCH LABORATORY, MILES LABORATORIES, INC.]

New Sedative and Hypotensive Phenylpiperazine Amides

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A number of *N*-(4-aryl-1-piperazyl)alkylpolymethoxybenzamides and *N*-polymethoxyphenyl(4-aryl-1-piperazyl)alkanoic acid amides and the corresponding hydrochlorides were prepared. Infrared spectra of stable amidonium chlorides are discussed. A transamidation reaction took place during the synthesis of butyramide derivatives and this may involve a cyclic intermediate.

The presence of the 3,4,5-trimethoxybenzoyl group in reserpine led to a search for pharmacologically active trimethoxybenzamide derivatives.[1] Weinberg *et al.*[2] reported that trimethoxybenzoic acid esters of amino alcohols lacking the indole ring system showed sedative properties of the reserpine type. Bovet[3] found that 1-phenylpiperazine and 1-methyl-4-phenylpiperazine reverse the pressor response to adrenaline. Also 1-phenyl-4-homoveratrylpiperazine[4] is reported to be similar to chlorpromazine in its central depressant properties.

These findings suggested the synthesis of new sedative and hypotensive agents which contain both 1-phenylpiperazine and 3,4,5-trimethoxybenzoyl groups. We prepared a series of *N*-(4-aryl-1-piperazyl)alkylpolymethoxybenzamides (Class A) and another series of *N*-polymethoxyphenyl(4-aryl-1-piperazyl)alkanoic acid amides (Class B) as follows:

(1) (a) Y. G. Perron, U. S. Pat. **2,870,145**; **2,870,156** (1959). (b) G. P. Schiemenz and H. Engelhart, *Ber.*, **92**, 857, 862 (1959).

(2) M. S. Weinberg *et al.*, Abstr. from 130th Am. Chem. Soc. Meeting, Atlantic City, 1956, 11N.

(3) D. Bovet and F. Bovet-Nitti, *Médicaments du Système Nérveux Vegetatif*, S. Karger, S. A. Bale, 1948, p. 247.

(4) J. Mills, M. M. Boren, and N. R. Easton, Abstr. from 132nd Am. Chem. Soc. Meeting, New York, 1957 11-O.