dene - β - D - ribofuranoside hydrochloride (XXV) in 40 ml. of absolute ethanol containing 1 ml. of concd. aqueous hydrochloric acid was heated on a steam bath for 0.5 hr., then cooled at 0° overnight to give 4.2 g. (58%) of white crystals, m.p. 138–140°, $[\alpha]_D^{25}$ −25° (1% in methanol); λ_{max}^{Nujol} 2.98, 3.08 (OH), 3.98, 4.08 μ (NH^+).

Vargha *et al.*[8] reported m.p. 142–144°, $[\alpha]_D^{20}$ −14.2° (1% in methanol).

Acknowledgment. The authors are indebted to Dr. Peter Lim and staff for the chromatograms and optical rotations, as well as the interpretation of the infrared spectra; and to Mr. O. P. Crews and staff for large-scale preparations of intermediates.

MENLO PARK, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

Synthesis of Potential Anticancer Agents. X. Nitrogen Mustards Derived from 4-Quinoline- and 1-Naphthalenemethanols[1,2]

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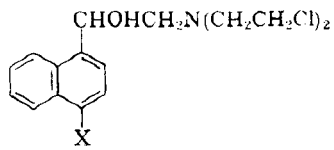
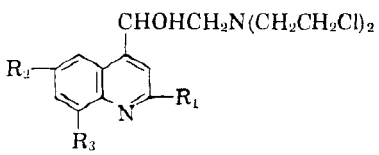
Synthesis of a series of nitrogen mustards derived from 4-quinoline- and 1-naphthalenemethanols is described.

In a preceding paper[3] the synthesis of a number of nitrogen mustards derived from standard antimalarial drugs (specifically the 8-aminoquinolines) has been described and the rationale underlying this approach to the management of neo-plastic disease has been indicated. Several of the substances described have shown high orders of activity against experimental animal tumors.[4] Paralleling this investigation we have investigated the synthesis of representative nitrogen mustards derived from 1-naphthalene- and 4-quinolinemethanols. (I–VII).



I. X = F
II. X = Cl



III $R_1 = C_6H_5$; $R_2 = R_3 = H$
IV $R_1 = R_3 = H$; $R_2 = OCH_3$
V $R_1 = C_6H_5$; $R_2 = H$; $R_3 = Cl$
VI $R_1 = C_6H_5$; $R_2 = R_3 = Cl$
VII $R = p\text{-}C_6H_4Cl$; $R_2 = R_3 = H$

Incentive for this study was provided by early reports of encouraginging activity against experimental tumors shown by alkylating agents derived from other types of antimalarials[5] as well as by the low order of activity reported for certain dialkylamino-4-naphthalenemethanols in which an alkylating function was absent.[6]

Choice of the methanol mustards to be prepared, particularly in the quinoline series, was based on pharmacological data accumulated with the analogous antimalarials.[7]

The reaction sequences employed in general paralleled those previously described for the preparation of aminomethanol derivatives of naphthalene and quinoline carrying alkyl groups on the amino nitrogen[8–11] with some modifications. In the naphthalene series these are represented by VIII–XI. Reduction of 4-fluoro-ω-bromo-1-acetonaphthone (VIII, X = F) with sodium borohydride proceeded smoothly to give α-bromomethyl-4-fluoro-1-naphthalenemethanol (IX, X = F) which could not be induced to crystallize and for which no other suitable method of purification could be found. Confirmation of the structure assigned to IX (X = F) was provided by its infrared spectrum, its chemical behavior and by the nature of the products prepared from it. The infrared spectrum showed a broad band at 3425 cm.$^{-1}$ (OH) but,

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(1) The work here reported was supported by a research grant (CY-2961) from the National Cancer Institute to the University of Michigan.

(2) For paper IX in this series see W. R. Vaughan, M. S. Habib, R. S. McElhinney, N. Takahashi and J. A. Waters, *J. Org. Chem.*, **26**, 2392 (1961).

(3) R. C. Elderfield and E. F. LeVon, *J. Org. Chem.*, **25**, 1576 (1960).

(4) Private communication from Dr. Ralph L. Jones, Jr., Jackson Memorial Hospital, University of Miami, Miami, Florida.

(5) For a summary of recent data see H. J. Creech, E. Breuninger, R. F. Hankowitz, Jr., G. Polsky and M. L. Wilson, *Cancer Research*, **20**, 471 (1960).

(6) Private communication from Dr. R. B. Ross, Cancer Chemotherapy National Service Center, Bethesda, Maryland.

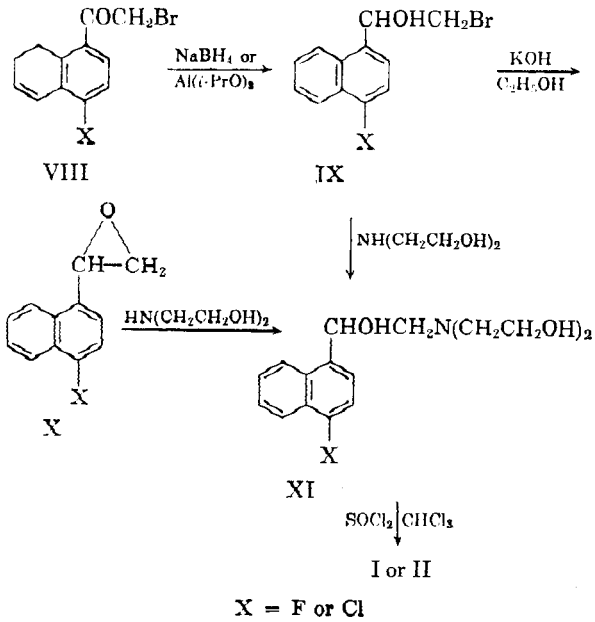
(7) *Survey of Anti-malarial Drugs*, 1941–1945, F. Y. Wiselogle (editor), J. W. Edwards, Inc., Ann Arbor, Mich., 1946, Vol. 1, p. 142.

(8) R. E. Lutz *et al.*, *J. Am. Chem. Soc.*, **68**, 1813 (1946).

(9) S. Winstein *et al.*, *J. Am. Chem. Soc.*, **68**, 1831 (1946).

(10) S. Winstein *et al.*, *J. Org. Chem.*, **11**, 150 (1946).

(11) T. L. Jacobs *et al.*, *J. Org. Chem.*, **11**, 21 (1946).



more significantly, complete absence of absorption in the carbonyl region of the spectrum. Retention of the bromine was indicated by precipitation of silver bromide by alcoholic silver nitrate and by precipitation of potassium bromide with alcoholic potassium hydroxide.

When the crude bromohydrin was stirred with a large excess of iminodiethanol at 120–130° for several days, the expected diol (XI, X = F) was formed in fair yield. Better yields were obtained from the epoxide (X, X = F) which was obtained on reaction of IX (X = F) with alcoholic potassium hydroxide. Again the epoxide could not be purified and its structure was assigned on the basis of its infrared spectrum (transparent in the hydroxyl region, but with absorption around 1266 and 882 cm.$^{-1}$ commonly associated with expoxides[12]), and by the formation of XI (X = F) when the substance was refluxed with iminodiethanol in chloroform in the presence of a small amount of zinc chloride.

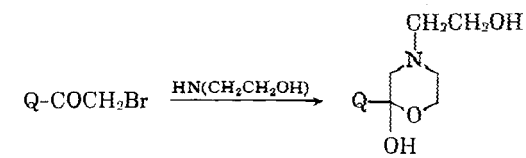
In contrast to the behavior of VIII (X = F) when VIII (X = Cl) was reduced with sodium borohydride in ethanol at 0°, debromination occurred with the formation of 4-chloro-α-methylnaphthalenemethanol. Accordingly IX (X = Cl) was prepared by use of aluminum isopropoxide as previously described by Winstein and co-workers.[10] Formation of the diol XI (X = Cl) occurred normally either from the bromohydrin or *via* the epoxide.

The quinolinemethanol mustards were prepared by essentially the same reaction sequences as those used for the naphthalene derivatives. The bromomethyl ketones were prepared by the Arndt-Eistert method from the appropriate acid chlorides[8] with the exception of ω-bromo-2-phenyl-4-acetoquinoline which was obtained by bromination of the methyl ketone.[11] Reduction of ω-bromo-2-phenyl-4-acetoquinoline with sodium borohydride gave the bromohydrin in 88% yield, but use of this reagent in other cases resulted in the formation of obscure products. Aluminum isopropoxide was therefore used.[10] The diols were prepared directly from the bromohydrins.

Conversion of the diols to the mustards was accomplished with thionyl chloride in anhydrous chloroform. Advantage was taken of the faster rate of formation of the intermediate chlorosulfites of the primary hydroxyl groups compared to the secondary hydroxyl group. On decomposition of the chlorosulfites, the mustards separated, sometimes as the hydrochlorides, before reaction of the secondary hydroxyl group with the reagent.

$$R\text{—}CHOHCH_2N(CH_2CH_2OH)_2 \xrightarrow{SOCl_2} R\text{—}CHOHCH_2N(CH_2CH_2OSO_2Cl)_2 \longrightarrow R\text{—}CHOHCH_2N(CH_2CH_2Cl)_2$$

In one instance condensation of the bromomethyl ketone with iminodiethanol was attempted. With ω-bromo-2-phenyl-4-acetoquinoline (XII) the product was not the expected amino ketone, but rather the cyclic hemiketal (XIII).[13] Reaction of XIII with thionyl chloride resulted only in the formation of the hydrochloride of XIII.



XII Q = 2-phenyl-4-quinolyl XIII

Results of evaluation of the substances here reported will be presented elsewhere.

EXPERIMENTAL[14,15]

1-Fluoronaphthalene. Dry decomposition of 1-naphthyldiazonium fluoroborate[16] proceeded with considerable violence when carried out on a large scale. The decomposition was therefore carried out in xylene.[17] A suspension of 250 g. of the dry diazonium salt in 1500 ml. of xylene was placed in a 5 l. three-necked flask equipped with two very efficient reflux condensers. The mixture was heated with a low flame until the reaction commenced. Heating was discontinued until the initial reaction subsided and then applied occasionally until evolution of boron trifluoride ceased. The xylene was then refluxed for 20 min. and then removed by distillation, first at atmospheric and finally under reduced pressure. The residue was steam distilled. Distillation of

(12) L. J. Bellamy, *Infrared Spectra of Complex Molecules*, 2nd. ed., J. Wiley & Sons, New York, 1958, p. 118.

(13) *Cf.* R. E. Lutz and co-workers, *J. Am. Chem. Soc.*, **71**, 996 (1949); **70**, 2015 (1948), for similar reactions of α-bromo ketones with *N*-alkyliminodiethanols.

(14) Melting points are corrected for stem exposure.

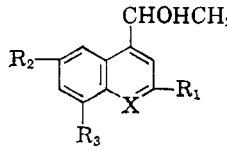
(15) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

(16) *Org. Syntheses*, Coll. Vol. II, 225 (1943); G. Schiemann, W. Gueffroy and W. Winkelmüller, *Ann.*, **487**, 270 (1931).

(17) *Org. Reactions*, **5**, 211 (1949).

TABLE I

BIS(HYDROXYETHYL)AMINOMETHYL QUINOLINE- AND NAPHTHALENEMETHANOLS

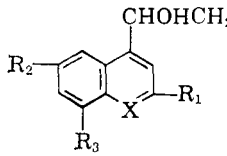


X	R_1	R_2	R_3	M.P.	Yield (%)	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
N	C_6H_5	H	H	147–148	74	71.57	6.86	7.95	71.53	6.89	7.98
N	H	OCH_3	H	187.5[a]	40	50.70	6.38	7.38	50.86	6.54	7.32
N	C_6H_5	H	Cl	127–128	65	65.18	5.99		65.19	5.91	
N	p-C_6H_4Cl	H	H	150.5–152	55	65.18	6.00	7.50	65.11	6.02	7.50
N	C_6H_5	Cl	Cl	176.5–178.5	35	59.87	5.26	6.65	60.03	5.28	6.63
CCl	H	H	H	114–116	50–75	62.00	6.51	4.52[b]	61.95	6.61	4.56
CF	H	H	H	125.5–126.5	50–67	65.51	6.87	4.78	65.53	6.94	4.67

[a] This is the dihydrochloride. [b] Cl, Calcd: 11.44; Found 11.55.

TABLE II

QUINOLINE- AND NAPHTHALENEMETHANOL MUSTARDS



X	R_1	R_2	R_3	Yield, %	M.P.	Calcd. C	Calcd. H	Calcd. N	Calcd. Cl	Found C	Found H	Found N	Found Cl
N	C_6H_5	H	H	58	171–171.5 dec.[a]	54.56	5.25		30.69	54.22	5.20		30.46
N	H	OCH_3	H	61	139–140 dec.[b]	50.61	5.58	7.37		50.84	5.41	7.27	
N	C_6H_5	H	Cl	53	113–115 dec.[c]	59.51	5.00	6.61		59.31	5.43	6.35	
N	p-C_6H_4Cl	H	H	77	157.5–158 dec.[d]	53.75	4.94	5.97		53.56	5.00	6.00	
N	C_6H_5	Cl	Cl	72	189–190.5 dec.[e]	55.04	4.40	6.12		54.94	4.67	6.11	
CCl	H	H	H	92	155–157[f]	55.43	5.23	4.04	30.67	55.18	5.46	3.87	30.36
CF	H	H	H	90	162–164[g]	58.20	5.49	4.24		58.06	5.69	4.35	

[a] Dihydrochloride recrystallized from absolute methanol-ether. [b] Monohydrochloride recrystallized from absolute methanol-ether and dried to constant weight at 50° and 1 mm. [c] Free base recrystallized from absolute methanol-ether. [d] The monohydrochloride hemihydrate recrystallized from absolute methanol-ether. [e] Free base recrystallized from absolute methanol. [f] Free base recrystallized from acetonitrile. [g] Free base recrystallized from acetonitrile-petroleum ether.

the product gave 67 g. (45%) of 1-fluoronaphthalene, b.p. 65–66° (3 mm.)

α-Bromomethyl-4-fluoro-1-naphthalenemethanol. (IX, X = F). To a solution of 100 g. of ω-bromo-4-fluoro-1-acetonaphthone[18] in 500 ml. of absolute ethanol chilled in an ice bath 4.75 g. of sodium borohydride was added in small portions over 15 min. The solution was stirred in the ice bath for 3 hr. and then at room temperature for an additional hour. After pouring the solution into 2.5 l. of ice water the pH was adjusted to 3 with hydrochloric acid. After stirring for several hours at 10°, a heavy yellow oil separated. The supernatant water was decanted and the oil was triturated three times with fresh ice and water. The oil was taken up in ether, washed with water and dried over anhydrous magnesium sulfate. Removal of the ether left the crude bromohydrin which was used as such.

4-Fluoro-1-vinylnaphthalene epoxide (X, X = F). To a solution of 47 g. of the above crude bromohydrin in 100 ml. of absolute ethanol was added a solution of 15.2 g. of potassium hydroxide in 125 ml. of absolute ethanol. An immediate precipitate of potassium bromide separated. After standing at room temperature with occasional shaking for 15 min. the solution was diluted with 1 l. of water and extracted with four 150-ml. portions of ether. After washing with water and drying over anhydrous potassium carbonate, removal of the ether below 50° left the epoxide as a very viscous pale yellow oil for which no method of purification could be found. Identification was based on the infrared spectrum and subsequent reactions.

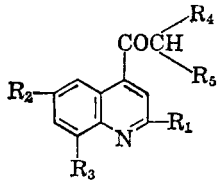
α-Bis-(β-hydroxyethyl)aminomethyl-4-fluoro-1-naphthalenemethanol (XI, X = F). A. *From the bromohydrin.* The crude bromohydrin (10 g.) was stirred with a seven fold excess of iminodiethanol at 120–130° for 7.5 hr. during which the solution turned cherry red. After cooling, the mixture was poured into a large volume of water. The aqueous layer was decanted and the residual yellow syrup was taken up in chloroform, washed five times with water and then extracted with four 70-ml. portions of 2*N* hydrochloric acid. Neutralization of the acid extracts gave the diol as a rapidly solidifying white solid. Recrystallization from benzene gave the pure material. The melting points, yields and analytical data for this and other bis(hydroxyethyl)aminomethyl methanols are given in Table I.

B. *From the Epoxide.* A solution of 11.5 g. of the crude epoxide described above, 7.9 g. of iminodiethanol and 0.5–1.0 g. of anhydrous zinc chloride in 100 ml. of anhydrous chloroform was refluxed for 6 days. The red solution wa

(18) T. L. Jacobs *et al., J. Org. Chem.*, 11, 27 (1946).

TABLE III

QUINOLYL-4-METHYL KETONES



R_1	R_2	R_4	R_5	M.P.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_6H_5	H	H	Br	233 (dec.)[a]						
C_6H_5	H	H	Br	100–101[b]	62.58	3.71		62.67	3.84	
H	OCH_3	H	Br	196.5–197[c]	39.92	3.08	3.88	40.07	3.21	3.79
C_6H_5	H	Cl	$R_4 + R_5 = N_2$	141–142° (dec.)	66.34	3.28	13.65	66.32	3.24	13.72

[a] Hydrobromide. Reported m.p., 225° dec. [b] Free base. Reported m.p., 91°. [c] Hydrobromide. Free ketone has been described.

clarified with charcoal and worked up as in the preceding case.

α-Bis(β-chloroethyl)aminomethyl-4-fluoro-1-naphthalenemethanol (I). To a solution of 1.0 g. of XI (X = F) in 40 ml. of anhydrous chloroform cooled to 0° was added a solution of 1.0 ml. of very pure thionyl chloride[19] in 20 ml. of chloroform dropwise over 10 min. The mixture was stirred for one hour longer at ice-bath temperature. The solid was collected, washed with cold chloroform and dried over potassium hydroxide *in vacuo*. Recrystallization from acetonitrile gave analytically pure material. The melting points, yields and analytical data for this and the other mustards are given in Table II.

α-Bis(β-chloroethyl)aminomethyl-4-chloro-1-naphthalenemethanol (II). This was prepared by the same route as I from ω-bromo-4-chloro-1-acetonaphthone[11] except that reduction of the bromo ketone was done with aluminum isopropoxide, using the short reaction time of Winstein and co-workers.[10]

4-Chloro-α-methyl-1-naphthalenemethanol. When the reduction of VIII (X = Cl) with sodium borohydride as with VIII (X = F) was attempted the bromine was removed and 4-chloro-α-methyl-1-naphthalenemethanol, m.p. 80.5–82° after several recrystallizations from methylcyclohexane-petroleum ether was formed in 86% yield.

Anal. Calcd. for $C_{12}H_{11}ClO$: C, 70.05; H, 5.39; Cl, 17.24. Found: C, 69.91; H, 5.47; Cl, 17.43.

α-Bis(β-hydroxyethyl)aminomethyl-2-phenyl-4-quinolinemethanol. A mixture of 9.8 g. of α-bromomethyl-2-phenyl-4-quinolinemethanol,[8] prepared by reduction of the bromo ketone with sodium borohydride, and 15 ml. of iminodiethanol was heated on the steam bath. The paste melted to a clear yellow liquid which began to turn green. After 1 hr. seed crystals from a pilot run were added and after 19 hr. the solution was poured from the crust of crystals into a mixture of aqueous sodium carbonate and chloroform. The crystalline material, m.p. 146–149°, amounted to 2.2 g. after washing with water and chloroform. The chloroform layer was separated and the aqueous layer was extracted thoroughly with chloroform. After thorough washing of the chloroform extract with water for removal of iminodiethanol, it was dried over anhydrous potassium carbonate and treated with charcoal. Removal of the chloroform left a residue which crystallized on trituration with dry ether which removed a brown resin and left 6.5 g. of slightly green material, m.p 143–147°. The two portions of crystalline product were combined and recrystallized from 500 ml. of acetone with decolorizing carbon to give fine white prisms.

α-Bis(β-chloroethyl)aminomethyl-2-phenyl-4-quinolinemethanol (III). To a stirred suspension of 13.4 g. of the above diol in 300 ml. of chloroform cooled in an ice bath was added a solution of 19 ml. of pure thionyl chloride[19] in 65 ml. of chloroform over a period of 15 min. The mixture was stirred for 15 min. in the ice bath and for 2.5 hr. at room temperature. After the mixture reached room temperature, the nearly colorless suspended solid began to turn to a red brown gummy mass which then slowly dissolved. A nearly colorless solid precipitated. This was collected, washed thoroughly with chloroform and recrystallized from absolute methanol–anhydrous ether. It was the dihydrochloride of the desired mustard.

Acid chloride of quininic acid. A mixture of 27.2 g. quininic acid and 150 ml. of thionyl chloride was refluxed for 4.5 hr. After cooling 40 ml. of anhydrous ether was added to the solution. The yellow solid was collected and washed several times with anhydrous ether yielding 30.1 g. of the acid chloride, m.p. 208–210°. An analytical sample was prepared by two recrystallizations from thionyl chloride–ether, m.p. 213–215°.

Anal. Calcd. for $C_{11}H_8ClNO_2$: C, 59.58; H, 3.65; N, 6.31. Found: C, 59.06; H, 3.21; N, 6.37.

α-Bromomethyl-6-methoxy-4-quinolyl ketone hydrobromide. We have found that a much shorter reaction time and low temperature gives yields of the bromomethyl ketones considerably higher than those previously obtained in the Arndt and Eistert reaction.[8] The reaction occurs rapidly and long periods of stirring at room temperature only lead to decomposition of the product. The following procedure is typical of that used in other instances. In some cases, the free ketone was liberated from its salt by sodium carbonate and isolated as such. Likewise, the intermediate diazomethyl ketone was isolated in some instances, although this is not necessary. Pertinent data on the ketones are given in Table III.

To a dried solution of 5.6 g. of diazomethane in 200 ml. of ether cooled to 5° was added 5.0 g. of the acid chloride with stirring over 30 min. The mixture was then stirred at 5° for 1 hr. and at room temperature for 1 hr. during which it became dark brown. The ether was removed under reduced pressure at room temperature. The residue was taken up in 50 ml. of ether and 8.8 ml. of 48% hydrobromic acid was added. After evolution of nitrogen was complete, removal of the solvent left a reddish brown mass which was recrystallized three times from glacial acetic acid containing a trace of hydrobromic acid to give fine yellow needles of the ketone hydrobromide. The yield was 27%. Other bromomethyl ketones were obtained in yields up to 88%.

α-Bromomethyl-6-methoxy-8-quinolinemethanol hydrochloride. This was prepared by reduction of 1.1 g. of the bromo

(19) Purity of the thionyl chloride is very critical. It was purified by successive fractional distillations from linseed oil and quinoline (A. I. Vogel, *Practical Organic Chemistry*, 3rd ed., Longmans, Green, New York, 1956, p. 189).

ketone with aluminum isopropoxide.[10] To the chilled purple reaction mixture was added 6 ml. of water followed by 6 ml. of concd. hydrochloric acid. After stirring for 30 min. the reddish brown solid was collected, washed thoroughly with water and recrystallized from a large volume of ethanol to give 0.7 g. (73%) of tan needles, m.p. 188°.

Anal. Calcd. for $C_{12}H_{13}BrClNO_2$: C, 45.23; H, 4.11; N, 4.39. Found: C, 44.98; H, 4.02; N, 4.51.

α-Bis(β-hydroxyethyl)aminomethyl-6-methoxy-4-quinolinemethanol dihydrochloride. A mixture of 0.6 g. of the above bromohydrin and 2.8 g. of iminodiethanol was stirred at 50° for 29 hr. After pouring into 15 ml. of water the mixture was extracted with chloroform. To the solid remaining after removal of the chloroform 2.5 ml. of 2*N* hydrochloric acid was added. Removal of the water in a vacuum desiccator left 0.45 g. of residue which was recrystallized from methanol-ether.

α-Bis(β-chloroethyl)aminomethyl-6-methoxy-4-quinolinemethanol hydrochloride. (IV). This was prepared by the general method from the above dihydrochloride. The air-dried product after recrystallization from methanol-ether formed clusters of tiny orange needles. This was a solvated dihydrochloride which lost solvent and one molecule of hydrogen chloride on drying under vacuum at 50°.

α-Bis(β-hydroxyethyl)aminomethyl-8-chloro-2-phenyl-4-quinolinemethanol. A mixture of 4.8 g. of α-bromomethyl-8-chloro-2-phenyl-4-quinoline methanol[8] and 16.0 g. of iminodiethanol was stirred and heated at 75° for 22 hr. and then allowed to stand at room temperature for 4 days. It was then poured into 100 ml. of cold water with stirring. The tan solid was collected and taken up in 100 ml. of hot benzene. After treatment with decolorizing carbon, petroleum ether (b.p. 60–75°) was added to turbidity. On scratching, the substance crystallized.

α-Bis(β-chloroethyl)aminomethyl-8-chloro-2-phenylquinolinemethanol. (V). Prepared by the standard procedure, this formed clusters of small yellow needles from methanol-ether.

α-Bis(β-hydroxyethyl)aminomethyl-2-(4'-chlorophenyl)-4-quinolinemethanol. A mixture of 1.5 g. of α-bromomethyl-2-(4'-chlorophenyl)-4-quinolinemethanol[8] and 5.6 g. of iminodiethanol was stirred and heated at 62° for 23 hr. On pouring into water, the product separated and was recrystallized from absolute ethanol.

α-Bis(β-chloroethyl)aminomethyl-2-(4'-chlorophenyl)-4-quinolinemethanol (VII). Prepared by the standard method this formed a hemihydrate from absolute methanol-ether. It could not be dried without decomposition.

α-Bromomethyl-6,8-dichloro-2-phenyl-4-quinolinemethanol. This was prepared by aluminum isopropoxide reduction of the bromo ketone.[8] A reaction time of 5 hr. was necessary for completion. The substance melted at 145° dec. after recrystallization from a 2:1 mixture of ligroin and dioxane. Reported[8] m.p. 130–131° dec.

Anal. Calcd. for $C_{17}H_{12}BrClNO$: C, 51.41; H, 3.04; N, 3.53. Found: C, 51.65; H, 3.08; N, 3.64.

α-Bis(β-hydroxyethyl)aminomethyl-6,8-dichloro-2-phenyl-4-quinolinemethanol. The above bromohydrin was stirred with a 10-fold excess of iminodiethanol at 100° for 4 days. After pouring into ice water, the crude compound was recrystallized from acetonitrile.

α-Bis(β-chloroethyl(aminomethyl-6,8-dichloro-2-phenyl-4-quinolinemethanol. (VI). This was prepared by the standard procedure. The crude product became slightly gummy on filtration and was dried immediately in a vacuum desiccator before recrystallization from absolute methanol.

2-Hydroxy-4-(2-hydroxyethyl-2-(2-phenyl-4-quinolyl)-morpholine (XIII). To a solution of 48 g. of iminodiethanol in 750 ml. of acetone was added with stirring, 40.8 g. of crude α-bromomethyl-2-phenyl-4-quinolyl ketone hydrobromide. A second liquid phase appeared as the ketone hydrobromide dissolved. After stirring for 30 min. 400 ml. of water was added and the mixture became homogeneous. After refrigeration, the solid was collected and washed successively with aqueous acetone, water and acetone. Recrystallization from 2 l. of acetone gave 17 g. (48%) of short square prisms, m.p. 160–164°. An additional 5.1 g. was obtained from the mother liquor.

Anal. Calcd. for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 8.00. Found: C, 71.95; H, 6.27; N, 8.07.

Hydrochloride of XIII. When XIII was dissolved in 2*N* hydrochloric acid the dihydrochloride separated as colorless crystals with no well-defined melting point. After drying in a desiccator the substance still retained two waters of crystallization.

Anal. Calcd. for $C_{21}H_{24}Cl_2N_2O_3 \cdot 2H_2O$: C, 54.91; H, 6.14; N, 15.44. Found: C, 55.12; H, 6.22; N, 15.31.

When XIII was treated with thionyl chloride in chloroform according to the standard procedure, only the hydrochloride was obtained. Identity was established on the basis of infrared spectra.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, SETON HALL UNIVERSITY]

Carcinogenic Activity of Analogs of *p*-Dimethylaminoazobenzene. III. The Quinoline Series

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All of the isomeric *p*-dimethylaminophenylazoquinolines have been prepared as well as the isomeric *p*-dimethylaminophenylazoquinoline *N*-oxides in order to compare their carcinogenic activity. In the latter syntheses it was necessary to prepare the isomeric acetamidoquinoline *N*-oxides and the corresponding aminoquinoline *N*-oxides.

As part of a general project on the relationship of chemical structure to carcinogenic activity, Brown and co-workers[2] have shown that there is a wide range of activity in the three possible isomers of the monopyridine analogs of *p*-dimethylaminoazo-

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(2) E. V. Brown *et al.*, *Cancer Research*, **14**, 22 (1954); **14**, 715 (1954).