[CONTRIBUTION FROM THE LABORATORY OF PHARMACEUTICAL CHEMISTRY, THE UNIVERSITY OF KANSAS SCHOOL OF PHARMACY AND THE RESEARCH DIVISION OF PARKE, DAVIS AND CO.]

Antiamebic Agents. V.[1] Promising Basic Amebicides Derived from 5-Chloro-8-quinolinol

J. H. BURCKHALTER,[2] WILLIAM S. BRINIGAR,[3] AND PAUL E. THOMPSON

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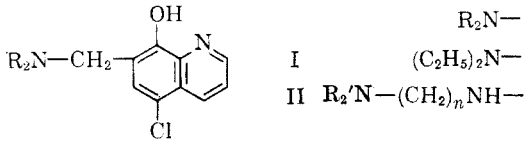
A continuation of the search for antiprotozoan agents among phenolic Mannich bases has led to the synthesis of a group of such bases from 5-chloro-8-quinolinol.

The quinolinol and hydrazine failed to give a product under Mannich conditions. However, success was achieved through amine exchange.

Decomposition of piperazine Mannich base IIId yielded a bis Mannich base (IIIh).

Several bases have been found to be highly effective against *Entamoeba histolytica in vitro* and against experimental intestinal amebiasis in rats and dogs. One of them, 5-chloro-7-(3-diethylaminopropylaminomethyl)-8-quinolinol (KAN-322) has been studied toxicologically and is now being investigated for antiamebic activity in man.

In a previous paper 5-chloro-7-diethylaminomethyl-8-quinolinol (I) and related compounds



having amebicidal activity were described.[4] I is more effective against intestinal amebiasis in rats than the known 8-hydroxyquinolines, but it lacks satisfactory activity against hepatic amebiasis in hamsters.[5] In an attempt to create compounds which might be better distributed and hence more effective systemically, we have prepared a group of 5-chloro-8-quinolinols having two basic groups in the side chain at the 7-position (II). One of these compounds (where $n = 2$ and R = CH_3) has been described in a previous report.[6]

Compounds c through o of Table I were synthesized from 5-chloro-8-quinolinol, paraformaldehyde and the appropriate diamine in alcoholic solution under the conditions of the Mannich reaction. The diamine 3-pyrrolidinopropylamine was prepared by the addition of pyrrolidine to acrylonitrile to give 2-pyrrolidinopropionitrile. The nitrile was reduced catalytically in the presence of Raney nickel to obtain the diamine. 3-(4-Methylpiperazinyl)-propylamine was similarly prepared from 1-methylpiperazine. 4-Diethylaminobutylamine and 4-pyrrolidinobutylamine were prepared by treatment of 3-chlorobutyronitrile with diethylamine and pyrrolidine, respectively, followed by catalytic reduction.

In general, the Mannich reaction proceeded satisfactorily. A small amount of by-product 7,7'-methylene-bis(5-chloro-8-quinolinol) usually formed in insignificant amount. Previous studies have shown that it may result from a reversal of the Mannich reaction.[6] The principal difficulty encountered in the synthesis of the compounds of Table I was in the isolation of the products. That the desired compounds were obtained in no greater yields (35–50%) is not surprising in view of the fact that primary amines in the Mannich reaction, in contrast to secondary amines, are known to give at least three different products.[7]

Attempts to synthesize IIa and b (Table I) by means of hydrazine and *unsym*-dimethylhydrazine in the Mannich reaction resulted in failure, with 5-chloro-8-quinolinol having been recovered unchanged.[8] Hydrazine IIa was synthesized by accident. In an effort to prepare the dihydrazide of 5-chloro-7-[bis(carbethoxyethyl)aminomethyl]-8-quinolinol (VII), the hydrochloride of VII was heated at reflux temperature with an excess of alcoholic hydrazine. The product obtained (IIa) was devoid of carbonyl absorption in the infrared. IIa was also prepared from either 5-chloro-7-diethylaminomethyl-8-quinolinol (I),[4] IId, IIId, or VI in yields of 75 to 80%. Reaction of IIa with salicylaldehyde gave the hydrazone. IIb was prepared

(1) Previous publication, W. L. Nobles, W. C. Stephens, L. Wei, and J. H. Burckhalter, *J. Am. Pharm. Assoc.*, **47**, 82 (1958).

(2) Present address: College of Pharmacy, The University of Michigan, Ann Arbor, Mich.

(3) Parke, Davis and Co. Fellow. The chemical part of this publication was taken from the Ph.D. thesis of William S. Brinigar, University of Kansas, 1957.

(4) J. H. Burckhalter and W. E. Edgerton, *J. Am. Chem. Soc.*, **73**, 4837 (1951).

(5) P. E. Thompson, J. W. Reinertson, A. Bayles, D. A. McCarthy, and E. F. Elslager, *Am. J. Trop. Med. Hyg.*, **4**, 224 (1955).

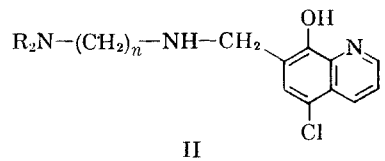
(6) J. H. Burckhalter, V. C. Stephens, H. C. Scarborough, W. S. Brinigar, and W. E. Edgerton, *J. Am. Chem. Soc.*, **76**, 4902 (1954).

(7) W. J. Burke, R. P. Smith, and C. Weatherbee, *J. Am. Chem. Soc.*, **74**, 602 (1952).

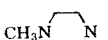
(8) Acetophenone likewise failed to undergo the Mannich reaction with *unsym*-dimethylhydrazine. However, a successful Mannich-type condensation with hydrazine has been reported. M. B. Frankel and K. Klager, *J. Am. Chem. Soc.*, **79**, 2953 (1957), obtained *sym*-bis-(2,2-dinitropropyl)-hydrazine by the reaction of 2,2-dinitropropanol with hydrazine in glacial acetic acid.

TABLE I

5-CHLORO-7-(DIALKYLAMINOALKYLAMINOMETHYL)-8-QUINOLINOLS



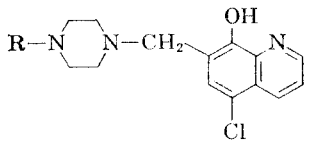
II

II	R_2N	n	Procedure	Yield, %	M.P.	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	Antiamebic Activity: *In vitro*,[r] minimal γ/ml.	Antiamebic Activity: Rats,[s] approx. CD_{50} mg./kg./day	Antiamebic Activity: Dogs,[t] approx. CD_{50} mg./kg./day
a	H_2N	0		80[a]	177	$C_{10}H_{10}ClN_3O$	53.70	53.93	4.51	4.67	<20	425[u]	
b	$(CH_3)_2N$	0		40[b]	206 dec.	$C_{14}H_{14}ClN_3O\cdot 2HCl$	44.38	44.08	4.97	5.18	<20	>175	
c	$(C_2H_5)_2N$[c]	2									8		
d	$(C_2H_5)_2N$[d]	2	A	50[e]	188 dec.	$C_{17}H_{24}ClN_3O\cdot 3HCl\cdot 1/2H_2O$	46.38	46.62	6.41	6.43	2.5	>675[u]	
e	$(CH_3)_2N$	3	A	20[f]	232 dec.	$C_{15}H_{20}ClN_3O\cdot 3HCl\cdot H_2O$	42.77	42.71	5.98	5.96	5	150[u]	
f	$(C_2H_5)_2N$	3	A	22[g]	203 dec.	$C_{17}H_{24}ClN_3O\cdot 3HCl$[h]	47.35	47.55	6.31	6.41	2.5	150	10
			B	39[i]	201 dec.	$C_{17}H_{24}ClN_3O\cdot 2HCl$	51.72	51.84	6.64	6.64			
g		3	A	38[g]	217 dec.	$C_{17}H_{22}ClN_3O\cdot 3HCl$	47.57	47.70	5.87	5.87	<200	150	10
			B	35[k]	221 dec.	$C_{17}H_{22}ClN_3O\cdot 2HCl$	51.98	52.00	6.16	6.17			
h		3	A	32[g]	223 dec.	$C_{18}H_{24}ClN_3O\cdot 3HCl$	48.77	48.27	6.14	6.26	2.5	75	10
i		3	A	52[l]	264 dec.	$C_{18}H_{25}ClN_4O\cdot 3HCl$	47.17	46.78	6.16	6.37	<200	225[u]	
j	$(C_2H_5)_3N$	4	A	45[b]	233 dec.	$C_{18}H_{26}ClN_3O\cdot 3HCl$	48.55	48.42	6.56	6.67	<200	275[u]	
k		4	A	45[b]	208 dec.	$C_{15}H_{24}ClN_3O\cdot 3HCl\cdot H_2O$	46.87	46.77	6.31	6.39	<200	275[u]	
l	$(C_2H_5)_2N$	4[m]	A	36[e]	236 dec.	$C_{19}H_{28}ClN_3O\cdot 3HCl$[n]	49.68	49.77	6.80	7.23	10	275[u]	>10
m	$(C_2H_5)_2N$[o]	5	A	30[e]	203 dec.	$C_{19}H_{28}ClN_3O\cdot 3HCl$	49.68	49.74	6.80	6.84	<200	250	
n		5	A	27[g]	237 dec.	$C_{20}H_{28}ClN_3O\cdot 3HCl\cdot H_2O$	49.08	49.04	6.80	6.57	5		
o	$(C_2H_5)_2N$[q]	6	A	30[e]	205 dec.	$C_{20}H_{30}ClN_3O\cdot 3HCl$	50.75	50.71	7.03	7.11	<200	>175	>6.3

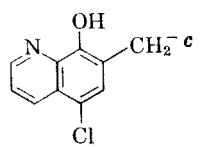
[a] Yellow solid from ethylene glycol monomethyl ether. Nitrogen: Calcd., 18.79. Found, 18.27. [b] Bright yellow crystals from methanol. [c] See ref. 6 for preparation. [d] Contains an N′-methyl. Side chain used *N,N*-diethyl-*N*′-methylethylenediamine from Dr. E. F. Elslager, Parke, Davis and Co. [e] Yellow solid from absolute ethanol. [f] Tan solid from ethanol-methanol. [g] Yellow solid from ethanol-methanol. [h] Ionic chlorine: Calcd., 24.67. Found, 24.84. [i] White solid from ethanol. [j] Intermediate diamine: J. Corse, J. T. Bryant and H. A. Shonle, *J. Am. Chem. Soc.*, **68**, 1911 (1946). [k] White solid from ethanol-methanol. [l] White solid from dimethylformamide containing a small amount of water. [m] Side chain actually from 4-diethylamino-1-methylbutylamine. [n] Ionic chlorine: Calcd., 23.16. Found, 23.36. [o] *N,N*-Diethylcadaverine, F. Kurtz, *Ann.*, **572**, 23 (1951), made by the procedure of H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 2348 (1926). [p] Kindly supplied by Dr. E. F. Elslager, Parke, Davis and Co. [q] *N,N*-Diethyl-1,6-hexanethylenediamine, K. N. Campbell *et al.*, *J. Am. Chem. Soc.*, **68**, 1559 (1946). Prepared by the method of Ing and Manske. [r] Tested in a protein-free liquid medium, usually for 48 hr. [s] Fed in the diet for 7 days. [t] Given in gelatin capsules as two daily portions 5 days/week for 2 weeks, P. E. Thompson *et al.*, *Antibiotics & Chemotherapy*, **6**, 337 (1956). [u] Amounts requisite for appreciable effect closely approached the toxic levels.

TABLE II

5-CHLORO-7-(4-SUBSTITUTED-1-PIPERAZINYLMETHYL)-8-QUINOLINOLS



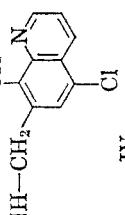
III

III	R	Yield, %	M.P.	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	Antiamebic Activity: *In vitro*,[d] minimal γ/ml.	Antiamebic Activity: Rats,[e] approx. CD_{50} mg./kg./day
a	CH_3—	50	247 dec.	$C_{15}H_{18}ClN_3O \cdot 2HCl \cdot 1/2H_2O$	48.21	48.49	5.66	5.75	5	>1000
			149	$C_{15}H_{18}ClN_3O$	61.74	61.12	6.22	6.23		
b	$CH_3(CH_2)_9$—	53	275 dec.	$C_{24}H_{36}ClN_3O \cdot 2HCl$	58.72	58.55	7.80	7.70	<200	350
c	$C_2H_5O_2C$—	77	133	$C_{17}H_{20}ClN_3O_3$	58.37	58.34	5.76	5.30	2.5	>1250
			188 dec.	$C_{17}H_{20}ClN_3O_3 \cdot 2HCl$	48.30	48.04	5.25	5.70		
d	H—	82	343 dec.	$C_{14}H_{16}ClN_3O \cdot 2HCl \cdot 2H_2O$[a]	43.48	43.47	5.74	5.63	<200	> 600
			230 dec.	$C_{14}H_{16}ClN_3O \cdot 2H_2O$	53.59	53.57	6.42	5.60		
e	$(C_2H_5)_2N$—CO—	56	200 dec.	$C_{19}H_{25}ClN_4O_2 \cdot 2HCl$[b]	49.25	49.16	6.20	6.34	<200	925
f	HO_2C—CH_2—	71	206	$C_{16}H_{13}ClN_3O_3$	57.23	57.27	5.40	5.63	<200	350
g	$C_2H_5SO_2$—	80	215 dec.	$C_{16}H_{20}ClN_3O_3S \cdot HCl$	47.29	47.24	5.21	5.21	<200	725
			158	$C_{16}H_{20}ClN_2O_3S$	51.95	52.02	5.45	5.50		
h									>2000	

[a] Anal. for ionic chlorine: Calcd., 18.34. Found, 18.30. [b] C—H and H_2O analysis corresponds to 3/4 H_2O: Calcd., 3.75. Found, 3.54. [c] See ref. 6 for original synthesis. [d] See footnote *r* of Table I. [e] See footnote *s* of Table I.

TABLE III

5-CHLORO-7-(ALKYLAMINOMETHYL)-8-QUINOLINOLS



IV

IV	R	Procedure	Yield, %	M.P.	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	Antiamebic Activity: *In vitro*,[a] minimal γ/ml.	Antiamebic Activity: Rats,[b] approx. CD_{50} mg./kg./day
a	$CH_3-(CH_2)_3-CH(C_2H_5)-CH_2-$	A	43[a]	209 dec.	$C_{18}H_{32}ClN_3O\cdot 2HCl$	54.90	55.28	6.91	7.14	6.3	375
b	$CH_3-(CH_2)_6-$	A	53[b]	197 dec.	$C_{17}H_{23}ClN_2O\cdot 2HCl$	53.76	53.92	6.64	6.64	<200	625
c	$CH_3-(CH_2)_7-$[c]	A	41[b]	190 dec.	$C_{18}H_{25}ClN_2O\cdot 2HCl$	54.90	55.21	6.91	7.08	<200	>300

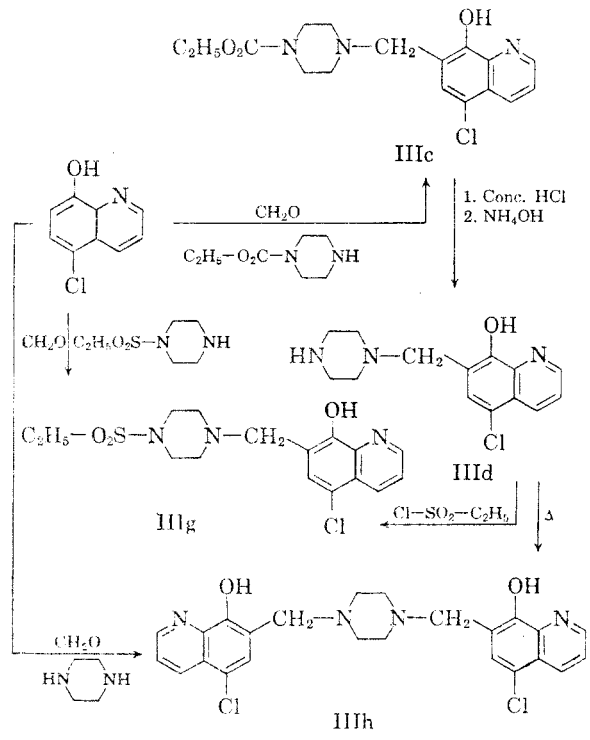
[a] Yellow solid from ethanol-methanol. [b] Yellow solid from absolute ethanol. [c] Intermediate octylamine made from octyl bromide and potassium phthalimide by use of the general procedure of J. C. Sheehan and W. A. Bolhofer, *J. Am. Chem. Soc.*, **72**, 2786 (1950). [d] See footnote *r*, Table I. [e] See footnote *s*, Table I.

by heating I, IId, or X with alcoholic *unsym*-dimethylhydrazone.[9]

It was decided to obtain another group of compounds in which the two nitrogens of the side chain of type II are incorporated into a piperazine ring system. Except for IIId, the compounds of Type III were synthesized directly by the Mannich reaction, and the results are summarized in Table II.

A variation of the reaction in which *N,N'*-methylenebiscarbethoxypiperazine[10] was used instead of a mixture of paraformaldehyde and 1-carbethoxypiperazine as the Mannich reagent gave a poorer yield of 5-chloro-7-(4-carbethoxy-1-piperazinylmethyl)-8-quinolinol (IIIc).

5-Chloro-7-1′-piperazinylmethyl-8-quinolinol (IIId) was obtained by hydrolysis of 5-chloro-7-(4-carbethoxy-1-piperazinylmethyl)-8-quinolinol (IIIc) in concentrated hydrochloric acid. When an aqueous solution of IIId hydrochloride was neutralized with ammonium hydroxide, the free base IIId precipitated. That the free base of IIId existed was shown by its conversion to IIIg by treatment with ethanesulfonyl chloride. But recrystallization of the base from dimethylformamide yielded a substance of higher melting point. Structure IIIh was assigned to this substance and confirmation was obtained through its alternate synthesis from two molar equivalents of 5-chloro-8-quinolinol and paraformaldehyde and one of piperazine.

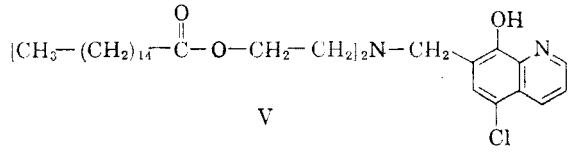


(9) We are currently studying the generality of the amine displacement by hydrazine in phenolic Mannich bases.

(10) N. W. Stewart, R. J. Turner, and J. J. Denton, *J. Org. Chem.*, **13**, 134 (1948).

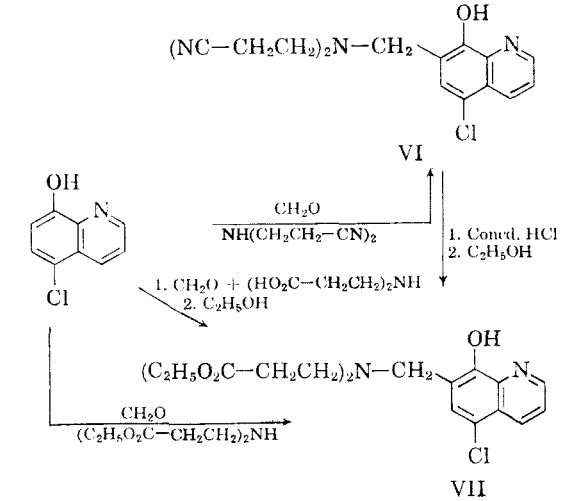
The compounds of Tables I and II were synthesized as a means of studying the effect of the introduction of further hydrophilic groupings upon antiamebic activity of basic 5-chloro-8-quinolinols (I). It was also considered desirable to learn the effect of increasing the lipophilic properties of I. A few compounds of this type (IVa, b, c), synthesized by the conditions of the Mannich reaction, are listed in Table III. They are waxy solids which are virtually insoluble in water even as the dihydrochloride salts.

A few other compounds which may not be conveniently listed in Tables I, II, or III were synthesized. 5-Chloro-7-[bis-(2-hydroxyethyl)aminomethyl]-8-quinolinol dipalmitate hydrochloride (V) was obtained by the action of palmitoyl chloride upon 5-chloro-7-[bis-(2-hydroxyethyl)aminomethyl]-8-quinolinol. Like the agents of Table III, it was virtually insoluble in water.



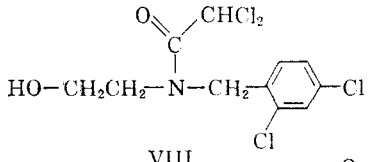
V

When 5-chloro-8-quinolinol, paraformaldehyde and β,β'-iminodipropionitrile were allowed to heat at reflux temperature in alcohol, the expected 5-chloro-7-[bis(2-cyanoethyl)aminomethyl]-8-quinolinol (VI) was obtained. Treatment of VI with boiling alkali failed to yield the corresponding diacid but instead gave 7,7'-methylenebis-(5-chloro-8-quinolinol), thus representing an example of the reversal of the Mannich reaction under basic conditions. Hydrolysis of VI in concentrated hydrochloric acid, either at room temperature or at 100°, gave a hydrochloride salt (m.p. 155–157°) which after recrystallization from alcohol was found to be insoluble in ammonium hydroxide. An intense peak at 1730 cm.$^{-1}$ in the infrared was suggestive of either an acid or ester. When either β,β'-iminodipropionic acid or its diethyl ester was used as the amine in the Mannich reaction and the product as the hydrochloride was recrystallized from alcohol, the same hydrochloride (m.p. 155–157°) was isolated in both cases. The product thus obtained in three different ways was assigned structure VII. It was somewhat surprising to find that complete esterification had occurred during the process of recrystallization of the diacid hydrochloride from alcohol.

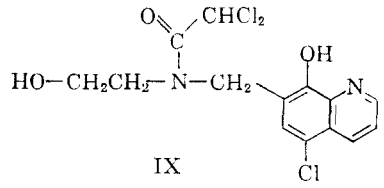


VII

Upon learning of the interesting antiamebic activity of *N*-(2,4-dichlorobenzyl)-*N*-(2-hydroxyethyl)-dichloroacetamide (VIII) in animals,[11] we decided

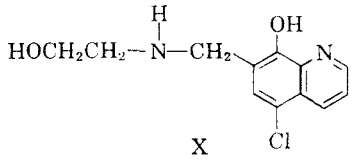


VIII



IX

to attempt the synthesis of *N*-(5-chloro-8-hydroxy-7-quinolinylmethyl)-*N*-(2-hydroxyethyl)dichloroacetamide (IX). Intermediate 2-(5-chloro-8-hydroxyquinolylaminomethylamino)ethanol (X) was prepared by use of ethanolamine in the Mannich reaction. X was then allowed to react with methyl dichloroacetate to give IX. Difficulty was encountered in this reaction owing to the low solubility of X in common organic solvents. Reaction was finally effected by allowing a suspension of X in excess methyl dichloroacetate to stand for several weeks.



X

Pharmacological results. The antiamebic evaluation of these compounds was oriented around the primary goal of developing useful drugs rather than a precise exploration of structure-activity relationships. The general plan was to examine each substance sequentially (as long as it exhibited a sufficient degree of promise in each successive type of test) *in vitro*, against intestinal amebiasis in rats, and against amebic dysentery in dogs; in addition, particularly promising substances were to be tested against hepatic amebiasis in hamsters. As past experience had suggested that greater emphasis be placed on *in vivo* performance than on *in vitro* potency, the endpoint of activity *in vitro* was determined for less than half of the compounds. It also is to be emphasized that the effects of most of the

(11) A. R. Survey, *J. Am. Chem. Soc.*, **76**, 2214 (1955).

compounds *in vivo* are based on relatively small numbers of animals and at best represent only rough approximations.

Data on the antiamebic activities are given together with a summary of the chemical data for the compounds in Tables I, II, and III. Antiamebic data on four additional compounds are given in Table IV.

TABLE IV

MISCELLANEOUS BASIC 5-CHLORO-8-QUINOLINOLS

Compound	Antiamebic Activity	
	In vitro,[a] minimal γ/ml.	Rats,[b] approx. CD_{50} mg./kg./day
V	>2000	>2150
VI	<200	375
VII	<20	>175
VIII	2.5	600

[a] See footnote *r* of Table I. [b] See footnote *s* of Table I.

Five of the compounds, all in Table I, were deemed worthy of trial in dogs. Four of these—IIf, IIg, IIh, and IIi—had in rats a therapeutic index (ratio of minimum effective to maximum tolerated dose) of two or more, and three of them cured infections in dogs without any gross evidence of toxicity. It is to be noted that compounds with three methylene groups appeared to be superior to those with either two or four to six methylene groups.

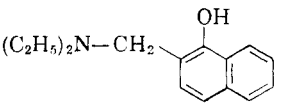
Compound IIf (KAN-322) [5-chloro-7-(3-diethylaminopropylaminomethyl)-8-quinolinol] of Table I appeared from several standpoints to be one of the most effective substances against experimental intestinal amebiasis in rats and dogs. It also proved to be as active as chloroquine when tested orally against hepatic amebiasis in hamsters.

Mechanism of action. 5-Chloro-7-(3-diethylaminopropylaminomethyl)-8-quinolinol (IIf) does not contain iodine. Thus, its antiamebic activity does not support the traditional theory that 8-quinolinols owe their effectiveness to the release of iodine.

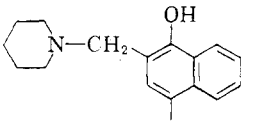
5-Chloro-7-(3-diethylaminopropylaminomethyl)-8-quinolinol is amebicidal at 2.5 γ/ml. *in vitro* and bactericidal at 10–20 γ/ml. against seven representative types of bacteria of the intestinal tract.[12] The higher dose level for bactericidal activity suggests that the compound acts directly against amebae rather than through inhibition of bacteria which support amebae.

The bactericidal effect of the 8-quinolinols has been shown in the case of certain Gram-negative organisms to depend upon their ability to chelate with certain heavy metals. The bacteria are injured by deprivation of necessary cobalt. In the case of Gram-positive organisms, they are injured by the formation of a toxic metal complex which induces, for example, oxidation of sulfhydryl groups associated with vital metabolic processes.[13]

2-Diethylaminomethyl-1-naphthol (XI) and 2-piperidinomethyl-4-chloro-1-naphthol (XII) were screened for antiamebic effectiveness as a means of



XI



XII

testing the importance of metal chelation to the pronounced activity of 8-quinolinols I and IIf. The low potency[5] of these naphthols suggests the importance of the heterocyclic nitrogen, and, therefore, of the potentiality for chelation to the antiamebic activity of such agents.

Results of the present studies indicate that considerable variation in the substituent at C-7 is possible without loss of intrinsic (*i.e., in vitro*) activity. This fact further suggests that C-7 is situated away from the site of any enzymatic processes.

It is noteworthy that the increased systemic activity of 5-chloro-7-(3-diethylaminopropylaminomethyl)-8-quinolinol (IIf) over I results from the longer side chain of the former which also contains an additional amino grouping.

EXPERIMENTAL[14]

Procedure A. Equimolecular amounts of 5-chloro-8-quinolinol,[15] paraformaldehyde and the appropriate amine were dissolved or suspended in warm ethanol. For each 0.1 mole of 5-chloro-8-quinolinol, 125 ml. of ethanol was used. The mixture was heated at reflux temperature for 2 hr. After removal by filtration of any 7,7′-methylene-bis-(5-chloro-8-quinolinol), the solvent from the filtrate was removed under reduced pressure, and the residue was dissolved in ether or an ether-acetone mixture. Anhydrous hydrogen chloride was then passed into the solution until the mixture was acid to *p*H paper. The hydrochloride salt was collected on a funnel and recrystallized from a suitable solvent. When difficulty was encountered by the isolation of mixed di- and trihydrochlorides, the use of recrystallizing solvent containing hydrogen chloride gave assurance of obtaining the yellow trihydrochloride.

Procedure B. When Procedure A led to a hygroscopic trihydrochloride or where it was desirable to obtain a dihydrochloride salt, a two-molar equivalent of hydrogen chloride in absolute ethanol was added to the reaction mixture. The solvent was then removed by distillation until the product began to crystallize.

It might be observed that when an excess of acid is present (Procedure A), a proton is held at the quinoline nitrogen and the product is colored, usually yellow. When just enough acid is present to satisfy the side chain nitrogens (Procedure B), the product is usually white.

5-Chloro-7-hydrazinylmethyl-8-quinolinol (IIa). (a) *From Mannich bases of 5-chloro-8-quinolinol.* A solution containing 3.2 g. (0.1 mole) of 95% hydrazine, 30 ml. of absolute ethanol, and 0.01 mole of any one of the following substances

(12) Dr. M. W. Fisher, private communication.

(13) S. D. Rubbo, A. Albert, and M. I. Gibson, *Brit. J. Exp. Pathol.*, **31**, 425 (1950); **34**, 119 (1953).

(14) For % yields and analyses of compounds, see Tables.

(15) B. L. Lemke and Co., Inc., Lodi, N. J.

was heated at reflux temperature for 2 hr.: 5-chloro-7-diethylaminomethyl-8-quinolinol dihydrochloride (I),[4] 5-chloro-7-[(3-dimethylaminopropylamino)methyl]-8-quinolinol trihydrochloride monohydrate (IIe), 5-chloro-7-[bis-(2-carbethoxyethyl)aminomethyl]-8-quinolinol dihydrochloride (VII), 5-chloro-7-[bis-(2-cyanoethyl)-aminomethyl]-8-quinolinol dihydrochloride (VI), 5-chloro-7-1′-piperazinylmethyl-8-quinolinol trihydrochloride (IIId). The volatile material was removed at the water pump and the residue washed first with a few milliliters of 95% ethanol and again with a few milliliters of water. Approximately 1.7 g. of yellow solid was obtained after drying, m.p. 170–173°. Admixture of the products obtained from the various starting materials showed no depression in the melting point.

(b) *From 5-chloro-8-quinolinol.* An ethanolic solution of 9 g. (0.05 mole) of 5-chloro-8-quinolinol, 1.5 g. (0.05 mole) of paraformaldehyde, and 3.7 g. (0.05 mole) of diethylamine was heated at reflux temperature for 1 hr. The reaction mixture was freed of insoluble 7,7′-methylene-bis-(5-chloro-8-quinolinol) and the volume of the filtrate reduced by half at the water pump. Sixteen grams (0.5 mole) of 95% hydrazine was added and the resulting solution heated at reflux for an additional hour. The yellow solid which had accumulated was filtered and washed with water, giving 15 g. (67%) of yellow solid, m.p. 174–175°. Recrystallization from ethylene glycol monomethyl ether gave a product identical with that of the analytical sample obtained by the foregoing procedure.

The salicylhydrazone derivative was obtained by heating IIa with an excess of salicylaldehyde for a few minutes on the steam bath. The solid which separated upon cooling was recrystallized from ethylene glycol monoethyl ether to give a white solid, m.p. 220–221°.

Anal. Calcd. for $C_{17}H_{14}ClN_3O_2$: C, 62.29; H, 4.30. Found: C, 62.13; H, 4.21.

5-Chloro-7-(N,N-dimethylhydrazinylmethyl)-8-quinolinol dihydrochloride (IIb). An ethanolic solution containing 6.0 g. (0.1 mole) of *N,N*-dimethylhydrazine and 0.01 mole of any one of the following substances was heated at reflux temperature for 10 hr.: 5-chloro-7-diethylaminomethyl-8-quinolinol dihydrochloride (I),[4] 5-chloro-7-(2-hydroxyethylaminomethyl)-8-quinolinol (X), 5-chloro-7-1′-piperazinylmethyl-8-quinolinol trihydrochloride (IIId). The solvent and excess dimethylhydrazine were removed at the water pump and the residue taken up in a few milliliters of water. The product was extracted with ether and the ether extract was dried over anhydrous sodium acetate. An orange gummy solid was obtained by passing hydrogen chloride through the ether solution. Recrystallization from methanol produced about 1.5 g. of a bright yellow crystalline material, m.p. 205–206° dec. No depression in melting point was observed when samples obtained from different starting materials were mixed.

2-(4-Methyl-1-piperazinyl)propionitrile. Fifty grams (0.5 mole) of 1-methylpiperazine and 40 g. (0.75 mole) of acrylonitrile were cautiously mixed in a cooled pressure bottle and heated on a steam bath for 72 hr. After being cooled to room temperature, the mixture was distilled to give 64 g. (83%) of a clear liquid boiling at 140–145° (31 mm.). A portion of this material was redistilled for the preparation of an analytical sample, b.p. 141–142° (32 mm.), n_D^{20} 1.4768.

Anal. Calcd. for $C_8H_{15}N_3$: C, 62.71; H, 9.87. Found: C, 62.67; H, 9.69.

3-(4-Methyl-1-piperazinyl)propylamine. Forty-six grams (0.3 mole) of 2-(4-methylpiperazinyl)propionitrile was dissolved in 150 ml. of absolute ethanol and 5 g. of Raney nickel was added to the solution. The mixture was hydrogenated at 70 p.s.i. for about 5 hr. when no further uptake of hydrogen occurred. A total of 0.55 mole (92% of theoretical) of hydrogen was absorbed. The catalyst was removed by filtration and the filtrate distilled under the pressure of the water pump. Thirty-four grams (74%) of clear liquid was obtained b.p. 120–123° (25 mm.), n_D^{20} 1.4808, b.p. 228° (atmospheric pressure).

Anal. Calcd. for $C_8H_{19}N_3$: C, 61.10; H, 12.18. Found: C, 61.05; H, 11.99.

A *dipicrate* was prepared in ethanol and recrystallized with difficulty from an acetone-methanol mixture, m.p. 245–246° dec.

Anal. Calcd. for $C_8H_{19}N_3 \cdot 2C_6H_3N_3O_7$: C, 39.03; H, 4.09. Found: C, 38.95; H, 3.97.

4-Pyrrolidinobutylamine. A solution of 35.5 g. (0.5 mole) of pyrrolidine and 20.7 g. (0.2 mole) of 3-chlorobutyronitrile was prepared by cooling each reactant separately and slowly mixing. This solution was allowed to warm slowly to room temperature. When a spontaneous exothermic reaction commenced, the solution was cooled in an ice bath to maintain the temperature as low as possible. After the exothermic reaction had ceased, the mixture was heated in an oil bath at 50–60° for 18 hr. The resulting brown oil was poured into ether and the by-product, pyrrolidine hydrochloride, was removed by filtration. The filtrate was dried over sodium sulfate and the ether distilled. The residue was then distilled to yield 20 g. (72%) of a clear liquid boiling at 116–122° (18 mm.). The 3-pyrrolidinobutyronitrile so obtained was dissolved in 50 ml. of methanol, and 3 g. of Raney nickel catalyst was added. The mixture was placed in a hydrogenator at room temperature at 80 p.s.i. After 3 hr., 0.25 moles (86% of the theoretical amount) of hydrogen had been taken up. The catalyst was filtered and the methanol was removed at the water pump. Distillation of the residue provided 12.5 g. (61% yield) of a clear liquid boiling at 106–112° (18 mm.). A *dipicrate* was obtained from ethanol, m.p. 158–159°. [Lit.[16] gives a b.p. of 90–100° (12 mm.) for the amine and a m.p. of 203–204° for the dipicrate.]

Anal. Calcd. for $C_8H_{18}N_2 \cdot 2C_6H_3N_3O_7$: C, 40.00; H, 4.03. Found: C, 39.98; H, 3.82.

5-Chloro-7-(methyl-1-piperazinylmethyl)-8-quinolinol dihydrochloride hemihydrate (IIIa). A mixture of 12 g. (0.1 mole) of 1-methylpiperazine and 3 g. (0.1 mole) of paraformaldehyde in 50 ml. of absolute ethanol was added to a suspension of 18 g. (0.1 mole) of 5-chloro-8-quinolinol in 50 ml. of ethanol and the resulting solution was allowed to heat at reflux temperature for 1.5 hr. The solvent was removed at the water pump and the residue dissolved in an ether-acetone mixture. An excess of anhydrous hydrogen chloride was passed into this solution and the hydrochloride salt collected on a filter, m.p. 210–225° dec. Recrystallization of this material from an ethanol-methanol mixture yielded 20 g. of a semiwhite solid, m.p. 245–247° dec.

The free base was prepared by neutralizing a water solution of the dihydrochloride salt with dilute ammonia, collecting the white solid on a filter and recrystallizing it from 95% ethanol, m.p. 148–149°.

5-Chloro-7-(4-decyl-1-piperazinylmethyl)-8-quinolinol dihydrochloride (IIIb). A mixture of 0.93 g. (0.031 mole) of paraformaldehyde and 7 g. (0.031 mole) of 1-decylpiperazine[17] in 20 ml. of absolute ethanol was added to 5.6 g. (0.031 mole) of 5-chloro-8-quinolinol in 50 ml. of absolute ethanol and the resulting solution allowed to heat at reflux for 5 hr. The solvent was removed at the water pump and the residue dissolved in an ether-acetone mixture. A stream of hydrogen chloride gas precipitated 14 g. (89%) of a yellow waxy solid, m.p. 140–160° (with foaming). Recrystallization from absolute ethanol yielded 8 g. of a white waxy solid which turned black quickly at 250–251° but did not decompose to a liquid until 275°.

5-Chloro-7-(4-carbethoxy-1-piperazinylmethyl)-8-quinolinol (IIIc). (a) A warm mixture of 15.8 g. (0.1 mole) of 1-carbethoxypiperazine[18] and 3 g. (0.1 mole) of paraformaldehyde in about 30 ml. of absolute ethanol was added to a heated suspension of 18 g. (0.1 mole) of 5-chloro-8-quinolinol in

(16) J. Von Braun and F. Zobel, *Ann.*, 445, 247 (1925); *Ber.*, 57, 188 (1924).

(17) R. Baltzly, *J. Am. Chem. Soc.*, 76, 1164 (1954).

(18) T. S. Moore, M. Boyle, and V. M. Thorn, *J. Chem. Soc.*, 39 (1929).

about 80 ml. of absolute ethanol. The resulting solution was heated at reflux for 2 hr. Ethanol was removed at the water pump until the solid began to precipitate. Cooling the solution yielded 25 g. of a white solid; reducing the volume of filtrate by half gave an additional 2 g., m.p. 125–127°.

The *hydrochloride* salt was prepared by dissolving the evaporated reaction mixture in an acetone-ether mixture and passing anhydrous hydrogen chloride through the solution. A bright yellow solid was filtered, m.p. 178–185° dec. Recrystallization from an ethanol-methanol mixture yielded 30 g. of material, m.p. 188–189° dec.

(b) A mixture of 1.8 g. (0.01 mole) of 5-chloro-8-quinolinol and 3.3 g. (0.01 mole) of *N,N'*-methylenebiscarbethoxypiperazine[10] in 25 ml. of absolute ethanol was heated at reflux temperature for 1 hr. The hydrochloride salt of the reaction mixture was prepared as described above. After recrystallization from an ethanol-methanol mixture, 1 g. (25%) of a yellow solid was obtained, m.p. 185–187° dec. No depression in melting point was observed when mixed with the material described in (a).

5-Chloro-7-1'-piperazinylmethyl-8-quinolinol dihydrochloride dihydrate (IIId). Twenty-two grams (0.063 mole) of IIIc was dissolved in 50 ml. of concd. hydrochloric acid and the resulting solution was heated on the steam bath for three days. The excess hydrochloric acid and water were removed at the water pump leaving a yellow residue. Washing with 20 ml. of boiling methanol yielded 19 g. (82%) of a yellow solid which did not melt below 300°. Repeated recrystallization from methanol gave a grey solid which sintered at 320° and decomposed at 341–343°.

The *free base* was prepared by dissolving the hydrochloric salt in water and adjusting the *p*H to 8 with dilute ammonia. The tan solid was collected on a filter, m.p. 229–230° dec. The product was not recrystallized because of its ready decomposition to IIIh.

5-Chloro-7-(4-diethylcarbamyl-1-piperazinylmethyl)-8-quinolinol dihydrochloride (IIIe). A war ethanolic suspension of 9.5 g. (0.05 mole) of diethylcarbamylpiperazine[19] and 1.5 g. (0.05 mole) of paraformaldehyde was added to an ethanolic suspension of 9 g. (0.05) mole) of 5-chloro-8-quinolinol and the resulting solution was heated at reflux temperature for 3 hr. The solvent was removed at the water pump and the residue dissolved in an acetone-ether mixture. Anhydrous hydrogen chloride was passed into the solution in excess and the yellow salt collected on a filter. Recrystallization was easily effected from ethanol containing a small amount of methanol to give 13 g. of a bright yellow solid which first melted at 145–150°, resolidified and again melted at 197–200° (dec.). Repeated recrystallization from absolute ethanol yielded a yellow solid, m.p. 158–160°.

4-(5-Chloro-8-hydroxy-7-quinolylmethyl)-1-piperazineacetic acid (IIIf). A mixture of 7.2 g. (0.05 mole) of 1-piperazineacetic acid[18] and 1.5 g. (0.05 mole) of paraformaldehyde in 30 ml. of water containing a few milliliters of ethanol was added to 9 g. (0.05 mole) of 5-chloro-8-quinolinol suspended in 100 ml. of 95% ethanol. Solution was effected while the mixture was heated at reflux temperature for 2 hr. When solvent was removed at the water pump, a tan residue was left which was triturated with 20 ml. of absolute ethanol. Ten grams of white solid remained undissolved and an additional 2 g. crystallized upon cooling the solution, m.p. 198–201°. Recrystallization from dimethylformamide raised the m.p. to 205–206°. Subsequent recrystallization from Methyl Cellosolve did not further alter the melting point.

5-Chloro-7-[4-(ethylsulfonyl)-1-piperazinylmethyl]-8-quinolinol monohydrochloride (IIIg). (a) A mixture of 9 g. (0.05 mole) of 5-chloro-8-quinolinol, 1.5 g. (0.05 mole) of paraformaldehyde and 10.8 g. (0.05 mole) of 1-ethylsulfonylpiperazine hydrochloride[20] in 150 ml. of absolute ethanol was allowed to heat at reflux for 8 hr. The ethanol was distilled until the volume remaining was approximately 75 ml. Cooling the solution in the refrigerator gave 16 g. of a semiwhite crystalline solid, m.p. 189–192° dec. Triturating this solid with a few milliliters of absolute ethanol raised the m.p. to 207–209° dec. and subsequent recrystallization from absolute ethanol yielded a pure white solid, m.p. 214–125° dec.

The *free base* was prepared by dissolving the hydrochloride salt in water and making the solution basic with dilute ammonia water. The white solid was collected on a filter and recrystallized from petroleum ether (b.p. 60–80°) m.p. 157–158°.

(b) One gram (0.0036 mole) of 5-chloro-7-1'-piperazinylmethyl-8-quinolinol (IIId) suspended in 50 ml. of ether was added to 1 g. of freshly distilled ethanesulfonyl chloride in 30 ml. of ether. The resulting mixture was allowed to stand at room temperature with frequent shaking for 30 min. The suspended solid was filtered and dissolved in water. From this solution, which had been made slightly basic with dilute ammonia, a white solid was isolated. Recrystallization of this material from petroleum ether (b.p. 60–68°) yielded 0.7 g. of a white solid, m.p. 157–158°. No depression in melting point was observed when this product was mixed with the material obtained in (a).

1,4-Bis-(5-chloro-8-hydroxy-7-quinolylmethyl)piperazine (IIIh). One gram (0.0036 mole) of 5-chloro-7-1'-piperazinylmethyl-8-quinolinol (IIId) was dissolved in 15 ml. of dimethylformamide and heated at reflux temperature for 30 min. Cooling the solution yielded 0.35 g. (42%) of tan solid, m.p. 249–251° dec. which remained unaltered after it had stood in an ether solution of ethanesulfonyl chloride for 30 min. Recrystallization from dimethylformamide followed by recrystallization from quinoline raised the m.p. to 258–259° dec. The melting point was not depressed by a sample prepared by a different procedure.[6]

5-Chloro-7-[bis-(2-hydroxyethyl)aminomethyl]-8-quinolinol dipalmitate hydrochloride (V). A mixture of 24 g. (0.07 mole) of 5-chloro-7-[bis-(2-hydroxyethyl)aminomethyl]-8-quinolinol monohydrochloride,[6] which had been thoroughly dried, and 100 ml. of palmitoyl chloride[21] was stirred for 7 hr. at 90–95° while anhydrous conditions were maintained. The contents of the flask was poured into an ether-water mixture and the mass stirred for several minutes. The maroon colored hydrate was collected on a filter and air dried. Recrystallization from dimethylformamide dehydrated the product. After it was washed with ethyl acetate, 30 g. (53% yield) of light yellow-colored solid was obtained, m.p. 103–104°.

Anal. Calcd. for $C_{46}H_{77}ClN_2O_5 \cdot HCl$: C, 68.20; H, 9.71. Found: C, 68.27; H, 9.67.

5-Chloro-7-[bis-(2-cyanoethyl)aminomethyl]-8-quinolinol (VI). A mixture of 6.2 g. (0.05 mole) of β,β'-iminodipropionitrile and 1.5 g. (0.05 mole) of paraformaldehyde in 30 ml. of absolute ethanol was added to a suspension of 9 g. (0.05 mole) of 5-chloro-8-quinolinol in 90 ml. of absolute ethanol and the resulting solution heated at reflux for 3 hr. About 25 ml. of ethanol was allowed to evaporate and the solution cooled. Filtration removed 6.7 g. (42%) of a grey solid, m.p. 104–110°. Repeated recrystallization from ethanol yielded 4.5 g. (28%) of grey-green needles, m.p. 110–110.5°.

Anal. Calcd. for $C_{16}H_{15}ClN_4O$: C, 61.05; H, 4.80. Found: C, 61.28; H, 5.08.

By dissolving the free base in acetone and adding an excess of alcoholic hydrogen chloride, a yellow *hydrochloride* salt was obtained, m.p. 137–139° (not analyzed).

β,β'-Iminodipropionic acid. A solution of 12.3 g. (0.1 mole) of β,β'-iminodipropionitrile and 50 ml. of concd. hydrochloric acid was allowed to stand at room temperature for several days. The white solid which had precipitated was filtered and extracted with absolute ethanol, leaving behind ammonium chloride. Cooling the ethanolic extract yielded 8.5 g. (43%) of white solid, m.p. 173–175°. A portion of this material was treated with silver carbonate in a boiling water solution. The excess silver was eliminated as the sulfide with

(19) S. Kushner *et al.*, *J. Org. Chem.*, **13**, 151 (1948).

(20) Brit. Patent 674,325 [*Chem. Abstr.*, **47**, 8780 (1953)].

(21) Kindly supplied by Parke, Davis and Co., Detroit Mich.

hydrogen sulfide and the filtrate evaporated to dryness to give white crystals, m.p. 151–153°. The same nitrile has been hydrolyzed with barium hydroxide, m.p. 151–151.5°[22]

5-Chloro-7-[bis-(2-carbethoxyethyl)aminomethyl]-8-quinolinol dihydrochloride (VII). (a). *By the hydrolysis of* VI. Ten grams (0.032 mole) of 5-chloro-7-[bis-(2-cyanoethyl)-aminomethyl]-8-quinolinol (VI) was dissolved in 75 ml. of concd. hydrochloric acid and the solution allowed to stand at room temperature for 24 hr. The water and excess acid were removed at the water pump, and the residue was treated with absolute ethanol. Insoluble ammonium chloride was removed by filtration and the filtrate was heated on the steam bath *in vacuo*, while from time to time an additional amount of ammonium chloride was removed from solution. When a yellow solid first appeared, the solution was heated to boiling at atmospheric pressure, filtered and allowed to cool. The yellow crystals which formed were filtered and recrystallized from ethanol, m.p. 158–159°. Recrystallization of a second crop increased the yield to 10.2 g. (67%).

Anal. Calcd. for $C_{20}H_{25}ClN_2O_5 \cdot 2HCl$: C, 49.85; H, 5.65; N, 5.82. Found: C, 49.79; H, 5.47; N, 5.73.

(b) *From β,β'-iminodipropionic acid.* A solution of 2.64 g. (0.015 mole) of 5-chloro-8-quinolinol, 0.44 g. (0.015 mole) of paraformaldehyde, and 2.9 g. (0.015 mole) of β,β'-iminodipropionic acid hydrochloride in 50 ml. of 95% ethanol was heated at reflux for 5 hr. The volume of the filtrate was reduced and made definitely acidic with a saturated ethanolic solution of hydrogen chloride. Cooling the resulting solution in the refrigerator gave a yellow crystalline solid, m.p. 140–152°. After recrystallization from absolute ethanol, 0.5 g. (9%) of the yellow solid remained, m.p. 154–156°. Admixture with a sample obtained by the foregoing procedure failed to depress the melting point.

(c) *From diethyl β,β'-iminodipropionate.* An ethanolic solution of 4.5 g. (0.025 mole) of 5-chloro-8-quinolinol, 0.75 g. (0.025 mole) of paraformaldehyde, and 5.4 g. (0.025 mole) of diethyl β,β'-iminodipropionate[23] was heated at reflux for 2 hr. The solvent was removed at the water pump and the residue dissolved in ether. Anhydrous hydrogen chloride passed through the ether solution precipitated a yellow solid, m.p. 141–147°. Recrystallization from *ethanol yielded 9 g.* (79%) of product, m.p. 155–157°, which did not depress the melting point of the material obtained in (a).

5-Chloro-7-(2-hydroxyethylaminomethyl)-8-quinolinol (X). An ethanolic solution of 18 g. (0.1 mole) of 5-chloro-8-quinolinol, 3 g. (0.01 mole) of paraformaldehyde, and 6.1 g. (0.01 mole) of ethanolamine was heated on the steam bath for about 15 min. when a yellow solid began to precipitate. Heating was continued for about another 30 min. and the reaction mixture was cooled to room temperature. Filtration removed 18 g. (67%) of light yellow solid, m.p. 174–175°. Recrystallization from dimethylformamide raised the m.p. to 184–185°.

Anal. Calcd. for $C_{12}H_{13}ClN_2O_2$: C, 57.03; H, 5.18. Found: C, 57.12; H, 5.50.

N-(5-Chloro-β-hydroxy-7-quinolylmethyl)-N-(2-hydroxyethyl)dichloroacetamide (IX). A mixture of 2.5 g. (0.01 mole) of X and 20 ml. (an excess) of methyl dichloroacetate was allowed to stand at room temperature for 4 weeks. The volatile material was removed at the water pump and the residue crystallized from a dimethylformamide and water mixture in yielding 2.7 g. (75%) of a tan solid, m.p. 140–145°. After two recrystallizations from the same solvent mixture, 1.8 g. (50%) of white solid was obtained, m.p. 168–169°.

Anal. Calcd. for $C_{14}H_{13}Cl_3N_2O_3$: C, 46.24; H, 3.60. Found: C, 46.03; H, 3.67.

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(23) G. M. Kuettel and S. M. McElvain, *J. Am. Chem. Soc.*, **53**, 2692 (1931).

[CONTRIBUTION FROM THE LABORATORY OF PHARMACEUTICAL CHEMISTRY, THE UNIVERSITY OF KANSAS SCHOOL OF PHARMACY]

Amino- and Chloromethylation of 8-Quinolinol. Mechanism of Preponderant *ortho* Substitution in Phenols under Mannich Conditions[1a,b]

J. H. BURCKHALTER[2] AND ROBERT I. LEIB[3]

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The formation of a quasi six-membered chelate ring preceding carbon-carbon substitution is offered as an explanation of the fact that *ortho* substitution occurs more readily than *para* in the Mannich reaction with phenols. Aminomethylation and chloromethylation of 8-quinolinol have been shown to occur at different positions, 7 and 5, respectively. Mechanisms are offered in explanation of these facts. 7-Piperidinomethyl-8-quinolinol (I) and 5-chloromethyl-8-quinolinol hydrochloride (IX) have been converted to a number of derivatives of pharmacological interest

During a search for reactive intermediates to be used in the synthesis of further antiamebic 8-quinolinols,[4] it became necessary to establish the structures of products resulting from the amino- and chloromethylation of 8-quinolinol. The structures of Mannich bases[5] I and II had been tentatively assigned[6] upon the basis of a similarity of

(1)(a) Presented at the F. F. Blicke Symposium, Division of Medicinal Chemistry, American Chemical Society Meeting, New York, N.Y., September 1960. (b) Antiamebic Agents, VI. Paper V, *J. Org. Chem.*, **26**, 4070 (1961). Prior publication: W. L. Nobles, V. C. Stephens, L. Wei, and J. H. Burckhalter, *J. Am. Pharm. Assoc.*, **47**, 82 (1958).

(2) Present address: The University of Michigan, Ann Arbor, Mich.

(3) Extracted from the Ph.D. Thesis of Robert I. Leib, The University of Kansas, 1957. Present address: Monsanto Chemical Co., St. Louis 77, Mo.

(4) J. H. Burckhalter, V. C. Stephens, H. C. Scarborough, W. S. Brinigar, and W. E. Edgerton, *J. Am. Chem. Soc.*, **76**, 4902 (1954).

(5) Mannich reaction reviews: F. F. Blicke, *Org. Reactions*, **1**, 303 (1942); B. Reichert, *Die Mannich-Reaktion*, Springer-Verlag, Berlin, 1959; H. Hellmann and G. Opitz, *α-Aminoalkylierung*, Verlag Chemie, Weinheim, Germany, 1960.

(6) J. H. Burckhalter, F. H. Tendick, E. M. Jones, W. F. Holcomb, and A. L. Rawlins, *J. Am. Chem. Soc.*, **68**, 1894 (1946).