ion chelate complex previously postulated as intermediate in other pyridoxal-catalyzed reactions of amino acids.[5,10,11] Catalysis of other pyridoxal-dependent reactions by aluminum ions[5] contrasts with their inactivity in this system, and suggests that alternate reduction of the metal ion by the amino acid and its reoxidation by oxygen may be a feature of these reactions. However, as noted previously, aluminum ions catalyze oxidative deamination of glutamate by 4-nitrosalicyladehyde,[4] and since a reversible oxido–reduction of the aluminum ion seems unlikely, the factor of primary importance in these oxidative systems may be fixation of the hydrogen acceptor in close proximity to the pyridoxal–amino acid–metal chelate system. In this connection, the role of iron and copper complexes as reversible oxygen carriers in natural systems, and the similar chemical behavior of cobalt-containing chelates of salicylaldehyde,[12] suggests that valence changes in the metal ion during these reactions may not be obligatory.

Of several amines (pyridoxamine, benzylamine, phenylethylamine, tyramine, histamine, β-alanine, γ-aminobutyric acid) and diamines (ethylenediamine, putrescine) tested, only pyridoxamine was oxidized under conditions used for α-amino acids. When the concentration of reactants was increased ten-fold, ammonia was formed slowly from benzylamine (which may be considered as analogous in some respects to pyridoxamine), and the odor of benzaldehyde could be detected. Even at these concentrations, the other amines tested were not oxidized.

The reactions described herein are in net result the same as those carried out by the amino acid and the amine oxidases, all of which so far studied contain a riboflavin derivative as prosthetic group.[13] Some of these enzymes, *e.g.*, the *ophio*-L-amino acid oxidase and especially diamine oxide, are strongly inhibited by carbonyl reagents, indicating the probable involvement in their action of a carbonyl compound.[13] Microbiological assays of suitable hydrolysates of rattlesnake venom and of concentrates of *ophio*-L-amino acid oxidase prepared therefrom as described by Singer and Kearney[14] have failed, however, to reveal the presence of pyridoxal in amounts that would indicate a functional role for it in this enzyme. Whether pyridoxal plays such a role in any of the amine oxidases, or whether its activity in catalyzing amine oxidation is a chemical property which nature failed to utilize, remains to be established.

(10) J. Baddiley, *Nature*, **170**, 711 (1952).

(11) Pfeiffer (ref. 2) postulated oxidation of amino acid esters through the analogous chelates formed with salicylaldehyde by a mechanism not involving valence changes in the metal ion.

(12) A. E. Martell and M. Calvin, "Chemistry of Metal Chelate Compounds," Prentice-Hall, Inc., New York, N. Y., 1952, p. 337.

Experimental

Quantitative Procedures.—Pyridoxal was determined spectrophotometrically, and keto acids colorimetrically after conversion to their 2,4-dinitrophenylhydrazones by methods described previously.[6] Reactions at *p*H 4.0 were carried out in 0.05 *M* acetate buffer in sealed tubes; those at *p*H 9.6 in the presence of 0.05 *M* sodium bicarbonate and 0.025 *M* sodium carbonate. In the latter case, 2-ml. aliquots of the reaction mixtures were connected to the acid-containing absorption tubes throughout the heating period to prevent losses of ammonia at the high *p*H used. Ammonia was determined by aeration from alkalinized samples into acid followed by Nesslerization.[9] Other experimental details are given with the tables.

(13) H. A. Krebs, in J. B. Sumner and K. Myrback, "The Enzymes," Vol. 2, pt. 1, Academic Press, Inc., New York, N. Y., 1951, p. 499; E. A. Zeller, *ibid.*, p. 536. Riboflavin was tested as a possible hydrogen acceptor in the presence and absence of pyridoxal in reaction mixtures containing amino compounds not oxidized by the copper–pyridoxal system. No significant deamination was observed except with ethylenediamine, where addition of riboflavin promoted ammonia production even in the absence of pyridoxal.

(14) T. P. Singer and E. B. Kearney, *Arch. Biochem. Biophys.*, **29**, 190 (1950).

AUSTIN, TEXAS

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

Antiamebic Agents. III.[1] Basic Derivatives of Chloro-8-quinolinols

BY J. H. BURCKHALTER, VERLIN C. STEPHENS, HOMER C. SCARBOROUGH, JR., WILLIAM S. BRINIGAR AND WILLIAM H. EDGERTON

RECEIVED APRIL 7, 1954

Fifteen new compounds related to the amebacidal agent, 5-chloro-7-diethylaminomethyl-8-quinolinol (I), have been synthesized by means of the Mannich reaction. Observations have been made concerning the instability of some compounds of this type, and the nature of certain by-products has been determined. In selecting the compounds to be prepared for testing against amebiasis, consideration was given to the probable influence of the groups introduced upon each of the two characteristic types of infection, namely, intestinal and extra-intestinal amebiasis. Two of the compounds appeared to be as effective as I against intestinal infections in dogs.

Poorly absorbed drugs such as Diodoquin (5,7-diiodo-8-quinolinol) are known to be clinically effective against intestinal amebiasis,[2] whereas certain drugs of the antimalarial type such as Atabrine, chloroquine and Camoquin, which are absorbed systemically, have been indicated to be clinically effective against hepatic amebiasis.[2,3] It was with this knowledge in mind that 5-chloro-7-diethylaminomethyl-8-quinolinol (I) was synthesized,[4] and it was considered that an intestinal amebacide, 5-chloro-8-quinolinol,[5] might be con-

(1) Previous publication, W. H. Edgerton and J. H. Burckhalter, THIS JOURNAL, **74**, 5209 (1952).

(2) H. H. Anderson and B. L. Hansen, *Pharmacological Revs.*, **2**, 402 (1950).

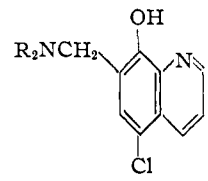
(3) P. E. Thompson and J. W. Reinertson, *Am. J. Trop. Med.*, **31**, 715 (1951).

(4) J. H. Burckhalter and W. H. Edgerton, THIS JOURNAL, **73**, 4837 (1951).

(5) Office of Publication Board Reports, Dept. of Commerce, Washington, D. C., PB 95022, 1948, pp. 85–95.

TABLE I

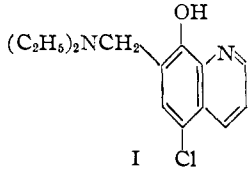
5-CHLORO-7-AMINOMETHYL-8-QUINOLINOLS



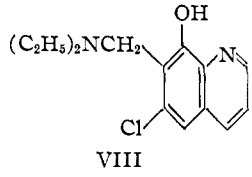
	R_2N	M.p., °C.	Formula	Ionic chloride, % Calcd.	Found
II	Dimethylamino	234 d.[a]	$C_{12}H_{13}ClN_2O\cdot HCl$	12.98	12.86
III	Ethyl-β-hydroxyethylamino	182 d.[a]	$C_{14}H_{17}ClN_2O_2\cdot 2HCl$	20.05	19.94
IV	Di-β-hydroxyethylamino	177 d.[b]	$C_{14}H_{17}ClN_2O_3\cdot 2HCl$	19.18	18.92
V	1-Pyrrolidyl	228 d.[a]	$C_{14}H_{15}ClN_2O\cdot HCl$	12.19	12.38[e]
VI	1-Piperidyl	224 d.[a]	$C_{15}H_{17}ClN_2O\cdot HCl$	11.32	11.25
VII	4-Morpholinyl	110[c]	$C_{14}H_{15}ClN_2O_2$[d]		

Recrystallizing solvents: [a] Alcohol. [b] Alcohol–methyl alcohol containing hydrogen chloride. [c] Once more from alcohol and twice from Skellysolve B. [d] *Anal.* Calcd.: C, 60.32; H, 5.42. Found: C, 60.02; H, 5.37. [e] *Anal.* Calcd.: C, 56.20; H, 5.39. Found: C, 56.49; H, 5.49.

verted to an hepatic amebacide through the introduction of the basic diethylaminomethyl group. Such a result was not forthcoming, for compound I possesses only slight oral or parenteral activity in the hamster. Preliminary studies indicate this poor activity resulted from too rapid excretion or degradation in the tissues.[6] However, animal studies have shown that I actually is more active as an intestinal amebacide than the well-known iodine-containing 8-quinolinol drugs.[6]



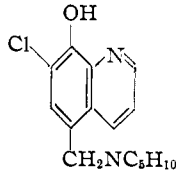
I



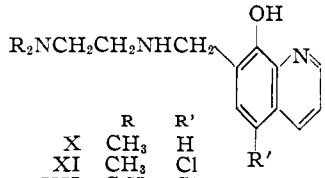
VIII

In searching for compounds more effective than I, certain bromo and iodo relatives were made.[4] Also, a number of 5-alkyl and 5-acyl analogs of I have been made,[1] but none are as good. We wish now to record additional chemical variants which have been prepared in attempts to increase the amebacidal activity of I or to convert the compounds to hepatic amebacides.

Six of the new compounds are close analogs of I. They may be represented by structure I where the diethylamino is replaced by six different substituted amino groupings (Table I). VIII has been made because it is a close isomeric relative of I and because the piperidyl analog showed appreciable activity.[4,6] IX was prepared in order to provide an isomeric chloro-8-quinolinol which contains the chloro group on the benzo ring.



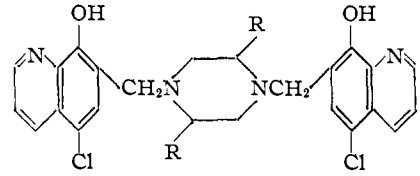
IX



	R	R'
X	CH_3	H
XI	CH_3	Cl
XII	C_2H_5	Cl

In considering the unexpected increase of intestinal amebacidal activity by the introduction of a basic grouping,[4] it was decided to introduce a second basic grouping into the type I molecule, and so compounds X, XI and XII were prepared. It was considered that such basic side chains, similar to those of the hepatic amebacides, might result in new types of effective hepatic amebacides.

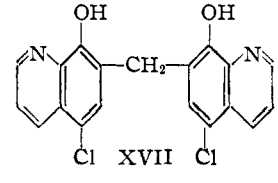
Another structural change in I, with the objective of alteration of physical properties and absorbability, was made possible through the synthesis of XIII and XIV, structures which possess two biologically important 5-chloro-8-quinolinol residues joined through a basic piperazine ring. As model experiments prior to the synthesis of XIII and XIV, β-naphthol was used in place of 5-chloro-8-quinolinol to give the non-heterocyclic analogs XV and XVI.



	R
XIII	H
XIV	CH_3

The preparative method used for compounds I–XVI, inclusive, involved condensation between a phenol, which was usually 5-chloro-8-quinolinol, paraformaldehyde and an appropriate aliphatic amine.[7] Under each heading in the Experimental section, special conditions are stated when necessary for the proper isolation of a particular compound.

Small amounts of a high-melting insoluble by-product usually were isolated from each reaction mixture. For example, where 5-chloro-8-quinolinol was involved, it was assumed that the insoluble product was 7,7′-methylene-bis-(5-chloro-8-quinolinol) (XVII). Elementary analysis and independent synthesis from 5-chloro-8-quinolinol and paraformaldehyde in glacial acetic acid confirmed this structure.



XVII

(6) Private communication: Dr. P. E. Thompson, Parke, Davis and Company, Detroit, Michigan.

(7) This method is commonly referred to as the Mannich reaction. See F. F. Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, Chapter 10.

In attempting to explain the isolation of bis compound XVII during the preparation of such products as I, it was considered that XVII might be formed from a degradation of I. To test this possibility, the plan was to heat the free base of I in alcohol in simulation of the preparative conditions for I. Neutralization of an aqueous solution of the dihydrochloride of I gave only a tar which could not be handled easily. Hence, neutralization was carried out in the presence of ether, and when the ether was replaced with alcohol, the heated mixture was found to yield some of the bis compound XVII.

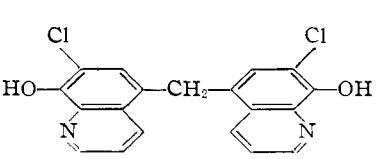
To test the possibility that XVII might also be formed directly from 5-chloro-8-quinolinol and paraformaldehyde during the preparation of I, diethylamine was replaced with triethylamine, which cannot undergo the Mannich reaction. It was found that some XVII was also produced in this medium.

While it cannot be stated with certainty whether one or both of these processes leading to XVII is operative during the preparation of I, it is apparent that they do not curtail seriously the yields of I.

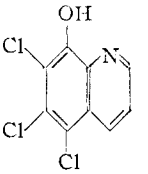
It has been stated that diethylamine appears to undergo the Mannich reaction less readily than dimethylamine or piperidine.[7,8] However, available evidence suggests that diethylamine will undergo easily the reaction,[9] but the products are often less stable to heat than those of its close analogs.[10] Further evidence is afforded by the ready isolation of the piperidyl analog of VIII[4] under conditions which have now been observed to cause a decomposition of VIII to diethylamine and a polymeric substance.[11] For the isolation of VIII, a minimum of heat was employed during and following its formation. Preparation of the "Mannich reagent"[9] from paraformaldehyde, diethylamine and methanol was initiated by warming, after which the reaction resulting in the formation of diethylaminomethyl methyl ether and methylene-bis-diethylamine[10] took place exothermically. This "Mannich reagent" mixture then was treated at room temperature with the reactive 6-chloro-8-quinolinol for the formation of VIII without perceptible thermal change.

The structure of VIII, while it has not been proved, has been assigned by reference to the same preparative method for the analogous 2-diethylaminomethyl-1-naphthol.[9] Also, an indication that VIII is the correct structure rather than the isomeric 6-chloro-5-diethylaminomethyl-8-quinolinol is the fact that the product isolated was insoluble in 5% alkali wash solution. Any of the isomer with its unsubstituted position adjacent to the phenolic hydroxyl might be expected to have been removed by the alkali wash.[12] That the yield of VIII was no greater than 30% is not surprising in view of the necessary mild conditions of the reaction. Also, nearly 30% of sublimed starting 6-chloro-8-quinolinol was recovered, and ready polymer formation in this reaction has been demonstrated (*vide supra*).

Further evidence of the lability of certain "Mannich phenols" is offered by our inability to isolate the diethylamino analog of IX by a standard procedure (*e.g.*, method for III) which readily gave IX. During the period of reflux, the insoluble 5,5'-methylene-bis-(7-chloro-8-quinolinol) (XVIII), an isomer of XVII, gradually formed in appreciable amounts.



XVIII



XIX

5,6-Dichloro-8-quinolinol was desired as an intermediate for the preparation of the 7-diethylaminomethyl derivative. Such a product, which also is the 6-chloro derivative of I, would be of considerable interest as an amebacidal agent, and its preparation was attempted several times using 6-chloro-8-quinolinol and varying amounts of chlorine in chloroform or alcohol as a solvent. Large excesses of chlorine gave 5,6,7-trichloro-8-quinolinol (XIX) in good yield, and less chlorine gave a mixture from which some XIX and some starting material was isolated with difficulty. None of the desired product was obtained using variable amounts of chlorine.

Pharmacological Results.[13]—Some of the compounds which had shown interesting amebacidal activity in the rat[14] approaching that of I[4] were selected for trial against amebic colitis in dogs.[15] Against the latter infection, II was less active than I, IV was about one-half as active but one-half as toxic as I, while V, VI and XIX appeared to be about as effective as I. In rats, compounds II, III, IV, V, VI, VII, VIII, IX and XIX were less active or no better than I, while X, XI and XVII were inactive or of a low order of activity. The other compounds prepared have not yet been tested against intestinal amebiasis. None of the compounds have yet been tried against the hepatic infection.

Acknowledgments.—The authors are gratetul to Parke, Davis and Company and the American Foundation for Pharmaceutical Education for fellowship funds which made the studies possible.

Experimental

5-Chloro-7-dimethylaminomethyl-8-quinolinol Monohydrochloride (II).—A mixture of 4.5 g. (0.025 mole) of 5-chloro-8-quinolinol, 1.2 g. (0.04 mole) of paraformaldehyde and 2.1 g. (0.026 mole) of dimethylamine hydrochloride in

(8) G. F. Grillot and W. T. Gormley, THIS JOURNAL, **67**, 1968 (1945); C. E. Dalgliesh, *ibid.*, **71**, 1697 (1949).

(9) *E.g.*, J. H. Burckhalter, *et al.*, *ibid.*, **68**, 1894 (1946).

(10) F. F. Blicke and J. H. Burckhalter, *ibid.*, **64**, 451 (1942), found that β-diethylaminopropiophenone can be formed easily, contrary to the statement of others, but it is difficult to isolate because of its ready decomposition to acrylophenone and diethylamine.

(11) That a polymer might be expected from decomposition of VIII rather than a bis compound isomeric with XVII and XVIII is explainable on the basis of an activated open position in VIII which will allow polymerization, while no such position is available in I, IX, XVII and XVIII.

(12) Note that 6-diethylaminomethyl-2-phenylphenol was separated from 4-diethylaminomethyl-2-phenylphenol by this means; J. H. Burckhalter, THIS JOURNAL, **72**, 5309 (1950).

(13) Furnished through the courtesy of Dr. Paul E. Thompson, Research Laboratories, Parke, Davis and Co., Detroit, Mich.

(14) P. E. Thompson, *et al.*, *Am. J. Trop. Med.*, **30**, 203 (1950).

(15) P. E. Thompson and Betty L. Lilligren, *ibid.*, **29**, 323 (1949).

100 ml. of alcohol was heated under reflux for 90 minutes. A small amount of insoluble solid was removed by filtration of the cooled solution. The filtrate was evaporated until the tan colored crystalline product began to separate from solution; 5.1 g. (75% yield), m.p. 230–232° dec. (see Table I).

5-Chloro-7-(ethyl-β-hydroxyethylaminomethyl)-8-quinolinol Dihydrochloride (III).—A mixture of **4 g.** (0.022 mole) of 5-chloro-8-quinolinol, 1 g. (0.033 mole) of paraformaldehyde, 2 g. of ethyl-β-hydroxyethylamine and 100 ml. of alcohol was heated under reflux for 90 minutes. The solvent was removed from the mixture by distillation and the residue dissolved in ether. The filtered solution was treated with an excess of hydrogen chloride, and a yellow gummy solvent was precipitated. Recrystallized from alcohol, it amounted to 6 g. (80% yield), m.p. 179–182° dec.

5-Chloro-7-(di-β-hydroxyethylaminomethyl)-8-quinolinol Dihydrochloride (IV).—A mixture of 9 g. (0.05 mole) of 5-chloro-8-quinolinol, 1.5 g. (0.05 mole) of paraformaldehyde and 5 ml. (0.05 mole) of di-β-hydroxyethylamine in 500 ml. of alcohol was heated under reflux for 90 minutes. The solution was filtered, concentrated to about 100-ml. volume and cooled, and excess hydrogen chloride was introduced. The precipitated yellow product weighed 13 g. (70% yield), m.p. 167–169° dec. It was recrystallized best by mixing first with absolute alcohol, introducing more hydrogen chloride and then adding a little methanol while heating.

Recrystallization of the compound from alcohol without the addition of excess hydrogen chloride resulted in the removal of one mole of hydrogen chloride and the production of the light pink colored **monohydrochloride of IV**, m.p. 161–162°. Results of repeated analyses suggest that a small quantity of the dihydrochloride (see Table I) is not removed by recrystallization.

Anal. Calcd. for $C_{14}H_{17}ClN_2O_3 \cdot HCl$: C, 50.46; H, 5.44; Cl (ionic), 10.64. Found: C, 49.78; H, 5.64; Cl, 11.08.

5-Chloro-7-(1-pyrrolidylmethyl)-8-quinolinol Monohydrochloride (V).—When using pyrrolidine in the procedure of III, the ether solution of the product was treated with a stream of hydrogen chloride until the solution was just acidic to *p*H paper. The crude tan solid was collected on a filter and dried; yield 62 g. (92%), m.p. 221–222° dec.

5-Chloro-7-(1-piperidylmethyl)-8-quinolinol Monohydrochloride (VI).—Using piperidine hydrochloride in the procedure of II and recrystallizing the product from alcohol, a yellow crystalline solid was obtained in 80% yield, m.p. 222–224°.

5-Chloro-7-(4-morpholinylmethyl)-8-quinolinol (VII).—When using 4-morpholine in the procedure of IV, the filtered reaction mixture was concentrated to a thick residue which solidified. Crystallized from alcohol, 21.7 g. (78% yield) of product was obtained, m.p. 100–102°.

A small sample of VII was dissolved in alcohol and hydrogen chloride passed into the solution to precipitate the yellow **dihydrochloride**, m.p. 238–242° dec. (darkening at 190°). It was recrystallized from 80% alcohol, m.p. 241–244° dec.

Anal. Calcd. for $C_{14}H_{15}ClN_2O_2 \cdot 2HCl$: C, 47.81; H, 4.87. Found: C, 47.60; H, 5.06.

6-Chloro-7-(diethylaminomethyl)-8-quinolinol Dihydrochloride (VIII).—A mixture of 0.6 g. (0.02 mole) of paraformaldehyde and 2.4 ml. (0.02 mole) of diethylamine in 50 ml. of methyl alcohol was warmed on a steam-bath until a clear solution was obtained. To this warm solution was added a warm solution of 3.5 g. (0.02 mole) of 6-chloro-8-quinolinol[16] in 150 ml. of methyl alcohol. The mixture was allowed to stand overnight without further heating, after which it was concentrated *in vacuo* without heat to a brown oil. An ether solution of the oil was extracted twice with cold 5% sodium hydroxide solution. The ether layer was washed twice with water and then dried over sodium sulfate. The solvent was removed by evaporation and the remaining oil dissolved in acetone. The addition of dry hydrogen chloride resulted in the formation of 2 g. (30% yield) of yellow solid, m.p. 174–177° dec. Two recrystallizations from acetone–methyl alcohol did not change the melting point.

Anal. Calcd. for $C_{14}H_{17}ClN_2O \cdot 2HCl$: Cl (ionic), 21.00. Found: Cl, 21.01.

From the alkaline extract there was recovered by neutralization and sublimation 1 g. of starting material, 6-chloro-8-quinolinol.

(16) C. Hoffmann, *Bull. soc. chim.*, [5] **14**, 969 (1947).

7-Chloro-5-(1-piperidylmethyl)-8-quinolinol Dihydrochloride (IX).—Using 7-chloro-8-quinolinol[17] and piperidine with methanol as the solvent in the procedure of III, a yield of 77% of crude yellow colored product was obtained, m.p. 209–213°. Recrystallization was difficult, but purification was achieved by dissolving the solid in methanol, concentrating the solution and adding acetone nearly to the saturation point, whereupon crystallization occurred, m.p. 225–227°.

Anal. Calcd. for $C_{15}H_{17}ClN_2O \cdot 2HCl$: Cl (ionic), 20.28. Found: Cl, 20.34.

7-(β-Dimethylaminoethylaminomethyl)-8-quinolinol Dihydrochloride (X).—Using β-dimethylaminoethylamine and 8-quinolinol in the procedure of III and after the removal of the alcohol, the residue was dissolved in an acetone–ether mixture and dried with potassium carbonate. Hydrogen chloride gas in excess was bubbled into the filtered solution. The solid was dried at 100° for 36 hours giving over 90% yield of a hydrated product, m.p. 175–185°. Following a recrystallization from absolute alcohol, the yield was reduced to 72% of yellow powder, m.p. 245–246° dec.

Anal. Calcd. for $C_{14}H_{19}N_3O \cdot 2HCl$: C, 52.84; H, 6.65; Cl (ionic), 22.28. Found: C, 52.84; H, 6.73; Cl, 22.08.

5-Chloro-7-(β-dimethylethylaminomethyl)-8-quinolinol Dihydrochloride (XI).—Using β-dimethylaminoethylamine in the procedure of III, there was obtained a 70% yield of an orange crystalline dihydrochloride hydrate (after recrystallization from methyl alcohol), m.p. 206–208°. After recrystallization from absolute alcohol, the crystals were nearly white and melted at 233–235° dec.

Anal. Calcd. for $C_{14}H_{18}ClN_3O \cdot 2HCl$: C, 47.67; H, 5.72; N, 11.91; Cl (ionic), 20.11. Found: C, 47.54; H, 5.71; N, 11.83; Cl, 20.37.

5-Chloro-7-(β-diethylaminoethylaminomethyl)-8-quinolinol Dihydrochloride (XII).—Using β-diethylaminoethylamine in the procedure of III, and recrystallizing the crude product from 95% alcohol, a yield of 55% of yellow colored salt was obtained, m.p. 162–163°.

Anal. Calcd. for $C_{16}H_{22}N_3O \cdot 2HCl \cdot 2H_2O$: C, 46.11; H, 6.77. Found: C, 46.22; H, 6.73.

1,4-Bis-(5-chloro-8-hydroxy-7-quinolylmethyl)-piperazine (XIII).—A mixture of 18 g. (0.1 mole) of 5-chloro-8-quinolinol, 3 g. (0.1 mole) of paraformaldehyde, 9.6 g. (0.05 mole) of piperazine hexahydrate and 250 ml. of alcohol was heated under reflux for two hours. When concentrated and cooled, the solution gave 11.6 g. (50% yield) of light yellow solid, m.p. 249–250° dec. Recrystallized once from quinoline and twice from pyridine, it melted at 256–257° dec.

Anal. Calcd. for $C_{24}H_{22}Cl_2N_4O_2$: C, 61.40; H, 4.73. Found: C, 61.85; H, 4.70.

1,4-Bis-(5-chloro-8-hydroxy-7-quinolylmethyl)-2,5-dimethylpiperazine (XIV).—Using *trans*-2,5-dimethylpiperazine[18] in the procedure of XIII, 42% yield of white powder was obtained, m.p. 246–247°. Recrystallized from quinoline and then pyridine, it melted at 249–250° dec.

Anal. Calcd. for $C_{26}H_{26}Cl_2N_4O_2$: C, 62.79; H, 5.27. Found: C, 63.03; H, 5.44.

1,4-Bis-(2-hydroxy-1-naphthylmethyl)-piperazine (XV).—Using β-naphthol in the procedure of XIII, 80% yield of white solid product was obtained, m.p. 242–243° dec. After three crystallizations from benzene, it melted at 254–255° dec.

Anal. Calcd. for $C_{26}H_{24}N_2O_2$: C, 78.36; H, 6.08. Found: C, 78.59; H, 6.63.

1,4-Bis-(2-hydroxy-1-naphthylmethyl)-2,5-dimethylpiperazine (XVI).—Using β-naphthol in the procedure of XIV, 87% yield of white crystalline product was obtained, m.p. 210–211° dec. After three recrystallizations from benzene, it melted at 216–217° dec.

Anal. Calcd. for $C_{28}H_{30}N_2O_2$: C, 78.82; H, 7.09. Found: C, 78.55; H, 7.04.

7,7'-Methylene-bis-(5-chloro-8-quinolinol) (XVII). (A).—The 1.5 g. of solid by-product, obtained by filtration of the reaction mixture during the preparation of IV, was recrystallized from phenyl ether to give light tan colored

(17) A. Albert and D. Magrath, *Biochem. J.*, **41**, 534 (1947).

(18) Through the courtesy of Carbide and Carbon Chemicals Corporation. The *trans* structure was suggested by work of H. W. Stewart, *et al.*, *J. Org. Chem.*, **18**, 1478 (1953).

needles, m.p. 303–305° dec. (further recrystallization gave a much darker product, m.p. 306–307° dec.).

Anal. Calcd. for $C_{19}H_{12}Cl_2N_2O_2$: C, 61.47; H, 3.26. Found: C, 61.47; H, 3.36.

(B).—A solution of 9 g. (0.05 mole) of 5-chloro-8-quinolinol and 0.75 g. (0.025 mole) of paraformaldehyde in 100 ml. of acetic acid was heated under reflux for 90 minutes. Then, 0.5 g. more of paraformaldehyde was added and heating continued for about four hours. The solution was diluted with water and 6.5 g. (70% yield) of product was collected by filtration, m.p. 304–305° dec. with no depression upon admixture with the analytical sample from A.

(C).—A mixture of 5.4 g. (0.03 mole) of 5-chloro-8-quinolinol, 0.9 g. (0.03 mole) of paraformaldehyde, 3.1 g. (0.03 mole) of triethylamine and 100 ml. of alcohol was heated at reflux. After 20 minutes of heating a precipitate was noted and the quantity increased as the heating continued. At the end of two hours, less than a gram of XVII was obtained, m.p. 285–290° dec. After washing with alcohol, it melted at 297–302° and was not depressed by admixture with XVII (A).

(D).—About a gram of 5-chloro-7-diethylaminomethyl-8-quinolinol (I) dihydrochloride[4] was dissolved in 20 ml. of water. After the mixture had been covered with an equal volume of ether, it was shaken with an excess of ammonia. The ether solution was decanted and to it was added 10 ml. of alcohol. The resulting solution was evaporated until the volume was only about 5 ml. Ten milliliters of alcohol was added and the solution was heated at reflux for 90 minutes. A few milligrams of tan solid was collected on a funnel, m.p. 301–302° dec., undepressed by admixture with XVII (C).

5,5'-Methylene-bis-(7-chloro-8-quinolinol) (XVIII).—During an attempt to apply the procedure of III to the preparation of the diethylamino analog of IX, from the reaction mixture there separated 2.1 g. of light tan colored solid, m.p. 309–310° dec. Recrystallized from phenyl ether and then from xylene, it melted at 310–311° dec.

Anal. Calcd. for $C_{19}H_{12}Cl_2N_2O$: C, 61.47; H, 3.26. Found: C, 61.76; H, 3.62.

An appreciable amount of what was apparently the hygroscopic hydrochloride (dec. > 165°) of the desired analog of IX was isolated, but it could not be purified readily.

5,6,7-Trichloro-8-quinolinol (XIX).—Solution of 4.5 g. (0.025 mole) of 6-chloro-8-quinolinol[16] in 250 ml. of absolute alcohol was effected by warming. Then, at room temperature, a stream of chlorine was bubbled into the solution for 40 minutes. After 12 hours, 4.5 g. of yellow solid was collected on a filter, m.p. 215–218°. Concentration of the filtrate and neutralization with dilute ammonia gave 2.5 g. of white solid, m.p. 217–219°. The first crop was slightly acidic and it lost its yellow color when suspended in water. Recrystallization from alcohol–acetic acid gave 6 g. (96% yield) of crystalline product, m.p. 219–220°. Two recrystallizations from acetic acid elevated the melting point only to 220–220.5°.

Anal. Calcd. for $C_9H_4Cl_3NO$: C, 43.50; H, 1.62. Found: C, 43.72; H, 2.04.

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[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

The Constitution of Sapote Gum. III. A Structural Evaluation

BY E. V. WHITE[1]

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Previous communications have dealt with the monosaccharide components of sapote gum. The present study is concerned with that portion of the macromolecule which is extremely resistant to hydrolysis. This fraction is composed, for the most part, of aldobiouronic acid residues and can be separated from the methanolysis products of the methyl ether derivative as a mixture of alkylated aldobiosiduronates. Evidence is given to indicate the presence of two compounds of this type. The glycosidic linkage is evidently the same in each instance because complete methylation of the mixture, after reduction of the methoxycarbonyl group to the primary alcohol function, provides the anomeric forms of a single disaccharide. Hydrolysis of the latter furnishes equimolar parts of 2,3,4,6-tetra-O-methyl-D-glucose and 3,4-di-O-methyl-D-xylose thus demonstrating a 1–2-glycosidic linkage in the original aldobiosiduronates. This new information, together with previous data, permits some description of the molecular architecture of the sapote gum polysaccharide.

The previous communications[2a,b] in this series have dealt with some of the products formed upon methanolysis of sapote gum methyl ether. The glycosidic components of the methanolysate proved to be derived from 3-O-methyl-D-xylose, 2,3,4-tri-O-methyl-D-xylose, 2,3,4-tri-O-methyl-L-arabinose and other compounds of glycosiduronate character. The arabinose component evidently arises from a novel structure in the polysaccharides and reveals for the first time the natural occurrence of the arabopyranose unit in these macromolecules.[3] This finding, so far as it concerns the polysaccharides, removes one objection to the hypothesis that D-galactose and L-arabinose are biosynthetically interconvertible since the improbable shift in ring structure accompanying the conversion from D-galactopyranose to L-arabofuranose is not, of necessity, a requirement.[4]

The glycosiduronate fraction of the methanolysis sirup has been more difficult to investigate because of the extreme resistance of the glycosidic linkage in the uronic acids to hydrolysis. This fraction is, for the most part, of aldobiosiduronate character. Its further treatment with methanolic hydrogen chloride eventually provided a sirup from which, by the usual methods, methyl (methyl 3,4-di-O-methyl-D-glucopyranosid)-uronate was isolated in its anomeric forms as one of the components. The crystalline acid was obtained therefrom after removal of the ester and aglycone groups by hydrolysis. Certain of the uronic acid residues of sapote gum are therefore resident in the internal structure of the macromolecule and are joined therein at C-1 and C-2 to other carbohydrate units. The latter type of glycosidic union has not been reported previously for uronic acid units occurring in the polysaccharides, although Lythgoe and Trippett[5] have recorded its occurrence in the carbohydrate component of glycyrrhinic acid. Prolonged aqueous hydrolysis of the glycosiduronate fraction has furnished 3-O-methyl-D-xylose as the only sugar component.

(1) University of Toronto, Toronto 5, Canada.

(2) (a) E. V. White, THIS JOURNAL, **75**, 257 (1953); (b) **75**, 4692 (1953).

(3) The isolation of 3-O-(β-L-arabopyranosyl)-L-arabinose from larch ε-galactan and from peach and cherry gum has now been reported by J. K. N. Jones, *J. Chem. Soc.*, 1672 (1953), and by P. Andrews, D. H. Ball and J. K. N. Jones, *ibid.*, 4090 (1953), respectively.

(4) E. L. Hirst, *ibid.*, 70 (1942).

(5) B. Lythgoe and S. Trippett, *ibid.*, 1983 (1950).