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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(22) J. H. Ford, *J. Am. Chem. Soc.*, **67**, 876 (1945).

(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]

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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.

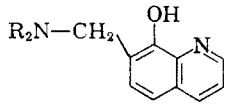
(3) Extracted from the Ph.D. Thesis of Robert I. Leib, The University of Kansas, 1957. Present address: Monsanto Chemical Co., St. Louis 77, Mo.

(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.

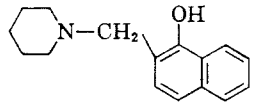
(6) J. H. Burckhalter, F. H. Tendick, E. M. Jones, W. F. Holcomb, and A. L. Rawlins, *J. Am. Chem. Soc.*, **68**, 1894 (1946).

preparative method to that of III and the similarity of structures of the starting materials, 8-quinolinol and 1-naphthol. The structure of III has been un-



I. $R_2N- = $ 

II. $R_2N- = (C_2H_5)_2N-$

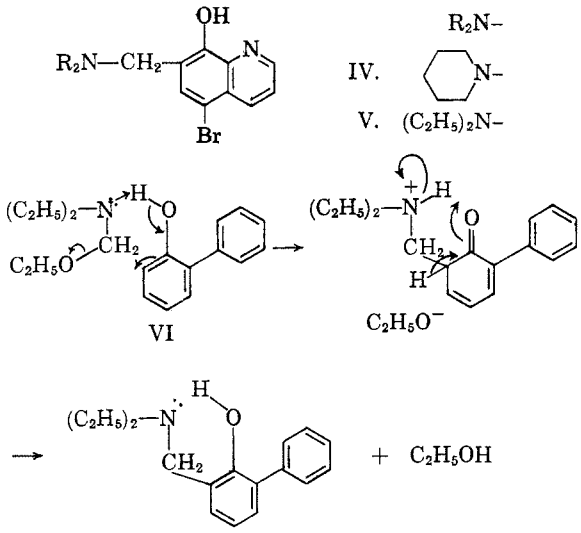


III

equivocally established.[7] While a definite product results from aminomethylation of 8-quinolinol, chloromethylation has led to various substances of uncertain identity.[8-11] Fernando and co-workers obtained a compound to which they assigned the structure of 7-chloromethyl-8-quinolinol, but no proof of structure was offered.[10] When we found that treatment of this product with piperidine failed to give I but rather led to an isomeric base, it was suspected that chloromethylation of 8-quinolinol occurs at the 5-position in contrast to aminomethylation, and it was decided to investigate the matter more thoroughly, offering, if possible, explanations for the products formed.[12]

First, as a means of confirming its structure, I as the hydrobromide was brominated in acetic acid solution to give 5-bromo-7-piperidinomethyl-8-quinolinol (IV), which proved to be identical on the basis of infrared spectra and mixed melting point determination with the same product obtained from authentic 5-bromo-8-quinolinol[13] by means of the Mannich reaction. Likewise, II[14] was brominated to give V which proved to be identical with V which had been previously prepared by the Mannich reaction.[15]

The question arises as to why only the products of *ortho* aminomethylation were isolated in the cases of 8-quinolinol and 1-naphthol. Similarly, there is the question of why there is a preponderance (42% yield) of *ortho*- substituted product from 2-phenylphenol and less than a third (13% yield) as much of the *para*- isomer.[16] An explanation of the



IV. R_2N-

V. $(C_2H_5)_2N-$

VI

fact of preponderant *ortho*- substitution is offered in a quasi six-membered chelate ring as pictured, for example, in VI. Hydrogen bonding between the phenolic hydrogen and the basic nitrogen of the Mannich reagent, diethylaminomethyl ethyl ether,[17] would be expected to precede the formation of the chelated intermediate which would then bring the reactive methylene group into position for electrophilic attack on the aromatic ring in the *ortho*- position.

It is known that an unsubstituted *ortho*- position is not obligatory in the formation of phenolic Mannich bases.[18] However, it is clear that an initial hydrogen bonding would increase the likelihood of *ortho*- substitution in preference to *para*.

Only a monosubstituted product was isolated from aminomethylation of 8-quinolinol under the usual conditions. Thus, 5,7-bis(piperidinomethyl)-8-quinolinol (XV) could not be prepared by means of the Mannich reaction. In explanation of these facts, six-membered chelate rings of I and III, formed through hydrogen bonding, would reduce the acidity of the compounds and, together with hindrance by the peri positions, would prevent Mannich disubstitution. The fact that 7-chloro-8-quinolinol reacts to yield 7-chloro-5-piperidinomethyl-8-quinolinol[4] can be explained on the basis of its acidity which is adequate for substitution despite the hindering effect of the peri position. Phenol gives 2,4,6-tris(dimethylaminomethyl)-phenol[19] and 2-phenylphenol gives 2,4-bis(diethylaminomethyl)-6-phenylphenol[16] since no hindering groups are present.[20]

(7) J. W. Cornforth, R. H. Cornforth, and R. Robinson, *J. Chem. Soc.*, 168 (1943).

(8) E. Noelting, *Chim. & ind. (Paris)*, **8**, 758 (1922); *Chem. Abstr.*, **17**, 473 (1922).

(9) Swiss patent **208,000**; *Chem. Abstr.*, **35**, 3649 (1941).

(10) Q. Fernando, W. Z. W. Ludekeus, and K. Gnanascoorian, *Anal. Chim. Acta*, **14**, 297 (1955).

(11) H. Schuller, *J. prakt. Chem.*, [2] **88**, 180 (1913).

(12) After the studies which constitute the subject matter of this publication had been completed,[3] H. Zinner and H. Fiedler, *Arch. Pharm.*, **291**, 493 (1958), reported reactions which were different from ours in establishing 5-chloromethyl-8-quinolinol as the product of chloromethylation of 8-quinolinol.

(13) A. Claus and H. Howitz, *J. prakt. Chem.*, [2] **44**, 444 (1891).

(14) J. P. Phillips and Q. Fernando, *J. Am. Chem. Soc.*, **75**, 3763 (1953).

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

(16) J. H. Burckhalter, *J. Am. Chem. Soc.*, **72**, 5309 (1950).

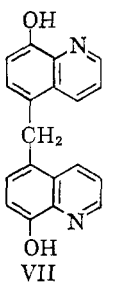
(17) The Mannich reagent may also be of the type $R_2NCH_2—OH$ or $R_2NCH_2—NR_2$.[6]

(18) For example, 2-chloro-6-phenylphenol, 2-allyl-6-phenylphenol, and 2,6-diphenylphenol give *para*- substituted Mannich bases in good yields.[6]

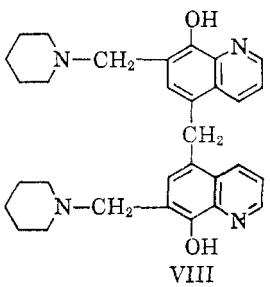
(19) H. A. Bruson and C. W. MacMullen, *J. Am. Chem. Soc.*, **63**, 270 (1941).

(20) Further studies along these lines are in progress in this laboratory.

When a mixture of 8-quinolinol, formalin, and concentrated hydrochloric acid was heated for ninety minutes, a compound with properties not expected of a chloromethyl derivative was obtained. A high melting point and elementary analysis suggested 5,5′-methylenebis-8-quinolinol (VII). As a confirmation of structure, Mannich base 7-piperidinomethyl-8-quinolinol (I) was treated similarly



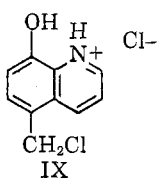
VII



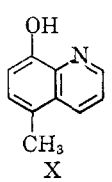
VIII

with formalin and hydrochloric acid to give VIII. Treatment of VII under Mannich conditions gave the same product (VIII).

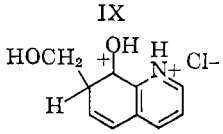
Since we obtained not I but its isomer by reaction of the so-called 7-chloromethyl-8-quinolinol with piperidine, the structural assignment for the products of chloromethylation of 8-quinolinol was in doubt. Hydrogenolysis of the substance gave an excellent yield of 5-methyl-8-quinolinol (X), which proved to be identical with an authentic sample of this compound prepared from 2-amino-*p*-cresol by the Skraup reaction.[21] Thus, IX is established as the correct structure for the product of chloromethylation of 8-quinolinol.



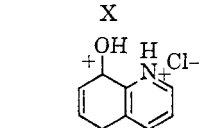
IX



X



XI



XII

During the inquiry into why chloromethylation of 8-quinolinol occurs at position 5 instead of 7, reference is made to the kinetic studies of Agata and Okano who have shown that the mechanism of chloromethylation[22] is based upon an electrophilic attack on an aromatic nucleus by the hydroxymethyl cation.[23] XI may be considered as one of seven canonical resonance structures (four Kekulé) of the transition state resulting if attack of protonated 8-quinolinol by the hydroxymethyl cation occurs at position 7. But since it is possible to write eight resonances structures (six Kekulé), such as XII, resulting from attack at position 5, it is considered that the 5-substituted transition state is better stabilized and thus more likely to lead to the product of chloromethylation.

5-Chloromethyl-8-quinolinol (IX) hydrochloride was used as the starting material for the synthesis of the compounds represented by structures XIII–XVI. Considerable difficulty was experienced in its use. Its instability even in the form of the hydrochloride is illustrated by the fact that heating under reflux with dilute hydrochloric acid or with dimethylformamide converted it in good yield to 5,5′-methylenebis-8-quinolinol (VII).[24] The hydrochloride was insoluble in solvents except those with which it reacted, such as water or alcohol. Attempts to prepare the free base IX by treatment of its hydrochloride with a calculated amount of sodium acetate, sodium hydroxide, or triethylamine resulted in hydrolysis to 5-hydroxymethyl-8-quinolinol (XIVa). Hydrolysis with dilute ammonia gave a virtually quantitative yield of XIVa.

Treatment of an ethyl acetate suspension of IX hydrochloride with a two-molar excess of the appropriate amine gave compounds XIIII (a–d). In the case of XIIId, there was a yield of only 13%, but a 61% yield of bis(8-hydroxy-5-quinolylmethyl)benzylamine was isolated from the same reaction mixture.

A group of 5-alkoxymethyl-8-quinolinols, XIV-(b–f) was synthesized by heating IX hydrochloride with the appropriate alcohol. XIVg was obtained in excellent yield by heating XIVf with piperidine in benzene solution.

It was not possible to prepare 5,7-bis(piperidinomethyl)-8-quinolinol (XV) by use of 8-quinolinol in the Mannich reaction. Even excess piperidine and formaldehyde yielded only the monosubstituted product (I). However, XIIIa, obtained from 5-chloromethyl-8-quinolinol, gave XV in 90% yield under conditions of the Mannich reaction. Ethers of the type XIV were similarly converted to a group of Mannich bases, XVI(a–e).

Pharmacological results. 5-Chloro-7-diethylamino-8-quinolinol (XVII) has shown promising activity as an antiamebic agent.[15,25] It has been assumed that a halogen atom at position 5 is essential for biological activity. To test this assumption, a number of substituted quinolinols described in this publication were screened for antiamebic activity in rats under the supervision of Dr. Paul E. Thompson, Research Laboratories, Parke, Davis and Co., Ann Arbor, Mich. Compounds VIII,

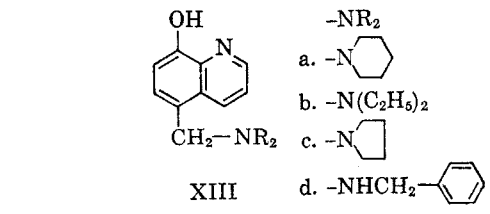
(21) Kindly supplied by Dr. Martin Black, Parke, Davis and Co. Research Laboratory, Ann Arbor, Mich.

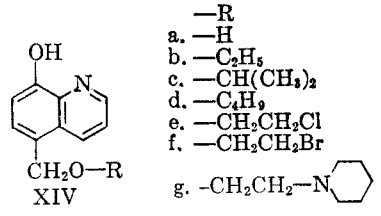
(22) R. C. Fuson and C. H. McKeever, *Org. Reactions*, 1, 63 (1942).

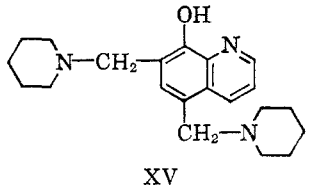
(23) Y. Agata and M. Okano, *J. Am. Chem. Soc.*, 78, 5423 (1956).

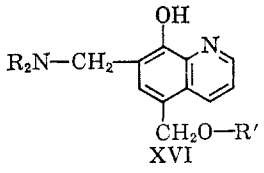
(24) The preparation of VIII from VII serves as another proof of structure of IX.

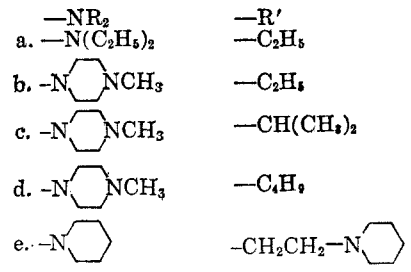
(25) P. E. Thompson, J. W. Reinertson, A. Bayles, D. A. McCarthy, and E. F. Elslager, *Am. J. Trop. Med. Hyg.*, 4, 224 (1955).











XIIIb, XIVc, XIVd, XIVe, XIVg, XV, XVIa, XVIb, XVIc, and XVId were evaluated and found to be inactive as tested or inferior to XVII.

EXPERIMENTAL

7-Piperidinomethyl-8-quinolinol (I). A mixture of 29 g. (0.2 mole) of 8-quinolinol, 6 g. (0.2 mole) of paraformaldehyde, and 17 g. (0.2 mole) of piperidine was mixed and melted on the steam bath without the use of solvent. After heating for 3 hr. the reaction was allowed to stand several days. The solid contents of the flask was triturated with petroleum ether (b.p. 60–68°) and then collected on a filter. The solid dried to give 23.1 g. (48% yield) of white solid, m.p. 114–117°. (lit.[26] m.p. 117°).

5-Bromo-7-piperidinomethyl-8-quinolinol (IV). (A) To a solution of 15 g. (0.062 mole) of I in 70 ml. of glacial acetic acid there was added with stirring 10.6 ml. of 48% hydrobromic acid. The solution was heated under reflux and 9.9 g. (0.062 mole) of bromine dissolved in 25 ml. of glacial acetic acid was added dropwise. After 3 hr. of heating the reaction was cooled and ether was added to the mixture. The precipitated yellow solid was collected on a filter and dried; yield 30 g. (99% yield), m.p. 246–247° dec. A sample was recrystallized four times from 95% alcohol to give IV monohydrobromide, m.p. 220–221.5° dec.

Anal. Calcd. for $C_{15}H_{17}N_2O \cdot HBr$: C, 44.79; H, 4.76. Found: C, 45.02; H, 4.68.

(B). A mixture of 5 g. (0.022 mole) of 5-bromo-8-quinolinol,[13] 1.87 g. (0.022 mole) of piperidine, 0.66 g. (0.022 mole) of paraformaldehyde, and 170 ml. of alcohol was heated under reflux for 60 min. The reaction mixture was refrigerated. The light tan solid was collected on a filter and dried; yield 4.6 g. (65% yield), m.p. 117–120°. It was recrystallized four times from petroleum ether, m.p. 124.9–125.9°. A sample of free base prepared from IV(A) was not depressed by admixture with IV(B).

Anal. Calcd. for $C_{15}H_{17}BrN_2O$: C, 56.08; H, 5.33. Found: C, 56.84; H, 5.54.

5-Bromo-7-diethylaminomethyl-8-quinolinol (V) *dihydrochloride.* An aqueous solution of 16.1 g. (0.53 mole) of 7-diethylaminomethyl-8-quinolinol (II) dihydrochloride[14] was treated with dilute ammonia. The solid was collected on a filter and dried; yield 11.5 g. (94% yield), m.p. 78–80°. It was dissolved in 50 ml. of glacial acetic acid and treated with 8.5 ml. of 48% hydrobromic acid. The solution was heated under reflux and 8.0 g. (0.05 mole) of bromine was added dropwise. After 3 hr. the reaction was concentrated at reduced pressure. On cooling the precipitated yellow solid was collected on a filter and dried; yield 12.1 g. (50% yield), m.p. 234–235° dec. This material was dissolved in water and treated with ammonia. The milky solution was extracted with ether and the ether layer dried over potassium carbonate. Hydrogen chloride gas in excess was bubbled into the filtered solution. The ether was decanted from the precipitated yellow gum and triturated with a few milliliters of warm alcohol to give a bright yellow solid, m.p. 199–204° dec. It was undepressed by admixture with a sample prepared by the method of Burckhalter and Edgerton.[15]

5,5'-Methylenebis-(8-quinolinol) (VII). A mixture of 29 g. (0.2 mole) of 8-quinolinol, 9 ml. (excess) of 37% formaldehyde and 85 ml. of concd. hydrochloric acid was heated under reflux for 90 min. After standing overnight the yellow solid was filtered and dissolved in water. The solution was treated with dilute ammonia. The white solid was collected on a filter and dried; yield 24.3 g. (80% yield), m.p. 212–230° dec. Recrystallized from dimethylformamide four times, it melted at 284–285° dec.

Anal. Calcd. for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67. Found: C, 75.33; H, 4.59.

5,5'-Methylenebis-(7-piperidinomethyl-8-quinolinol) (VIII). (A) A dimethylformamide solution of 0.61 g. (0.0072 mole) of piperidine and 0.21 g. (0.022 mole) of paraformaldehyde previously warmed was added to a suspension of 1.1 g. (0.0036 mole) of VII in dimethylformamide. The mixture was warmed on the steam bath for 2.5 hr. The solvent was removed at reduced pressure and the residue was taken up in benzene. The benzene solution was concentrated and cooled. The precipitated white solid weighed 1.5 g. (80% yield), m.p. 175–179°. After recrystallization from benzene–ethyl acetate mixture and twice from benzene, the material melted at 177.5–178.5°.

Anal. Calcd. for $C_{31}H_{36}N_4O_2$: C, 74.96; H, 7.30. Found: C, 74.88; H. 7.48.

(B) A mixture of 4.6 g. of I, 20 ml. of concd. hydrochloric acid, and 5 ml. (excess) of 37% formaldehyde was heated under reflux for 2.5 hr. The reaction mixture was poured on ice and treated with dilute ammonia. The precipitated grey solid was filtered, dried, and extracted with benzene. The benzene was concentrated and cooled. The white solid was collected on a filter and dried; yield 2.3 g. (24% yield), m.p. 175–177°. It was not depressed by admixture with VIII (A).

5-Chloromethyl-8-quinolinol hydrochloride (IX). A mixture of 7.3 g. (0.05 mole) of 8-quinolinol, 8 ml. of cond. hydrochloric acid, and 8 ml. (0.05 mole) of 37% formaldehyde was treated with hydrogen chloride gas for 90 min. The yellow solid was collected on a filter and dried to give 8.9 g. (77.5% yield), m.p. 280° dec. (lit.[8] m.p. 283° dec.).

5-Methyl-8-quinolinol (X). To a suspension of 10 g. (0.0434 mole) of IX in 200 ml. of alcohol there was added 1 g. of 10% palladium on charcoal. The mixture was subjected to 50 lbs.

(26) Ger. Patent 92,309; Frdl., 4, 103 (1899).

of hydrogen pressure at room temperature. The reaction was stopped after the theoretical amount of hydrogen had been absorbed. The solid was collected and then extracted with water and filtered to remove the catalyst. The alcohol filtrate and the aqueous filtrate were combined and concentrated under reduced pressure. The residue was redissolved in water and treated with solid sodium acetate. The precipitated white product weighed 6.2 g. (96% yield), m.p. 115–120°. Recrystallization from alcohol raised the melting point to 122–123°. The melting point was not depressed by admixture with an authentic sample of 5-methyl-8-quinolinol, prepared by the Skraup reaction from 5-methyl-2-aminophenol.[21]

5-Hydroxymethyl-8-quinolinol (XIVa). An aqueous solution of 10 g. (0.0434 mole) of IX contained in a separatory funnel was covered with ether. Dilute ammonia was dropped into the mixture with frequent shaking until the aqueous layer was basic to litmus. The ether layer was evaporated to yield 7.9 g. (99% yield) of product, m.p. 133–136°. Recrystallized once from alcohol and four times from benzene, it melted at 138–139°.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.54; H, 5.17. Found: C, 68.55; H, 5.19.

5-Hydroxymethyl-8-quinolyl p-toluenesulfonate was prepared by treatment of XIVa with an excessive amount of *p*-toluenesulfonyl chloride in pyridine solution. The mixture was warmed on the steam bath for 30 min., whereupon it was cooled and poured into crushed ice. Several days later, a white solid was obtained. It was recrystallized from alcohol, m.p. 208–212°. Further recrystallization elevated the melting point to 218–219° dec. The compound gave a negative phenol test while the starting material was positive.

Anal. Calcd. for $C_{17}H_{15}NO_4S$: C, 61.98; H, 4.59. Found: C, 62.03; H, 4.52.

5-Piperidinomethyl-8-quinolinol (XIIIa). To a suspension of 36.6 g. (0.159 mole) of IX in ethyl acetate there was added 40.5 g. (0.477 mole) of piperidine. The mixture was warmed on the steam bath for 1 hr. with occasional shaking The reaction was cooled and the piperidine hydrochloride was filtered and washed with ethyl acetate. The filtrate was concentrated and the residue was extracted with petroleum ether and the solution filtered. Concentration of the filtrate gave 29.2 g. (75% yield), m.p. 89–96°. Recrystallization from petroleum ether (b.p. 60–68°) raised the melting point to 97–99°.

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.34; H, 7.38. Found: C, 74.45; H, 7.49.

5-Diethylaminomethyl-8-quinolinol (XIIIb). To a suspension of 46 g. (0.2 mole) of IX in ethyl acetate there was added 43.9 g. (0.6 mole) of diethylamine. The mixture was warmed on the steam bath for 1 hr. with occasional shaking. The reaction was cooled and the diethylamine hydrochloride filtered and washed with ethyl acetate. Concentration of the filtrate yielded 25.6 g. (55% yield) of white solid, m.p. 69–72°. Recrystallization from petroleum ether raised the melting point to 70–72.8°.

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.00; H, 7.87. Found: C, 73.16; H, 7.61.

5-Pyrrolidinomethyl-8-quinolinol (XIIIc). To a suspension of 38.2 g. (0.166 mole) of IX in ethyl acetate there was added 35.4 g. (0.498 mole) of pyrrolidine. The reaction was warmed on the steam bath with occasional shaking. The reaction was filtered and washed with ethyl acetate. The filtrate was evaporated to dryness and the residue was extracted with petroleum ether. The petroleum ether was concentrated and cooled to give 20 g. (80% yield) of white solid, m.p. 111–114.5°. Recrystallized twice from petroleum ether and three times from benzene, it melted at 113.9–115.1.

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06. Found: C, 73.71; H, 6.59.

Bis(8-hydroxy-5-quinolylmethyl)benzylamine. To a solution of 9.5 g. (0.088 mole) of benzylamine in 200 ml. of ethyl acetate there was added 6.67 g. (0.029 mole) of IX. The reaction was warmed on the steam bath with occasional shaking until the yellow color no longer persisted. The precipitated benzylamine hydrochloride was filtered and washed with ethyl acetate. Concentration of the filtrate yielded 3.7 g. (61% yield) of white solid, m.p. 176–181°. Recrystallized twice from benzene and once from ethyl acetate, it melted at 182–183.2.

Anal. Calcd. for $C_{27}H_{23}N_3O_2$: C, 76.93; H, 5.49; N, 9.96. Found: C, 76.71; H, 5.26; N, 10.40.

5-Benzylaminomethyl-8-quinolinol (XIIId) *dihydrochloride.* The ethyl acetate filtrate from the concentrate of bis(8-hydroxy-5-quinolylmethyl)benzylamine was evaporated to dryness. The residue was extracted with ether and filtered. Hydrogen chloride gas in excess was bubbled through the ether filtrate. The precipitated yellow solid was collected and dried to give 1.5 g. (13% yield), m.p. 206–209°. Recrystallized five times from alcohol, it melted at 200–201° dec.

Anal. Calcd. for $C_{17}H_{16}N_2O \cdot 2HCl \cdot 1H_2O$: C, 57.47; H, 5.67; volatile loss, 15.4. Found: C, 56.98; H, 5.70; volatile loss, 15.8 (corresponds to 1 H_2O and 1 HCl).

5-Ethoxymethyl-8-quinolinol (XIVb). To a suspension of 23 g. (0.1 mole) of IX in alcohol there was added 8.4 g. (0.1 mole) of sodium bicarbonate.[27] The mixture was warmed on the steam bath with occasional shaking until most of the alcohol had evaporated. The yellow solid was dissolved in water and made basic with dilute ammonia. The white solid was collected on a filter and dried to give 22.5 g. (99% yield), m.p. 76–80°. Recrystallization from petroleum ether raised the melting point to 83–83.5°.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.99; H, 6.45. Found: C, 71.22; H, 6.13.

5-Isopropoxymethyl-8-quinolinol (XIVc). To a suspension of 39.4 g. (0.171 mole) of IX in isopropyl alcohol there was added 14.4 g. (0.171 mole) of sodium bicarbonate.[27] The reaction was heated on the steam bath with occasional shaking until the isopropyl alcohol was evaporated. The yellow residue was dissolved in water and treated with dilute ammonia. After several hours the precipitate was filtered and dried; yield 21 g., m.p. 60–63°. A second crop increased the amount to 35 g. (93% yield). Recrystallized three times from petroleum ether, it melted at 65–66°.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.95. Found: C, 71.83; H, 6.93.

5-Butoxymethyl-8-quinolinol (XIVd). To a suspension of 43.6 g. (0.19 mole) of IX in butanol there was added 16 g. (0.19 mole) of sodium bicarbonate.[27] The reaction was warmed on the steam bath with occasional shaking for several hours. The excess butanol was removed by distillation at reduced pressure. The yellow residue was treated with dilute ammonia. The precipitated white solid was filtered and dried and dissolved in petroleum ether. Concentration and cooling gave 18.7 g. (42% yield) of white solid, m.p. 46–49°. Recrystallized four times from petroleum ether, it melted at 46–47.2°.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.69; H, 7.41. Found: C, 73.37; H, 7.71.

5-(2-Chloroethoxymethyl)-8-quinolinol (XIVe). To a suspension of 10 g. (0.0434 mole) of IX in 2-chloroethanol there was added 3.56 g. (0.0434 mole) of sodium acetate.[27] The mixture was warmed on the steam bath overnight. The excess 2-chloroethanol was removed by distillation at reduced pressure. The yellow residue was dissolved in water and treated with dilute ammonia. The precipitate was collected by filtration, dried to give 7.6 g. (73% yield) of white solid, m.p. 83–88°. After four recrystallizations from petroleum ether, it melted at 90.7–91°.

Anal. Calcd. for $C_{12}H_{12}NO_2$: C, 60.63; H, 5.09. Found: C, 60.67; H, 4.89.

5-(2-Bromoethoxymethyl)-8-quinolinol (XIVf). To a suspension of 23 g. (0.1 mole) of IX in 80 ml. of 2-bromoethanol there was added 8.4 g. (0.1 mole) of sodium bicarbonate.[27] The mixture was warmed on the steam bath with occasional

(27) After these studies were completed, it was found that a base was not required to effect condensation.

shaking for 60 min. The yellow solid was collected on a filter and the filtrate was distilled at reduced pressure. The solid and the residue left after distillation were dissolved in water and treated with dilute ammonia. The precipitate was collected by filtration; dried to give 24.8 g. (88% yield) of white solid, m.p. 97–100°. Recrystallized once from benzene and twice from petroleum ether, it melted at 103.8–105°.

Anal. Calcd. for $C_{12}H_{12}NO_2Br$: C, 51.07; H, 4.28. Found: C, 51.35; H, 4.58.

5-(2-Piperidinoethoxymethyl)-8-quinolinol (XIVg). A. A mixture of 5.95 g. (0.025 mole) of XIVe, 25 ml. of piperidine and 25 ml. of benzene was heated under reflux for 90 min. The piperidine hydrochloride was removed by filtration. The filtrate was concentrated to a thick residue which was extracted several times with petroleum ether. The extract was concentrated to give a red oil which on trituration with ether gave 2.05 g. (28% yield) of white solid, m.p. 104–108°. Recrystallization twice from petroleum ether and twice from ethyl acetate raised the melting point to 109°.

Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.29; H, 7.74. Found: C, 71.10; H, 7.62.

B. A mixture of 13.2 g. (0.046 mole) of XIVf, 20 ml. of piperidine, and 40 ml. of benzene was heated under reflux for 4 hr. The piperidine hydrobromide was removed by filtration. The filtrate was concentrated and the residue was extracted with benzene and ether. Concentration of the extract and cooling yielded 12.7 g. (95% yield) of material, m.p. 108–110° with no depression upon admixture with XIVg. (A).

5,7-Bis(piperidinomethyl)-8-quinolinol (XV) *dihydrochloride.* A mixture of 12.1 g. (0.05 mole) of IX, 1.5 g. (0.05 mole) of paraformaldehyde and 4.26 g. (0.05 mole) of piperidine was mixed and melted on the steam bath without use of solvent. After heating for 3 hr., the sirupy residue was cooled and triturated with ether. The solid was collected on a filter. Several crops gave a total of 15.3 g. (90% yield), m.p. 73.5–77.5°. Recrystallization from petroleum ether raised the melting point to 74–76°. A sample of the free base was treated with the calculated amount of hydrogen chloride to precipitate the dihydrochloride, m.p. 210–211.5° dec. Recrystallized six times from isopropyl alcohol-ethanol mixture, it melted at 221–221.9° dec.

Anal. Calcd. for $C_{21}H_{29}N_3O \cdot 2\ HCl \cdot H_2O$: C, 58.59; H, 7.72. Found: C, 58.59; H, 7.71.

5-Ethoxymethyl-7-diethylaminomethyl-8-quinolinol (XVIa) *oxalate.* An alcoholic solution of 3.65 g. (0.05 mole) of diethylamine and 1.5 g. (0.05 mole) of paraformaldehyde was added to an alcohol solution of 10.05 g. (0.05 mole) of XIVb. The reaction was heated under reflux for 3 hr. The solvent was removed at reduced pressure and the residue was triturated with dry ether. A very small amount of a light tan solid was collected on a filter and the filtrate was treated with an alcohol-ether solution saturated with oxalic acid. The precipitate was collected and dried to give 14.2 g. (74% yield) of solid, m.p. 142–144° dec. Recrystallized five times from alcohol, it melted at 147–148° dec.

Anal. Calcd. for $C_{17}H_{24}N_2O_2 \cdot C_2H_2O_4 \cdot {}^1/_2\ H_2O$: C, 58.89; H, 7.02. Found: C, 58.72; H, 7.03.

5-Ethoxymethyl-7-N-methylpiperazinylmethyl-8-quinolinol (XVIb). An alcohol solution of 10 g. (0.1 mole) of *N*-methylpiperazine and 3 g. (0.1 mole) of paraformaldehyde was added to an alcohol solution of 20.3 g. (0.1 mole) of XIVb The resulting mixture was heated under reflux for 2.5 hr. The volatile materials were removed at reduced pressure and the light grey residue was taken up with benzene, cooled, and 17.1 g. of tan solid was collected. Further crops increased the amount to 28.4 g. (90% yield) of this material, m.p. 112–116°. Recrystallized twice from ethyl acetate, it melted at 117–118°.

Anal. Calcd. for $C_{18}H_{25}N_3O_2$: C, 68.56; H, 7.99. Found: C, 68.15; H, 7.84.

5-Isopropoxymethyl-7-N-methylpiperazinylmethyl-8-quinolinol (XVIc). An alcohol solution of 8.5 g. (0.085 mole) of *N*-methylpiperazine and 2.55 g. (0.085 mole) of paraformaldehyde was added to an alcohol solution of 18.5 g. (0.085 mole) of XIVc. The resulting mixture was heated under reflux for 2.5 hr. The volatile materials were removed at reduced pressure and the residue was taken up with petroleum ether cooled to yield 15.65 g. of tan solid. Further crops increased the amount to 23.5 g. (71% yield) of product, m.p. 100–103°. Recrystallized once from benzene–petroleum ether mixture and once from ethyl acetate, it melted at 103.8–105°.

Anal. Calcd. for $C_{19}H_{27}N_3O_2$: C, 69.26; H, 8.26. Found: C, 69.01; H, 8.08.

5-Butoxymethyl-7-N-methylpiperazinylmethyl-8-quinolinol (XVId). An alcohol solution of 8.2 g. (0.082 mole) of *N*-methylpiperazine and 2.46 g. (0.028 mole) of paraformaldehyde was added to an alcohol solution of 18.96 g. (0.082 mole) of XIVd. The mixture was heated under reflux for 2.5 hr. The volatile materials were removed at reduced pressure and the residue was collected on a filter and dried; yield 27 g. (95% yield), m.p. 72–76°. Recrystallized once from benzene–petroleum ether mixture and three times from petroleum ether, it melted at 77–78°.

Anal. Calcd. for $C_{20}H_{29}N_3O$: C, 69.93; H, 8.51. Found: C, 70.02; H, 8.31.

5-(2-Piperidinoethoxymethyl)-7-piperidinomethyl-8-quinolinol (XVIe) *dihydrochloride.* A mixture of 18 g. (0.062 mole) of XIVg, 1.86 g. (0.062 mole) of paraformaldehyde, 5.27 g. (0.062 mole) of piperidine, and 250 ml. of alcohol was heated under reflux for 3 hr. The solvent was removed at reduced pressure and the residue was triturated with ether and allowed to stand in the cold. The solid was collected on a filter, dried, m.p. 53.5–57°. Consequent crops increased the yield to 21.2 g. (88% yield). Recrystallization from petroleum ether raised the melting point to 54.5–57.8°. A portion of this material was treated with the calculated amount of hydrogen chloride to precipitate the dihydrochloride, m.p. 164–168° dec. Recrystallized three times from isopropyl alcohol, it melted at 160.8–161.1° dec.

Anal. Calcd. for $C_{23}H_{33}N_3O_2 \cdot 2HCl \cdot H_2O$: C, 58.17; H, 7.80. Found: C, 58.15; H, 8.37.

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