[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

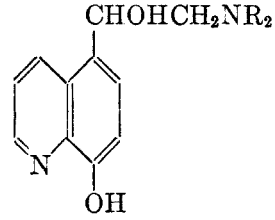
ANTIMALARIAL STUDIES IN THE QUINOLINE SERIES

ALFRED BURGER, KENNETH C. BASS, JR., AND JAMES M. FREDERICKSEN

Received April 6, 1944

Quinine has often been regarded as a complex quinoline amino alcohol, and simpler compounds retaining these structural features have been synthesized in the search for new antimalarials. Amino alcohol groups —$CHOHCH_2NR_2$ were placed in positions 3 and 4 but not in the benzenoid ring of the quinoline system. Fränkel and Grauer (1) prepared an aminoacetyl-8-methoxyquinoline but did not reduce the carbonyl group.

We have now attempted to synthesize 1-(8-hydroxy-5-quinolyl)-2-dialkylaminoethanol derivatives (I) starting from 5-chloroacetyl-8-hydroxyquinoline.



I

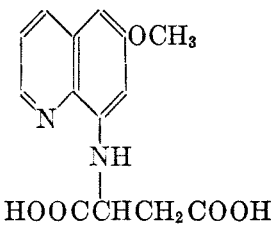
Matsumura (2), who first prepared this chloro ketone by chloroacetylation of 8-hydroxyquinoline, did not mention any difficulty in separating it from aluminum salts in acid solution, while Rosenmund and Karst (3) had to break up the insoluble aluminum complex salts of several 8-hydroxy-5-acyl quinolines by acetylation, separation of the aluminum acetate, and hydrolysis of the 8-acetoxy group. Our product from the Friedel and Crafts reaction consisted largely of aluminum complex salts of the desired chloro ketone, and had to be decomposed by digestion with hot concentrated hydrochloric acid.

5-Chloroacetyl-8-hydroxyquinoline reacted with secondary amines to yield the respective tertiary-amino ketones. Aluminum isopropoxide reduction of these compounds was not feasible because, again, insoluble complex salts precipitated out and were thus withheld from the reaction. Therefore, hydrogenation in the presence of Adams' catalyst was tried. Not all the amino ketones could be reduced under the conditions employed, but the morpholino ketone hydrochloride absorbed slowly 1.3 moles of hydrogen. The analytical values of the reduction product agreed closely with those calculated for 1-(8-hydroxy-5-quinolyl)-2-(4-morpholino)ethanol hydrochloride, but the figures for a Py-tetrahydroquinolyl morpholino ketone of corresponding structure lie within the limits of the experimental error of those found for our product, and a decision between these two structures has not been reached.

Another approach to antimalarials was based on the observation of Oesterlin (4) that succinic and fumaric acids and similar cell respiration factors increase

the activity of plasmoquine. Frisch and Bogert (5) prepared several succinamides, succinimides, and related substances substituted by methoxyquinoline groups in order to test the effect of connecting the two types of compounds.

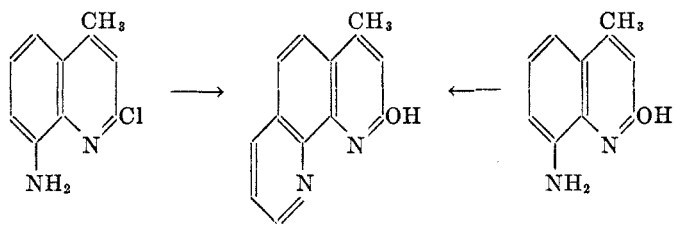
It appeared possible that the biological interaction of 8-aminoquinoline derivatives and succinic or fumaric acid could be due to the formation of an α-amino acid having the aminoquinoline system directly attached to the linkage participating in biological oxidations. We have therefore synthesized *dl*-N-(6-methoxy-8-quinolyl)aspartic acid (II). Diethyl bromosuccinate and 6-methoxy-



II

8-aminoquinoline were condensed under mild conditions, the resulting ester was hydrolyzed, and the dicarboxylic acid isolated as its hydrochloride in 32% yield.

Basic derivatives of various tricyclic systems containing the quinoline nucleus as part of their ring structure have been tested successfully as antimalarials. We had available 2-chloro- (III) and 2-hydroxy-4-methyl-8-aminoquinoline (IV) (6) and have used these materials now in the synthesis of suitably substituted 1,10-phenanthrolines. The Skraup reaction with IV yielded 2-hydroxy-4-methyl-1,10-phenanthroline (V) which was also formed from III by the same



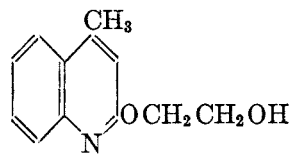
III V IV

reaction accompanied by hydrolysis of the reactive halogen atom. 2-Chloro-4-methyl-1,10-phenanthroline, obtained by treating V with phosphorus chlorides, reacted with 4-(2-aminoethyl)morpholine to give 2-[4-(2-aminoethyl)morpholino]-4-methyl-1,10-phenanthroline.

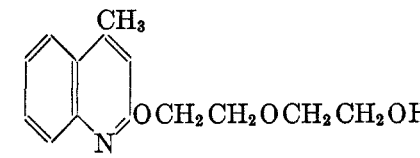
In order to study the effect of further nuclear substitution on the antimalarial activity of such dialkylaminoalkylamino phenanthrolines, the nitration of V was investigated. Under conditions comparable to those used with 2-hydroxylepidine (7) a dinitro derivative was formed. A comparison with the orientation in the analogous 2-hydroxylepidine series (8), and the non-availability of the favored 8- position of the lepidone portion of the molecule, indicate that one nitro group must have entered position 3, and the other one position 6 of the 1,10-phenanthroline system.

Since direct nitration did not stop at a mononitro-2-hydroxy-4-methyl-1,10-phenanthroline, we attempted to synthesize such a compound by another route. 5-Nitro-8-aminoquinoline, prepared from 5-nitro-8-hydroxyquinoline (9) with ammonia under pressure, was converted to 5-nitro-8-acetoacetaminoquinoline. Ring closure of this compound to 2-hydroxy-4-methyl-6-nitro-1,10-phenanthroline could not be effected under a variety of conditions, including heating with sulfuric acid at 60° and 100°, in paraffin oil at 220°, with phosphorus pentoxide in paraffin oil at the same temperature, or in syrupy phosphoric acid, or with phosphorus pentoxide or pentachloride in boiling xylene. Analogous difficulties had been encountered by Balaban (10) in the ring closure with *p*-nitroacetoacetanilide, and by Utermohlen and Hamilton (11) in the Skraup synthesis with nitronaphthylamines.

Aside from dialkylaminoalkylamino derivatives, certain aromatic amidine ethers (12) and quinoline dialkylamino ethers (13) have shown protozoicidal action. As part of an investigation of such compounds we have synthesized the mono-2-lepidyl ethers of ethylene glycol (VI), and diethylene glycol (VII), with the hope of converting the terminal alcohol groups through the halides to amino groups.



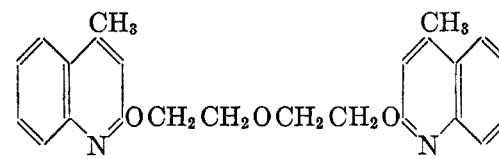
VI



VII

The ethers were prepared from 2-chlorolepidine and the respective monosodium glycolates. Numerous attempts to replace the primary alcohol group with halogen by the action of thionyl chloride or phosphorus halides under mild conditions, failed. These reagents only caused a scission of the heterocyclic ether linkage, splitting the compounds practically quantitatively to 2-hydroxylepidine.

Disodium diethylene glycolate and 2-chlorolepidine furnished the dilepidyl ether of diethylene glycol VIII, which could be nitrated to 2,2′-di-(4-methyl-6-



VIII

nitro-2-quinolinoxy)ethyl ether. Reduction with tin and hydrochloric acid produced the corresponding diamine.

Several of the compounds described have been found inactive in antimalarial tests carried out in the Lilly Research Laboratories. Details of these tests will be communicated elsewhere.

EXPERIMENTAL

5-Chloroacetyl-8-hydroxyquinoline. To a mixture of 87 g. of 8-hydroxyquinoline,[1] 600 cc. of *sym.*-tetrachloroethane and 150 cc. of nitrobenzene was added 72.4 g. of chloroacetyl chloride at 0°. Aluminum chloride (234.2 g.) was added in five to ten portions with good cooling and agitation. The mixture was then placed on a steam-bath and heated for about thirty hours until no more hydrogen chloride was evolved. After cooling to room temperature it was poured onto 300 g. of crushed ice and 200 cc. of 10% hydrochloric acid. The precipitated aluminum complex salts were filtered from the ice-cold solution, washed with 500 cc. of ether, and digested with 100 cc. of concentrated hydrochloric acid on a steam-bath for one-half hour. The crude chloro ketone hydrochloride was filtered with some difficulty, and recrystallized from 10 l. of boiling water. The insoluble black tar was re-digested with hot hydrochloric acid, yielding additional amounts of the hydrochloride, which were recrystallized from the aqueous mother liquors of the first batch. The total yield was 51%.

The free phenolic chloro ketone was obtained by stirring the hydrochloride with 800 cc. of 6% sodium acetate solution for thirty minutes. The yield was 60.6 g. (45.6% based on 8-hydroxyquinoline). Recrystallization from 2 l. of ethanol rendered 52 g. of colorless crystals, m.p. 157–158°.

Borsche and Groth (14) reported the melting point 159° for 8-methoxy-5-chloroacetylquinoline. We found that the methyl ether group of 8-methoxyquinoline is readily cleaved in Friedel and Crafts reactions, and it is not unlikely that these authors actually isolated the hydroxy ketone.

8-Hydroxy-5-piperidinoacetylquinoline. A solution of 11.9 g. of 8-hydroxy-5-chloroacetylquinoline in 800 cc. of ether was treated with 4.9 g. of piperidine, and the mixture allowed to stand for three weeks. The separated piperidine hydrochloride was filtered, and the filtrate neutralized with alcoholic hydrogen chloride. The salt mixture was recrystallized repeatedly from large amounts of ethanol, and the mono- and di-hydrochlorides of the piperidino ketone were isolated.

The *monohydrochloride* melted at 262° (decomp.).

Anal. Calc'd for $C_{16}H_{18}N_2O_2 \cdot HCl$: C, 62.63; H, 6.24.
Found: C, 62.36; H, 6.58.

The colorless crystals of the *dihydrochloride* melted at 246–249° (decomp.).

Anal. Calc'd for $C_{16}H_{18}N_2O_2 \cdot 2HCl$: N, 8.16. Found: N, 7.98.

8-Hydroxy-5-morpholinoacetylquinoline. Twelve and one-half grams of the chloro ketone was suspended in a solution of 10.3 g. of morpholine in 1200 cc. of ether and allowed to stand for four days with occasional shaking. The mixture was extracted with dilute hydrochloric acid, the acid solution made alkaline with sodium bicarbonate, and the deep red solution extracted exhaustively with ether. The residual yellow semi-solid from the ether extract was heated at 70° under reduced pressure in order to remove any unchanged morpholine, and converted to the hydrochloride in acetone-methanol solution. Four recrystallizations from methanol-acetone gave 2.5 g. of colorless crystals, m.p. 250° (decomp.).

Anal. Calc'd for $C_{15}H_{16}N_2O_3 \cdot HCl$: N, 9.07. Found: N, 9.11.

1-(8-Hydroxy-5-quinolyl)-2-(4-morpholino)ethanol. One-tenth gram of platinum oxide was added to a solution of 2.5 g. of 8-hydroxy-5-morpholinoacetylquinoline hydrochloride in 75 cc. of methanol, and hydrogenation carried to completion over a period of thirty-six hours. The morpholino alcohol hydrochloride was isolated in the customary manner and recrystallized from ethanol-ether. The colorless crystals melted at 274° (decomp.). The salt was readily soluble in water; the yield was 1 g.

Anal. Calc'd for $C_{15}H_{18}N_2O_3 \cdot HCl$: C, 57.96; H, 6.16.
Found: C, 57.89; H, 6.06.

dl-N-(6-Methoxy-8-quinolyl)aspartic acid (II). A solution of 5.2 g. of 6-methoxy-8-

[1]Kindly furnished by Mr. H. A. Shonle, The Lilly Research Laboratories, Indianapolis, Ind.

aminoquinoline and 9.0 g. of diethyl bromosuccinate in 20 cc. of absolute ether was allowed to stand at room temperature. A crystalline precipitate of 6-methoxy-8-aminoquinoline hydrobromide began to appear after one day and increased slowly on further standing. After three months, it was filtered and washed with ether. The filtrate was evaporated, and the oily residue refluxed with 100 cc. of a 3% ethanolic potassium hydroxide solution for thirty minutes. The mixture, which now contained a yellow precipitate, was evaporated under reduced pressure, the yellow solid digested with 150 cc. of boiling water, cooled, and unchanged 6-methoxy-8-aminoquinoline (2.5 g.) extracted into ether. The alkaline solution was acidified with concentrated hydrochloric acid and deposited slowly yellow crystals of *dl*-N-(6-methoxy-8-quinolyl)aspartic acid dihydrochloride. The yield was 3.5 g. (32%). The salt was recrystallized from ethanol-ether, m.p. 214–216° (decomp.).

Anal. Calc'd for $C_{14}H_{14}N_2O_5 \cdot 2HCl$: C, 46.29; H, 4.44; N, 7.71.
Found: C, 46.46; H, 4.18; N, 8.01.

2-Hydroxy-4-methyl-1,10-phenanthroline (V). A mixture of 4.2 g. of 2-hydroxy-4-methyl-8-aminoquinoline, 3.48 g. of arsenic acid, 6.6 g. of sulfuric acid, and 7.2 g. of glycerol was refluxed for three hours in a bath at 155–160°. After cooling, the liquid was poured into ice-water, neutralized with sodium hydroxide solution, and allowed to stand overnight. The resulting precipitate was filtered, dissolved in hot toluene, and the solution concentrated. The colorless crystalline product from this solution was purified by sublimation at 120° and 1 mm. It was soluble in hot sodium hydroxide solution and melted at 177–179°. The yield in several runs averaged 20 to 30%.

Anal. Calc'd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.80.
Found: C, 73.84; H, 5.01.

The same hydroxyphenanthroline was obtained by an analogous Skraup reaction with 2-chloro-4-methyl-8-aminoquinoline using the same relative amounts of reagents as above.

2-Chloro-4-methyl-1,10-phenanthroline. A mixture of 7 g. of 2-hydroxy-4-methyl-1,10-phenanthroline, 7 g. of phosphorus pentachloride and 56 cc. of phosphorus oxychloride was heated at 130° for five hours, decomposed with ice, the solution filtered, and made ammoniacal. The precipitate thus obtained was recrystallized from ethanol; the yellow needles melted at 210–212°. The yield was 5.3 g. (69%).

Anal. Calc'd for $C_{13}H_9ClN_2$: C, 68.27; H, 3.97; N, 12.25.
Found: C, 67.87; H, 4.29; N, 12.98.

2-[4-(2-Aminoethyl)morpholino]-4-methyl-1,10-phenanthroline. Ten grams of 2-chloro-4-methyl-1,10-phenanthroline and 20 cc. of 4-(2-aminoethyl)morpholine[2] was heated at 150° for four hours. After cooling, the liquid was extracted with dilute hydrochloric acid, the acid solution made ammoniacal, and the precipitated oil extracted into ether. Neutralization of the dried ether solution with alcoholic hydrogen chloride gave fine yellow needles of the dihydrochloride, m.p. 261–263°, yield 6.0 g. (35%).

Anal. Calc'd for $C_{19}H_{22}N_4O \cdot 2HCl$: C, 57.72; H, 6.12; N, 14.18.
Found: C, 56.91; H, 6.35; N, 14.20.

2-Hydroxy-4-methyl-(3,6 ?)-dinitro-1,10-phenanthroline. Six grams of 2-hydroxy-4-methyl-1,10-phenanthroline was stirred slowly into a mixture of 18 cc. of concentrated sulfuric acid and 18 cc. of nitric acid (d = 1.5) at 0°. After heating on a steam-bath for fifteen minutes, the solution was poured into cold water; the yellow dinitro product precipitated in quantitative yield. Sublimation of the dried material at 2 mm. and 150° furnished bright yellow needles, m.p. 255–260° (decomp.).

Anal. Calc'd for $C_{13}H_8N_4O_5$: C, 52.00; H, 2.67.
Found: C, 51.78; H, 3.13.

5-Nitro-8-aminoquinoline. A sealed tube containing 1 g. of 5-nitro-8-hydroxyquinoline (9), 1 cc. of ethanol, and 10 cc. of 20% ammonium hydroxide was heated at 180–190° for six hours. A quantitative yield of a red amorphous solid was obtained by filtration of the cooled reaction mixture. Recrystallization from benzene gave orange-red needles, m.p.

[2] Kindly supplied by Carbide and Carbon Chemicals Corporation.

195–196°. A mixture melting point with an authentic sample of 5-nitro-8-aminoquinoline showed no depression.

5-Nitro-8-acetoacetaminoquinoline. A mixture of 1 g. of 5-nitro-8-aminoquinoline and 1.0 g. of ethyl acetoacetate was boiled for ninety seconds. On cooling, an orange solid crystallized in a yield of 0.8 g. (55%). It was recrystallized from ethyl acetate and appeared as orange needles, m.p. 156–158°.

Anal. Calc'd for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.02.
Found: C, 57.46; H, 4.38.

2,2'-Di-(4-methyl-2-quinolinoxy) ethyl ether (VIII). Seven grams of sodium was dissolved in 45 cc. of diethylene glycol with reflux, toluene being added as solution progressed in order to prevent oxidation of the sodium derivative. When all the sodium had gone into solution, 38 g. of 2-chlorolepidine in 50 cc. of toluene was added, the mixture refluxed for seven hours, and washed with water. The toluene was removed under reduced pressure, the solidified residue dissolved in alcoholic hydrogen chloride, and the salt precipitated with ether. It melted at 140–142°. It was dissolved in water, and the colorless solid base precipitated with sodium bicarbonate solution. Recrystallization from acetone yielded 30 g. (72%) of colorless crystals, m.p. 121°.

Anal. Calc'd for $C_{24}H_{24}N_2O_3$: C, 74.19; H, 6.23; N, 7.22.
Found: C, 74.02; H, 6.64; N, 7.11.

2,2'-Di-(4-methyl-6-nitro-2-quinolinoxy) ethyl ether. To an ice-cold solution prepared by dissolving 3.0 g. of 2,2'-di-(4-methyl-2-quinolinoxy) ethyl ether in 24 cc. of concentrated sulfuric acid, a mixture of 6 cc. of nitric acid (d = 1.43) and 6 cc. of concentrated sulfuric acid was added slowly. After standing at room temperature for two hours the mixture was poured into water. The dinitro ether precipitated out partly, the rest appeared when sodium carbonate was added to the solution. Recrystallization from β,β'-dichloroethyl ether furnished the pure product, m.p. 210.5°. The yield was 1.3 g. (37%).

Anal. Calc'd for $C_{24}H_{22}N_4O_7$: N, 11.72. Found: N, 11.30.

2,2'-Di-(4-methyl-6-amino-2-quinolinoxy)ethyl ether. A solution of 8 g. of the dinitro ether just described and 80 g. of stannous chloride in 25 cc. of 18% hydrochloric acid was refluxed for two hours, poured into ice-water, and made alkaline with strong potassium hydroxide solution. The resulting precipitate was filtered, dissolved in dilute hydrochloric acid, and the tin ions were removed with hydrogen sulfide. The diamino ether, purified through the hydrochloride, and finally by recrystallization from dioxane-ether, melted at 214°.

Anal. Calc'd for $C_{24}H_{26}N_4O_3$: C, 68.87; H, 6.27.
Found: C, 68.67; H, 6.77.

2-(4-Methyl-2-quinolinoxy)-2'-hydroxyethyl ether (VII). To a solution of 10.5 g. of sodium in 75 cc. of boiling diethylene glycol a solution of 100 g. of 2-chlorolepidine in 100 cc. of toluene was added. The mixture immediately turned deep red. It was boiled under reflux for five hours, the separated sodium chloride dissolved in water, and the toluene removed by steam distillation. The residual oil was dissolved in alcohol, and this solution deposited 7.5 g. of the diether VIII on standing. The filtrate was concentrated, the oily residue extracted into ether, the ether solution dried over sodium sulfate, and the solvent distilled. The residue was fractionated under 5 mm. pressure. A clear viscous oil distilled at 202–205°. It was converted to the hydrochloride in alcohol solution, and the colorless salt recrystallized from alcohol-ether; m.p. 151.5–153.5°, yield, 73 g. (45%).

Anal. Calc'd for $C_{14}H_{17}NO_3 \cdot HCl$: C, 59.24; H, 6.40.
Found: C, 58.88; H, 6.49.

2-(2-Hydroxyethoxy)-4-methylquinoline (VI). One gram of sodium was dissolved in 8 cc. of hot ethylene glycol, and a solution of 5 g. of 2-chlorolepidine in 10 cc. of benzene was added. After refluxing for six hours, the precipitated sodium chloride was dissolved in water, and the benzene distilled. The residual clear mobile oil was converted to the hydrochloride in alcohol-ether solution. The colorless salt melted at 167°.

Anal. Calc'd for $C_{12}H_{13}NO_2 \cdot HCl$: N, 5.85. Found: N, 5.71.

SUMMARY

1. The preparation of two 8-hydroxyquinoline-5-α-tertiary-amino ketones, and the reduction of one of them to the corresponding amino alcohol has been described.

2. *dl*-N-(6-Methoxy-8-quinolyl)aspartic acid has been synthesized.

3. 2-Hydroxy-4-methyl-1,10-phenanthroline has been prepared, and converted to a dinitro derivative, as well as to 2-[4-(2-aminoethyl)morpholino]-4-methyl-1,10-phenanthroline.

4. Some mono- and di-2-lepidyl ethers of ethylene glycol and diethylene glycol, and some derivatives of the latter have been studied.

CHARLOTTESVILLE, VA.

REFERENCES

(1) FRÄNKEL AND GRAUER, *Ber.*, **46**, 2551 (1913).
(2) MATSUMURA, *J. Am. Chem. Soc.*, **52**, 4433 (1930).
(3) ROSENMUND AND KARST, *Arch. Pharm.*, **279**, 154 (1941).
(4) OESTERLIN, *Arch. Schiffs.-u. Tropen-Hyg.*, **41**, 720 (1939); *Chem. Abstr.*, **33**, 4667 (1939).
(5) FRISCH AND BOGERT, *J. Org. Chem.*, **8**, 331 (1943).
(6) KRAHLER AND BURGER, *J. Am. Chem. Soc.*, **64**, 2417 (1942).
(7) KRAHLER AND BURGER, *J. Am. Chem. Soc.*, **63**, 2367 (1941).
(8) K. C. BASS, JR., *Dissertation*, University of Virginia, **1943**.
(9) KOSTANECKI, *Ber.*, **24**, 152 (1891).
(10) BALABAN, *J. Chem. Soc.*, 2346 (1930).
(11) UTERMOHLEN AND HAMILTON, *J. Am. Chem. Soc.*, **63**, 156 (1941).
(12) LOURIE AND YORKE, *Ann. Trop. Med. and Parasitol.*, **33**, 289 (1939).
(13) HAHN AND VICTOR, "Synthèse et étude pharmacologique de nouvelles bases quinoleiques à fonction éther-oxyde aminée," Paris, **1938**.
(14) BORSCHE AND GROTH, *Ann.*, **549**, 238 (1941); *Chem. Abstr.*, **37**, 3754 (1943).