[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

Quinolinequinones. IV. Derivatives of 7-Hydroxy-5-8-quinolinequinone[1]

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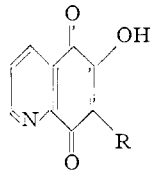
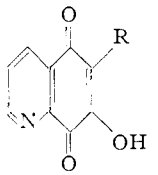
Derivatives of 7-hydroxy-5,8-quinolinequinone (VI) which are isomeric with the previously reported 7-substituted-6-hydroxy-5,8-quinolinequinones have been prepared. The known 5,7-diamino-8-hydroxyquinoline was oxidized to the corresponding quinone-imine which on acid hydrolysis yielded the parent 7-hydroxy-5,8-quinolinequinone (VI). Like 6-hydroxy-5,8-quinolinequinone (I), it is strongly acidic. It forms 7-methoxy-5,8-quinolinequinone when treated with methanol in the presence of an acid catalyst. The 7-hydroxyquinone VI undergoes alkylation with diacyl peroxides, and its 6-propyl derivative VII has been shown to be identical with the Hooker oxidation product of 7-butyl-6-hydroxy-5,8-quinolinequinone (III). Hooker oxidation was also found to occur normally with 6-alkyl-7-hydroxy-5,8-quinolinequinones. By means of the Mannich reaction certain 6-aminomethyl-7-hydroxy-5,8-quinolinequinones (X–XII) have been prepared. These amines and some of the above alkyl derivatives will be tested against amebiasis.

The preceding paper of this series[2] described the preparation of certain 7-substituted 6-hydroxy-5,8-quinolinequinones from the parent hydroxyquinone I by the Mannich reaction or peroxide alkylation and conversion of the alkylation products to 6-alkyl-7-hydroxy-5,8-quinolinequinones by Hooker oxidation. The present work is concerned with the synthesis of 7-hydroxy-5,8-quinolinequinone (VI) and derivatives isomeric with those of 6-hydroxy-5,8-quinolinequinone (I) which proved to be of biological interest. The Mannich product obtained from I with *n*-hexylamine (I, R = $-CH_2NH(CH_2)_5CH_3$) displayed significant amebicidal activity against induced *E. histolytica* infection in the guinea pig and 7-undecyl-6-hydroxy-5,8-quinolinequinone (V) was somewhat more effective.[3,4] Since the Hooker oxidation product of V, 6-decyl-7-hydroxy-5,8-quinolinequinone (VIII), was inactive it was of interest to synthesize and determine the activity of the isomeric pair, *i.e.*, 6-undecyl-7-hydroxy-5,8-quinolinequinone (IX) and 7-decyl-6-hydroxy-5,8-quinolinequinone (IV).[5] Mannich products from 7-hydroxy-5,8-quinolinequinone (VI) have also been prepared for amebicidal assay.





I, R = $-H$
II, R = $-CH_3$
III, R = $-(CH_2)_3CH_3$
IV, R = $-(CH_2)_9CH_3$
V, R = $-(CH_2)_{10}CH_3$

VI, R = $-H$
VII, R = $-(CH_2)_2CH_3$
VIII, R = $-(CH_2)_9CH_3$
IX, R = $-(CH_2)_{10}CH_3$
X, R = $-CH_2N(CH_2)_4CH_2$
XI, R = $-CH_2N(C_2H_5)_2$
XII, R = $-CH_2NH(CH_2)_5CH_3$

A logical source of 7-hydroxy-5,8-quinolinequinone (VI) was the known compound 5,7-diamino-8-hydroxyquinoline easily obtained from 8-hydroxyquinoline by nitration[6,7] and subsequent reduction.[7] An improvement in yield in the latter step was achieved by reducing the nitro compound with sodium dithionite and precipitating the sensitive diamine from the reaction mixture as its relatively stable sulfate.[8] Oxidation with ferric chloride yielded the salt of 7-amino-5,8-quinolinequinone-5-imine which was identified by elementary analysis of its diacetyl derivative. Like the analogous 2-amino-1,4-naphthoquinone-4-imine, this intermediate is comparatively stable. Attempts to hydrolyze it with alkali resulted only in decomposition, which also occurred extensively during acid hydrolysis as evidenced by a drop in yield as reaction time was extended beyond an optimum period. Acceptable yields of 7-hydroxy-5,8-quinolinequinone (VI) could be obtained, however, by conducting the acid hydrolysis in an apparatus in which the product was extracted continuously from the aqueous reaction mixture with hot chloroform. The over-all yield in the three-step conversion of 5,7-dinitro-8-hydroxyquinoline to VI was only about 30%, but advantages of the process are the ready availability of the starting material and the facility with which the reactions can be carried out.

Like 6-hydroxy-5,8-quinolinequinone (I), the 7-hydroxyquinone VI reacts readily *via* the *o*-quinonoid form with *o*-phenylenediamine to give a hydroxypyridophenazine. The hydroxyquinone VI, the vinylog of an acid, is strongly acidic and is converted to a methoxyl derivative when heated with methanol in the presence of an acid catalyst. The product obtained under these conditions is exclusively 7-methoxy-5,8-quinolinequinone although 5-methoxy-7,8-quinolinequinone is also a possible product. The methoxyquinone does not react rapidly with *o*-phenylenediamine but undergoes slow replacement of the methoxyl group and subsequent ring closure to form the same hydroxypyridophenazine as obtained from VI. This reac-

(1) This investigation was supported by a research grant (PHS E-665) from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, Public Health Service.

(2) Y. T. Pratt with N. L. Drake, THIS JOURNAL, **77**, 4664 (1955).

(3) The authors thank Dr. D. Jane Taylor of the National Institutes of Health for these test results. For procedure see D. J. Taylor and J. Greenberg, *Am. J. Hygiene*, **56**, 58 (1952).

(4) Neither of these compounds was significantly active as an anthelmintic and none of the derivatives of 6-hydroxy-5,8-quinolinequinone tested was found to be tuberculostatic. The authors thank the biological division of the Lilly Research Laboratories for conducting these tests.

(5) The significance of the hetero atom will also be determined by tests of the analogous 3-undecyl- and 3-decyl-2-hydroxy-1,4-naphthoquinones. These compounds have been reported by L. F. Fieser, M. T. Leffler, *et al.* (THIS JOURNAL, **70**, 3174 (1948)).

(6) A number of pertinent references appear in a review by J. P. Phillips, *Chem. Revs.*, **56**, 282 (1956).

(7) A. Albert and D. Magrath, *Biochem. J.*, **41**, 534 (1947); T. Urbański, *Roczniki Chem.*, **25**, 297 (1951) [*C. A.*, **48**, 4546*h*, 9370*i* (1954)].

(8) This isolation procedure is useful also in the preparation of 5 amino-8-hydroxyquinoline, the precursor of the parent compound, 5,8-quinolinequinone.

tion also was observed with 6-methoxy-5,8-quinolinequinone.[9]

The structure of the previously reported[2] 6-propyl-7-hydroxy-5,8-quinolinequinone (VII), prepared by Hooker oxidation of 7-butyl-6-hydroxy-5,8-quinolinequinone (III), has now been confirmed by direct synthesis from 7-hydroxy-5,8-quinolinequinone (VI) with dibutyryl peroxide. In a single exploratory experiment 7-methyl-6-hydroxy-5,8-quinolinequinone (II) was converted to VI by Hooker oxidation.

The undecyl derivative IX of 7-hydroxy-5,8-quinolinequinone was prepared by alkylating VI with dilauroyl peroxide and converted by Hooker oxidation to 7-decyl-6-hydroxy-5,8-quinolinequinone (IV).

Under previously reported conditions[2] Mannich products were obtained from VI with piperidine and diethylamine in high yield. With the primary amine *n*-hexylamine, however, slight modifications were necessary to retard the formation of by-products.[10] Simultaneous addition of formaldehyde and base prevented precipitation of the amine salt of VI and permitted use of a solvent from which the product separated so that further reaction was retarded. The yield of XII was 53%, considerably lower than that of the isomeric 6-hydroxy derivative.[2] The three products X, XI and XII were obtained in an analytically pure state after filtration from the reaction mixture and washing with acetone.

The results of biological assays will be reported elsewhere.

Experimental[11,12]

5,8-Diamino-8-hydroxyquinoline.—A suspension of 42.5 g. (0.18 mole) of 5,7-dinitro-8-hydroxyquinoline in 1350 ml. of water containing 0.43 mole of potassium hydroxide was warmed for a short time on a steam-bath to ensure complete conversion to the salt.[13] At 60°, 315 g. of sodium dithionite was added with shaking and nitrogen was passed into the solution while it was maintained at 75 to 85° for 15 minutes. The mixture was then cooled to 35° under nitrogen and treated cautiously with 450 ml. of 12 *N* sulfuric acid. After the evolution of sulfur dioxide had subsided the solution was filtered rapidly through a large Büchner funnel to remove traces of impurities. The filtrate was transferred to a 5-l. round-bottomed flask and warmed at 70–80° for 10 minutes while a rapid stream of nitrogen was introduced. The warm suspension was then stirred under reduced pressure with occasional rewarming until most of the sulfur dioxide had been removed (about 1 hr.). After the mixture had been cooled in an ice-bath the orange sulfate of the product contaminated with sulfur was filtered off and washed with 50 ml. of cold 2 *N* sulfuric acid. The product was purified by dissolving it in 600 ml. of boiling 0.15 *N* sulfuric acid containing a trace of dithionite and filtering the solution through a layer of decolorizing carbon which was washed well with the dilute acid. Upon cooling there was obtained 44 g. of the orange salt of the diamine.[7] This material, pure enough for the subsequent step, contained one molecule each of sulfuric acid and water.

Anal. Calcd. for $C_9H_9ON_3 \cdot H_2SO_4 \cdot H_2O$: C, 37.11; H, 4.50; S, 11.01. Found: C, 37.46, 37.66; H, 4.42, 4.85; S, 10.81, 10.53.

The twice-recrystallized product gave more accurate analytical results.

Anal. Found: C, 37.09, 37.03; H, 4.65, 4.60.

7-Amino-5,8-quinolinequinone-5-imine.—Thirty grams of the once-recrystallized diamine sulfate was added in one portion to a solution of 60 g. of ferric chloride hexahydrate in 150 ml. of water at 45° with vigorous hand stirring. The amine dissolved and the product began to precipitate immediately. After the addition of 15 ml. of 12 *N* sulfuric acid the mixture was cooled rapidly to room temperature and allowed to stand for 15 minutes. It was then cooled in an ice-bath and the deep red sulfate of the quinone-imine was filtered off and washed with a very small volume of cold, dilute sulfuric acid and then with alcohol and ether. The yield was 21 g.

A sample of the above imine salt was converted to the diacetyl derivative by the procedure of Fieser for the corresponding carbocyclic compound.[14] After recrystallization from alcohol the product was obtained as long, glistening, yellow needles which gradually decomposed above 235° and melted to a black liquid at 250°.

Anal. Calcd. for $C_{13}H_{11}N_3O_3$: C, 60.69; H, 4.31. Found: C, 60.82, 60.86; H, 4.10, 4.03.

7-Hydroxy-5,8-quinolinequinone (VI).—The hydrolysis of the above quinone-imine salt was conducted in a continuous extraction apparatus[15] with a return tube at the bottom connected to a 1-l. round-bottomed flask half filled with chloroform. The imine salt was ground and almost completely dissolved in 12 *N* sulfuric acid (5 ml. per g.). When the undissolved material was reduced to a fine suspension, the solution was decanted into the extraction tube, which had been filled with warm chloroform. The remaining salt was washed into the apparatus with a volume of warm water equal to that of the sulfuric acid, making the final acid concentration slightly over 6 *N*. The apparatus was surmounted by a highly efficient condenser and the boiling flask was heated with a Glas-col mantle operating at 110 volts. To maintain maximum reflux rate, the apparatus was wrapped in glass wool except for the region occupied by the reaction mixture, which was only very slightly below 60°. After 24 hours the chloroform solution was cooled and extracted with 0.5 *M* disodium phosphate solution (7 to 8 ml. per g. of starting material) in portions to facilitate transfer of the sodium salt to the cleaned extraction tube where it was continuously washed with chloroform for about one hour. The flask was then replaced with one containing fresh chloroform and the solution of the sodium salt of VI was acidified in the apparatus with about 10% excess of 12 *N* sulfuric acid over that required to neutralize the disodium phosphate. Continuous extraction of the product was allowed to proceed for about 20 hours although the extraction rate was very slow after the first two hours. The chloroform solution was dried by boiling a short time on the steam-bath and then treated with decolorizing carbon. It was concentrated until the bright yellow product began to separate; low-boiling petroleum ether was added and after filtration of the cooled suspension a second crop of clean product was obtained by concentrating the mother liquor. This material, which was suitable for subsequent reactions, gradually decomposed above 190–195°.

The yields, at the same flow rate of chloroform during the extractions,[16] depended upon batch size. In a 5-g. run the yield was 1.8 g. or approximately 55% of theory; on a 10-g. scale the yields were about 2.7 g. or 40% of theory.

(9) Y. T. Pratt with N. L. Drake, THIS JOURNAL, **77**, 37 (1955).

(10) The procedure of D. N. Robertson and K. P. Link, *ibid.*, **75**, 1883 (1953), for coumarin derivatives was followed.

(11) All melting points are corrected. Decomposition points were determined by placing the samples in the bath at 10° below the decomposition points given and heating at the rate of about 3° per minute.

(12) The authors wish to thank Professor Katherine Gerdeman for the microanalyses.

(13) The nitro compound was ground in a mortar with portions of the solution to aid conversion to the sparingly soluble potassium salt and to avoid difficulties due to static electricity.

(14) L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., Boston, Mass., 1941, p. 286.

(15) The apparatus was an all-glass modification of that described by A. A. Morton, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1938, p. 207. For 10-g. runs the inside diameter of the tube was 36 mm.; for smaller runs, 34 mm. The return rate of chloroform was about 50 ml. per minute under the conditions given.

(16) Yields on batch scale presumably could be increased by more efficient extraction of the product or by decreasing the reaction rate. In experiments with more dilute acid some of the starting material remained undissolved and migrated to the organic layer where it did not hydrolyze.

A sample recrystallized from chloroform and petroleum ether for analysis gradually decomposed above 195°.

Anal. Calcd. for $C_9H_5O_3N$: C, 61.72; H, 2.88. Found: C, 61.58, 61.44; H, 2.82, 2.76.

A phenazine was obtained by heating VI under reflux for 30 minutes with one equivalent of *o*-phenylenediamine in absolute alcohol solution. A yellow precipitate began to form at once. It was recrystallized from absolute alcohol (by dissolving in a large volume and concentrating before cooling). When placed in a copper block at 295° this derivative gradually darkened above 320° but did not liquefy at 350°.

Anal. Calcd. for $C_{15}H_9N_3O$: C, 72.86; H, 3.67. Found: C, 72.86, 72.69; H, 3.41, 3.47.

7-Methoxy-5,8-quinolinequinone.—A solution of 0.40 g. of *p*-toluenesulfonic acid monohydrate in 20 ml. of methanol and 20 ml. of chloroform was heated under reflux with a thimble containing Drierite inserted between the flask and condenser so that the returning solvent was dried by passing through the thimble. After about one hour, 2 millimoles of 7-hydroxy-5,8-quinolinequinone was added and vigorous refluxing was continued for 2 hours longer. The solution was cooled, treated with excess sodium acetate solution and extracted with chloroform. The chloroform solution was washed with saturated sodium chloride containing a trace of sodium acetate and then with saturated sodium chloride. It was dried with Drierite, shaken with decolorizing carbon and after filtration, boiled down to 3 or 4 ml. The bright yellow product (0.185 g., 49%) was precipitated by the addition of low-boiling petroleum ether. (Loss due to decomposition was indicated by the recovery of only a small proportion of the starting material from the sodium acetate solution.) The glistening yellow crystals, obtained on recrystallization from methanol, melted at 242.5–243.0° dec., gradually decomposing when placed in the bath at 235°.

Anal. Calcd. for $C_{10}H_7O_3N$: C, 63.49; H, 3.73. Found: C, 63.74, 63.80; H, 3.87, 3.78.

Under the same conditions 6-hydroxy-5,8-quinolinequinone (I) was converted to the 6-methoxyquinone in 66% yield.

The methoxyl derivative of 7-hydroxyl-5,8-quinolinequinone (VI) failed to react with *o*-phenylenediamine when heated 30 minutes under reflux in alcohol solution. Upon prolonged treatment with *o*-phenylenediamine the methoxyl compound formed a phenazine under conditions previously described for 6-methoxy-5,8-quinolinequinone.[9] The crude greenish-yellow precipitate obtained in 95% yield decomposed above 300°. After recrystallization from absolute alcohol, using decolorizing carbon (only 40% recovery), it was yellow. It displayed the same melting point behavior as the phenazine from VI and the decomposition point was unchanged when the two were mixed. Conclusive evidence for the elimination of the methoxyl group to form the phenazine was the absence of methoxyl in a micro Zeisel determination and the fact that the compound dissolved in alkali and reprecipitated when just neutralized with acetic acid (distinction from VI).

Peroxide Alkylations.[17]—The previously described procedure,[2] that of Fieser and co-workers, was followed for the alkylation of VI.

6-Propyl-7-hydroxy-5,8-quinolinequinone (VII) was isolated by evaporating the reaction mixture to dryness, extracting the residue with ether, concentrating the ether solution and finally precipitating the product with low-boiling petroleum ether. There was thus obtained a 29% yield of material melting at 131.0–132.5° and a second crop (9%) melting at 128–133°. After recrystallization from high boiling petroleum ether the substance VII melted at 136.5–138° and did not depress the melting point of the Hooker oxidation product of III.[2]

6-Undecyl-7-hydroxy-5,8-quinolinequinone (IX) crystallized from the cooled reaction mixture. The crude product, contaminated with lauric acid, recrystallized from high-boiling petroleum ether (decolorizing carbon) as bright yellow needles in 34% yield, m.p. 104.5–105.5°. The yield was raised to only 37% by evaporating the filtrate of the reaction mixture, extracting the ether-soluble material and precipitating the quinone with petroleum ether. The melting point of the product was unchanged on further recrystallization.

Anal. Calcd. for $C_{20}H_{27}O_3N$: C, 72.91; H, 8.26. Found: C, 73.15, 73.14; H, 8.02, 8.19.

Hooker Oxidations.[18]—The known 7-methyl-6-hydroxy-5,8-quinolinequinone[18] (II) was obtained by oxidation of 6-ethyl-7-hydroxy-5,8-quinolinequinone[2] according to Hooker's procedure for the related naphthoquinone.[19] The product precipitated from the acidified reaction mixture in only 37% yield (m.p. 238–239° dec.). It was also prepared by alkylating I in the usual fashion with diacetyl peroxide and was isolated by continuous extraction of the precipitated product with benzene. The purified material obtained by this method melted at 236–237° dec.

Anal. Calcd. for $C_{10}H_7O_3N$: C, 63.49; H, 3.73. Found: C, 63.95, 64.09; H, 3.59, 3.78.

By Hooker oxidation the above compound was converted to 7-hydroxy-5,8-quinolinequinone (VI) which was isolated in only 28% yield by extracting the acidified reaction filtrate with chloroform, concentrating the solution, and precipitating the quinone with low-boiling petroleum ether. It decomposed above 190° and the probable absence of a significant amount of starting material was indicated by its failure to liquefy at 240°. After recrystallization from chloroform–petroleum ether the product decomposed above 195° and gave satisfactory analytical data for VI.

Anal. Calcd. for $C_9H_5O_3N$: C, 61.72; H, 2.88. Found: C, 61.76, 61.93; H, 2.88, 3.04.

When treated with *o*-phenylenediamine this material formed a phenazine which decomposed above 320°.

6-Undecyl-7-hydroxy-5,8-quinolinequinone was dissolved in alkali with the aid of pyridine and oxidized as previously described for the isomer[2] except that the reactant solutions were cooled to 0° before mixing and the mixture was kept in an ice-bath for the first 15 minutes. After one recrystallization from 60–80° petroleum ether using decolorizing carbon, the product V was obtained in 67% yield, m.p. 89.0–90.5°. On further recrystallization the melting point rose to 90.5–91.5°.

Anal. Calcd. for $C_{19}H_{25}O_3N$: C, 72.35; H, 7.99. Found: C, 72.42, 72.49; H, 7.97, 7.89.

Mannich Reactions.—The reactions of VI with diethylamine and piperidine were carried out on a 5-millimole scale as previously described.[2] When *n*-hexylamine was added to a suspension of 7-hydroxy-5,8-quinolinequinone (VI) in absolute alcohol an insoluble salt was formed. Although a clear solution was obtained with methanol as the solvent, the product did not precipitate and a considerable quantity of by-product was obtained. Following the procedure of Robertson and Link[9] an alcohol solution of the amine and the formaldehyde was added to a stirred suspension of VI at room temperature. All of the starting material appeared to dissolve before precipitation of the product occurred. After one hour at room temperature, the mixture was cooled in an ice-bath for one hour. Increasing the reaction period to 3 hours did not increase the yield.

The three Mannich products were filtered from the cooled reaction mixtures, washed with ether and triturated with acetone. The material thus obtained was analytically pure. Attempts to recrystallize these substances from methanol and ether led to decomposition.

Compound X was obtained in 92% yield as an orange solid, soluble in water and gradually decomposing above 198° without melting.

Anal. Calcd. for $C_{15}H_{16}O_3N_2$: C, 66.16; H, 5.92. Found: C, 66.26, 65.98; H, 5.88, 5.86.

Compound XI, obtained in 89% yield, was orange, soluble in water, and melted with decomposition at 177–178° when placed in the bath at 170°.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20. Found: C, 64.76, 64.76; H, 6.06, 5.99.

Compound XII, obtained in 53% yield, was red, insoluble in water and decomposed rapidly above 151°.

Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 7.00. Found: C, 66.89, 66.65; H, 7.03, 6.96.

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(17) All of the alkyl derivatives of 6- and 7-hydroxy-5,8-quinolinequinone reported in this paper are bright yellow compounds.

(18) R. Long and K. Schofield, *J. Chem. Soc.*, 3919 (1953), prepared this compound by oxidation of 7-methyl-5,8-quinolinequinone and report a melting point of 230–235° dec. and similar analytical data.

(19) S. C. Hooker, THIS JOURNAL, **58**, 1163 (1936).