nitrobenzene–petroleum ether, was sublimed at bath temperature 145° (0.08 mm.), to give pure *m*-nitrophenylpyruvic acid, m.p. 158–159°, sintering at 152°. *m*-Nitrophenylpyruvic acid exhibits an intense green ferric chloride color test.

Anal. Calcd. for $C_9H_7O_5N$: C, 51.68; H, 3.37; N, 6.71. Found: C, 51.98; H, 3.69; N, 7.06.

m-Nitrophenylpyruvic acid, 35 mg., was dissolved in 350 mg. of concentrated sulfuric acid and heated on the steam-bath for 1.5 hours, by which time the solution was dark brown and gas evolution had ceased. Eight cc. of water was added to the cooled solution, the suspension centrifuged, and the filtrate extracted with ether. Evaporation of the ether extract left 15 mg. of crystalline yellow residue; two recrystallizations from water brought the m.p. to 116–117°, mixed m.p. with authentic *m*-nitrophenylacetic acid, synthesized by the method of Gabriel and Borgmann[16] showed no depression.

(16) S. Gabriel and O. Borgmann, *Ber.*, **16**, 2065 (1883).

Dehydration of *threo*-Methyl β-Phenylglycerate[17] with Sulfuric Acid.—A solution of 0.190 g. of *threo*-methyl β-phenylglycerate and 0.35 g. of concentrated sulfuric acid was heated for 3 minutes on the steam-bath, at the end of which time the color was dark brown. On adding ice-water and cooling, a red oil appeared which was extracted with ether. Extraction of the ether solution with aqueous sodium bicarbonate three times, followed by acidification of the combined bicarbonate extracts, deposited an amorphous mass. This was distilled (short path, 120° (0.2 mm.)) and recrystallized from benzene. The colorless phenylpyruvic acid melted at 156–157° with decomposition; estimated yield was 15%. Literature values are given variously as 154–155°, 156° and 159–160°.[18] The acid gives a strong green color with acidic ferric chloride.

(17) K. Rüber, *ibid.*, **54**, 1960 (1921); R. P. Linstead, L. N. Owen and R. F. Webb, *J. Chem. Soc.*, 1218 (1953).

(18) C. Granacher, *Helv. Chim. Acta*, **5**, 613 (1922).

NEW HAVEN, CONN.

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

Quinolinequinones. III. Derivatives of 6-Hydroxy-5,8-quinolinequinone[1]

BY YOLANDA T. PRATT WITH NATHAN L. DRAKE

RECEIVED MARCH 24, 1955

7-Alkyl-6-hydroxy-5,8-quinolinequinones have been prepared by the alkylation of 6-hydroxy-5,8-quinolinequinone (I) with diacyl peroxides and these products have been converted, by means of Hooker oxidation, to 6-alkyl-7-hydroxy-5,8-quinolinequinones with one less carbon in the side-chain. 7-Aminomethyl-6-hydroxy-5,8-quinolinequinones have been obtained by treating 6-hydroxy-5,8-quinolinequinone (I) with formaldehyde and a primary or secondary amine.

Numerous biologically active compounds have been prepared from 2-hydroxy-1,4-naphthoquinone by the introduction of side-chains at the 3-position. The 3-alkyl derivatives obtained by the action of diacyl peroxides on the parent compound[2] or by Hooker oxidation of the next higher 3-alkyl homolog[3] are active as antimalarials; the 3-aminomethyl derivatives, synthesized by means of the Mannich reaction,[4] have been patented as parasiticides. In the present work, the application of these three reactions to the analogous 6-hydroxy-5,8-quinolinequinone[5,6] (I) (6-hydroxy-5,8-dihydroquinolinedione) has been investigated in the hope that pharmacological tests on representative examples of the resulting products will furnish clues as to the most promising types of derivatives for further studies.

The alkylation of I with diacyl peroxides was carried out according to the method of Fieser, Leffler and co-workers[2b] except that a 10% excess of the peroxides was used. The yield of the propyl derivative[6a] II was somewhat lower (18%), and that of the undecyl derivative IV was higher (11%) than those reported for the corresponding naphthoquinones. The undecyl derivative IV is not only related to the naphthoquinone antimalarials but contains the side-chain of embelin, a dihydroxybenzoquinone derivative which is reportedly an anthelmintic.[7]

TABLE I

DERIVATIVES OF 5,8-QUINOLINEQUINONE

Cmpd.	M.p.,[a] °C.	Yield, %[c]	Carbon, % Calcd.	Carbon, % Found[b]	Hydrogen, % Calcd.	Hydrogen, % Found[b]
II	151.0–152.5	46	66.35	66.56	5.11	5.13
III	134.0–135.0	39	67.52	67.64	5.67	5.57
IV	91.5–92.5	44	72.91	72.77	8.26	8.04
V	203.5–206.0[d]	37	65.02	65.25	4.47	4.45
VI	138.0–139.0	75	66.35	66.59	5.11	4.88
VII	110.0–111.0	68	72.35	72.27	7.99	8.01
VIII	167.0–168.5[d]	81	64.60	64.47	6.20	6.25
IX	203.0–203.5[d]	93	66.16	65.95	5.92	5.96
X	151.5–152.0[d]	78	66.64	66.82	7.04	7.12

[a] Melting point of the purest sample. [b] Averages of duplicates. [c] Based upon the amount of starting material taken although much of it was recovered (25% in II and 20% in III). [d] Decomposes below the melting point; sample placed in the bath at 10° below the melting point and heated at the rate of 2° a minute. [e] By the hydrogen peroxide–copper sulfate method.

Hooker[3a] found that under the influence of alkaline permanganate 3-alkyl-2-hydroxy-1,4-naphthoquinones undergo ring opening and reclosure to form the next lower homologs with the positions of the

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

(2) (a) L. F. Fieser and A. E. Oxford, THIS JOURNAL, **64**, 2060 (1942); (b) L. F. Fieser, M. T. Leffler, *et al.*, *ibid.*, **70**, 3174 (1948).

(3) (a) S. C. Hooker, *ibid.*, **58**, 1163–1179 (1936); (b) L. F. Fieser and M. Fieser, *ibid.*, **70**, 3215 (1948).

(4) M. T. Leffler and R. J. Hathaway, *ibid.*, **70**, 3222 (1948); M. T. Leffler, U. S. Patent 2,541,473 (1951) [*C. A.*, **45**, 7149f (1951)].

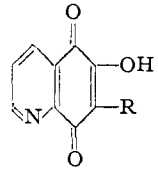
(5) Y. T. Pratt with N. L. Drake, THIS JOURNAL, **77**, 37 (1955).

(6) In related studies of the mode of addition of various reagents to 5,8-quinolinequinone, we have found that 5,6,8-triacetoxyquinoline may be isolated in 47% yield after the addition of acetic anhydride (Thiele reaction; J. Thiele and E. Winter, *Ann.*, **311**, 347 (1900); L. F. Fieser, THIS JOURNAL, **70**, 3165 (1948)). This triacetoxyquinoline may be converted to I by methods used for the analogous conversion in the naphthoquinone series (L. F. Fieser, *loc. cit.*). Since 5,8-quinolinequinone is obtained from the readily available 8-hydroxyquinoline (O. Fisher and E. Renouf, *Ber.*, **17**, 1644 (1884)), this series of reactions provides a suitable alternative synthesis for I. Details will be published in a later communication.

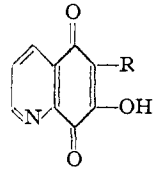
(6a) Previously prepared by a different procedure by R. Long and K. Schofield, *J. Chem. Soc.*, 3919 (1953).

(7) A. S. Paranjpé and G. K. Gokhalé, *Arch. intern. pharm.*, **42**, 212 (1932) [*C. A.*, **27**, 1400 (1933)]; L. F. Fieser and E. M. Chamberlain, THIS JOURNAL, **70**, 71 (1948).

hydroxyl groups and the side-chains reversed. The mechanism of this reaction was elucidated by Fieser and Fieser[3b] who developed an improved procedure, particularly suited to quinones with unsaturated side-chains, in which two successive oxidations were carried out with alkaline peroxide and copper sulfate in alkaline solution. When Hooker oxidation was applied to 7-butyl-6-hydroxy-5,8-quinolinequinone (III) the expected 6-propyl-7-hydroxy-5,8-quinolinequinone (VI) was obtained as indicated by the analytical data, by the formation of a phenazine derivative and by comparison with the isomeric 7-propyl-6-hydroxy-5,8-quinolinequinone (II). Although excellent yields were obtained by the peroxide–copper sulfate method of oxidation in the naphthoquinone series, only 32–37% yields were obtained with the quinolinequinones II and III. The possibility exists that the oxidation of the heterocyclic quinone with hydrogen peroxide could yield N-oxide derivatives, but no evidence of such products was observed. By means of Hooker's original procedure (modified by the addition of pyridine for the oxidation of the 7-undecyl derivative) 6-propyl- and 6-decyl-7-hydroxy-5,8-quinolinequinones (VI and VII) were obtained in yields of 75 and 68%. These products are the first of a projected series of 7-hydroxy-5,8-quinolinequinone derivatives which, it is believed, may be more conveniently prepared directly from the parent hydroxyquinone.



I, R = –H
II, R = $-(CH_2)_2CH_3$
III, R = $-(CH_2)_3CH_3$
IV, R = $-(CH_2)_{10}CH_3$
VIII, R = $-CH_2N(C_2H_5)_2$
IX, R = $-CH_2N(CH_2)_4CH_2$



V, R = $-C_2H_5$
VI, R = $-(CH_2)_2CH_3$
VII, R = $-(CH_2)_9CH_3$

X, R = $-CH_2NH(CH_2)_5CH_3$

It has been reported[4] that 2-hydroxy-1,4-naphthoquinone reacts readily with formaldehyde and a primary or secondary amine to form the 3-aminomethyl derivative in high yields. One exception noted was diethylamine which failed to form the expected Mannich product. It has been found that 6-hydroxy-5,8-quinolinequinone (I) undergoes the Mannich reaction with extreme ease and that the formation of by-products, especially with hexylamine and with diethylamine, was minimized by conducting the reaction entirely at room temperature rather than at the reflux temperature recommended for the related naphthoquinones. In contrast to hydroxynaphthoquinone, the hydroxyquinolinequinone I formed the diethylamino derivative VIII in 80% yield. This product, like certain other Mannich products from diethylamine, is unstable to heat.[8] The products from piperidine (IX) and *n*-hexylamine (X) were obtained in roughly the same yields as those reported for the related naphthoquinones. These compounds, which may exist as the isomeric 7-aminomethyl-8-hydroxy-5,6-quinolinequinones, are related to the 5-chloro-7-aminomethyl-8-hydroxyquinolines, which are effective amebicides.[8]

The results of pharmacological tests will be reported elsewhere.

(8) J. H. Burckhalter and co-workers, THIS JOURNAL, **73**, 4837 (1951); **76**, 4902 (1954).

Experimental[9,10]

Peroxide Alkylations.—The general procedure of Fieser, Leffler and co-workers[2b] was followed except that a 10% excess of the diacyl peroxide (assayed by titration) and 10% additional acetic acid were used. The tabulated results were obtained using 4 to 5-g. quantities of quinone I. Since this quinone did not dissolve readily, it was previously powdered and at least the last fourth of the peroxide was not added until essentially all of I had dissolved. After the reaction was complete, the mixture was concentrated under reduced pressure.

In the isolation of the propyl and butyl derivatives II and III the residue was extracted with ether and unreacted quinone I was recovered as a brown crystalline solid highly insoluble in ether at room temperature. The ether solution was evaporated to dryness and the residue was recrystallized from high-boiling petroleum ether to give the product in the yields indicated in the table. All of these compounds were yellow.

When II was recrystallized from benzene and low-boiling petroleum ether it melted at 145–148° and contained 0.5 mole of benzene per mole of quinone.

Anal. Calcd. for $C_{12}H_{11}NO_3 \cdot {}^1/_2C_6H_6$: C, 70.30; H, 5.51. Found: C, 70.41, 70.34; H, 5.30, 5.51.

After the benzene was removed under reduced pressure at room temperature over several fresh portions of paraffin, the tabulated analytical data were obtained.

In the preparation of 7-undecyl-6-hydroxy-5,8-quinolinequinone (IV) the residue obtained after removal of the solvent was suspended in ether. The ether-insoluble fraction was filtered off and found to be a mixture from which it was not practicable to recover the starting material. The ether solution of the product was shaken with 5% sodium bicarbonate solution, the liquid layers were separated as well as possible and the precipitated sodium salt was filtered and washed with ether. The combined ether solutions were extracted further with bicarbonate until no more red solid precipitated. After the precipitate was washed with low-boiling petroleum ether and finally with water, it was suspended in dilute hydrochloric acid and the product was extracted with ether. The ether extract was washed with water, dried over Drierite and treated with decolorizing carbon. Upon removal of most of the ether the pure product was obtained in 44% yield by precipitation with low-boiling petroleum ether.

7-Propyl-6-hydroxy-5,8-quinolinequinone (II) formed a derivative with *o*-phenylenediamine much less readily than did the parent compound I.[5] In more concentrated solution (50 mg. in 3 ml. of alcohol) the propyl derivative yielded only 52% of the expected phenazine after a reflux period of two hours. After recrystallization from alcohol and from benzene and low-boiling petroleum ether, it melted at 207.0–207.5° with preliminary sintering.

Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23. Found: C, 75.07, 74.83; H, 5.15, 5.08.

Hooker Oxidations.—The procedure of Fieser and Fieser[2b] was followed except that 10% more sodium carbonate was required in the first step to maintain strong alkalinity because of the formation of acidic by-products. After the final acidification of the reaction mixture, the product was extracted with chloroform. The yields of crude product in the preparation of the 6-ethyl- and 6-propyl-7-hydroxy-5,8-quinolinequinones (V and VI) were 37 and 32%.

The original Hooker procedure was followed for the oxidation of 7-butyl-6-hydroxy-5,8-quinolinequinone (III), but it was necessary to add pyridine to dissolve the salt of the 7-undecyl derivative IV. A solution of 1 g. of this quinone in 20 ml. of pyridine was treated with 40 ml. of water and 60 ml. of 2 *N* potassium hydroxide and the solution was

(9) All melting points are corrected.

(10) The authors wish to thank Dr. Mary Aldridge and Miss Katherine Gerdeman for the microanalyses and Mr. Daniel Lima for the preparation of a supply of 6-methoxy-5,8-quinolinequinone.

cooled to 10°. A cold solution of 0.71 g. of potassium permanganate in 70 ml. of water then was added and the mixture was allowed to warm up to room temperature. After 3.5 hours at room temperature the mixture was filtered through Super-cel and the precipitate was washed well with water. The filtrate was acidified to congo red and the product was filtered, washed with water and dried over sulfuric acid. The crude product, obtained in 94% yield, contained an amorphous impurity. After recrystallization from high-boiling petroleum ether it weighed 0.65 g. (68%) and melted at 106.5–109.5°.

6-Propyl-7-hydroxy-5,8-quinolinequinone (VI) was converted to the phenazine derivative with *o*-phenylenediamine by the procedure used for II (above). The yield was the same. After recrystallization from benzene this phenazine had no definite melting point; it gradually decomposed above 240° and became black at about 250° without melting.

Anal. Calcd. for $C_{18}H_{15}NO_3$: C, 74.72; H, 5.23. Found: C, 74.80, 74.90; H, 5.09, 5.04.

Mannich Reactions.—To a suspension of 0.025 mole of I in 30 ml. of absolute alcohol a 10% excess of amine was added with cooling. When solution was complete, 2.1 ml. of 40% formaldehyde solution was added with stirring at 5–10°. The reaction then was allowed to continue overnight at room temperature although it appeared to be essentially complete in about 4 hours. The crystalline products, which precipitated from the reaction mixture, melted no more than 2° below the melting points of the purest samples. The diethylamino derivative VIII, however, was best isolated after the addition of anhydrous ether to the suspension; the product was washed well with ether and purified by dissolving in methanol at about 40° and precipitating with anhydrous ether. The hexylamino compound X also was recrystallized from this solvent mixture and the piperidino derivative IX from 95% ethanol and ether. Both VIII and IX were very soluble in water, but the hexylamino compound X was insoluble. The piperidino derivative was slightly hygroscopic. Compound VIII was orange; compounds IX and X were deep red.

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NOTES

The Solubility of DDT in Water Determined Radiometrically

BY FRANK H. BABERS

RECEIVED MAY 18, 1955

The solubility of DDT in water has been given by Gauvadan and Poussel[1] as approaching 0.1 p.p.m. at 18°, by Roeder and Weiant[2] as between 0.1 and 0.01 p.p.m., and by West and Campbell[3] as "practically insoluble." Gauvadan and Poussel used a nephelometric method, and Roeder and Weiant used for their calculations the time required for the appearance of symptoms of DDT poisoning in the ventral nerve cord of a roach following treatment with saline-saturated solutions of DDT.

Recently in connection with experiments on the physiological action of DDT on insects, the insecticide labeled with carbon-14 has become available. Because of its physiological interest and the paucity of data on the subject, the water solubility of the material has been determined at three temperatures by radiochemical methods.

Experimental

A solution of the radioactive DDT was prepared by dissolving 3.046 mg. in 2 ml. of acetone. 300 Microliters were transferred to a 100-ml. flask and the acetone evaporated at room temperature. Water redistilled from glass was added and the flask heated on a steam-bath with shaking for 1 hour. After cooling somewhat, the flask was put in a constant-temperature bath and shaken for at least 1 week. Samples were then removed and centrifuged at the bath temperature, a portion was filtered through a fine sintered-glass funnel, and aliquots of each portion were taken for analysis. To 1 ml. of acetone containing 1 mg. of non-radioactive DDT in an aluminum counting cup 0.5 ml. of the water solution of radioactive DDT was added, and most of the solvent was evaporated with an infrared lamp. One milliliter of acetone was then added, followed by a second 0.5-ml. portion of the DDT–water solution. The sample was then evaporated to dryness and its radioactivity determined in a proportional counter.

The solubility results were not altered by filtration through sintered glass. At least 10 replications were made and the results compared with the activity obtained from 10 samples of known size. Because of the reproducibility of the results, correction for self absorption was not made. Each preparation was about 0.35 mg./cm.^{2} in thickness. From the results of these experiments, the solubility of DDT in water is 5.9 ± 0.4 micrograms per liter (0.0059 ± 0.0004 p.p.m.) at 2°, 37.4 ± 0.5 micrograms (0.0374 ± 0.0005 p.p.m.) at 25°, and 45 ± 1 micrograms (0.045 ± 0.001 p.p.m.) at 37.5°.

It was found that in very thin layers and microgram qualities DDT is appreciably volatile at room temperatures. This became apparent in preliminary experiments when after 17 samples to which non-radioactive DDT had not been added had been counted, the background of the counting chamber had risen from 59 counts per minute at the start to 311 at the end due to contamination. By the addition of non-radioactive DDT, the sample size was greatly increased and at the same time, the percentage of active DDT decreased so that no further contamination was noted.

(1) P. Gauvadan and H. Poussel, *Compt. rend.*, **224**, 683 (1947).

(2) K. D. Roeder and E. A. Weiant, *Science*, **103**, 304 (1946).

(3) T. F. West and G. A. Campbell, "DDT and Newer Persistent Insecticides," 2nd Ed. rev., Chapman and Hall, Ltd., London, 632 pp. (1950).

(4) The radioactive material used in these experiments was procured under the authority of the United States Atomic Energy Commission.

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The Uncatalyzed Thermal Addition of Formaldehyde to Olefins

BY NEAL O. BRACE

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The uncatalyzed thermal addition of formaldehyde (from paraformaldehyde) to dialkyl-substituted terminal olefins such as diisobutylene,[1] β-pinene[2] and methylenecyclohexane,[3] or to an alkyl-

(1) J. J. Ritter, U. S. Patent 2,335,027; *C. A.*, **38**, 2662 (1944).

(2) J. P. Bain, THIS JOURNAL, **68**, 638 (1948).

(3) R. T. Arnold and J. F. Dowdall, *ibid.*, **70**, 2590 (1948).