with stirring was complete after 17 hours; distillation afforded a colorless oil of b.p. 145–165° (0.15–0.3 mm.), yield 36.2 g. (96.5%). A sample solidified on Dry Ice, and on seeding the material crystallized completely as silky, white needles. The analytical sample, recrystallized three times from petroleum ether at Dry Ice temperature, formed minute, white needles, m.p. 47.0–47.7°.

Anal. Calcd. for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 83.17; H, 11.07.

4-Nitroso-2,3-dimethyl-6-(4'cyclohexylbutyl)-phenol (XV).—Nitrosation of XII (26.0 g., 0.10 mole) by the procedure described for the preparation of XIII gave 28.8 g. (99.7%) of yellow solid, which crystallized from benzene–ligroin as a light-yellow powder of m.p. 125.3–126.3°; yield 17.7 g. (61.3%). A sample, recrystallized twice from benzene–ligroin, gave microcrystalline yellow solid, m.p. 126.2–126.9°.

Anal. Calcd. for $C_{18}H_{27}O_2N$: C, 74.70; H, 9.41. Found: C, 74.70; H, 9.45.

4-Amino-2,3-dimethyl-6-(4'-cyclohexylbutyl)-phenol (XVIII).—Reduction of the nitrosophenol XV (2.89 g., 0.01 mole) in aqueous ethanolic sodium hydroxide solution with excess sodium hydrosulfite gave a granular white solid (2.75 g., 100% yield). It crystallized from ligroin as grayish-white leaflets that partially melted at 102°, resolidified, and remelted at 111–112.5°; yield 2.60 g. (94.5%). Two recrystallizations from ligroin afforded a light-yellow powder that melted at 101–102°, resolidified, and remelted at 110–111°.

Anal. Calcd. for $C_{18}H_{29}ON$: C, 78.49; H, 10.61. Found: C, 78.47; H, 10.55.

Hydrochloride.—Owing to the instability of this aminophenol, it was better purified through its hydrochloride. The crude aminophenol from an identical reduction of XV (2.89 g., 0.01 mole) was dissolved at once in 25 cc. of hot 95% ethanol containing 2 cc. of 6 *N* HCl. The solution was filtered over a pad of Darco, 25 cc. of concentrated hydrochloric acid added, and the mixture cooled. The white needles were collected and dried; m.p. 200.5–202.2°; yield 2.81 g. (90.0%). A sample crystallized from ethanol on addition of hydrochloric acid as cottony clusters of white needles, m.p. 198–200°.

Anal. Calcd. for $C_{18}H_{30}ONCl$: C, 69.31; H, 9.70. Found: C, 69.34; H, 9.63.

2,3-Dimethyl-5-(4'-cyclohexylbutyl)-benzoquinone (XXI).—Purified hydrochloride of XVIII (3.12 g., 0.01 mole) was dissolved in hot acetic acid and treated with 6 g. (0.02 mole) of sodium dichromate in slightly diluted acetic acid. The dark solution was cooled, diluted, and the oily quinone extracted with ether. The ether extract was washed several times, dried, and evaporated to leave 2.77 g. (quantitative yield) of light-orange oil. The quinone crystallized at Dry Ice temperature but remelted at room temperature. A sample was distilled at 130–140° (0.5 mm.) in a short-path apparatus; it was a bright-yellow oil.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.62; H, 9.34.

Hydroquinone.—A small sample of the distilled quinone (XXI) was shaken in ether solution with aqueous sodium hydrosulfite until the color was discharged. The ether residue, after two recrystallizations from benzene–ligroin, formed white needles, m.p. 141.0–141.6°.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.01; H, 10.20.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Synthesis of Some Hydroxy Alkylbenzoquinones

BY W. M. MCLAMORE[1]

Several new hydroxy alkylbenzoquinones have been prepared through the Thiele addition of acetic anhydride to the appropriate alkylated benzoquinones; steric factors in the Thiele addition are qualitatively discussed. In proving the structure of two of the quinones by independent syntheses, new routes to quinones of this type have been developed, one of which appears to be of preparative value. Two additional quinones were prepared by peroxide alkylation of a hydroxy alkylbenzoquinone. None of the quinones prepared possessed significant antimalarial activity in preliminary tests.

In connection with an extensive investigation in these laboratories of 2-alkyl-3-hydroxynaphthoquinones as antimalarial drugs,[2] it was desired to prepare for testing some representative examples of the structurally analogous hydroxy alkylbenzoquinones. Very few quinones of this class are described, and the most promising general approach appeared to be that of Thiele,[3] who found that toluquinone undergoes acid-catalyzed addition of acetic anhydride to give a hydroxytoluhydroquinone triacetate. Hydrolysis of this product, followed by oxidation led to a hydroxytoluquinone considered to be 4-hydroxytoluquinone on the basis of somewhat inconclusive evidence. With the availability through improved procedures[4] of several appropriately alkylated[5] benzoquinones, the method of Thiele has now been employed for preparation of the corresponding hydroxy alkylbenzoquinones. Moreover, in proving the structures of two of the quinones by independent syntheses, several new routes to compounds of this type have been discovered, at least one of which appears to be of preparative value.

Cyclohexylbenzoquinone (I) undergoes the Thiele reaction smoothly,[6] and one of the possible triacetates (II) can be isolated easily in moderate yield. Alkaline hydrolysis of II (in an atmosphere of nitrogen) followed by ferric chloride oxidation gave the sensitive 2-hydroxy-5-cyclohexylbenzoquinone (III). The structure of the quinone follows from its preparation from 4-cyclohexylresorcinol (XVI) by two independent routes. The required 4-cyclohexylresorcinol was prepared in excellent yield by alkylation of resorcinol with cyclohexanol in the presence of the acidic earth Superfiltrol X-365D.[7] Boron fluoride-catalyzed acetylation of XVI produced 4-cyclohexyl-6-acetylresorcinol (XVII), and this on treatment with dilute alkaline hydrogen peroxide in the Dakin reaction as modified by Baker[8] gave a small amount of 2-hydroxy-5-cyclohexylhydroquinone, isolated

(1) Standard Brands Fellow, 1945–1948. Chas. Pfizer and Co., Inc., Brooklyn, N. Y.

(2) Fieser, Leffler and co-workers, THIS JOURNAL, **70**, 3151 (1948).

(3) Thiele and Winter, *Ann.*, **311**, 341 (1900).

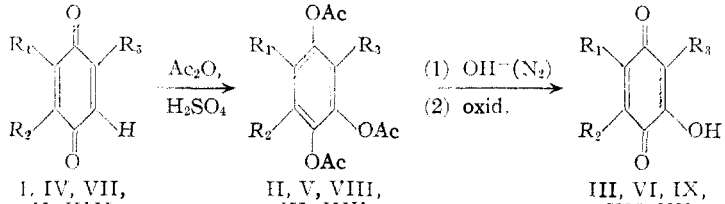
(4) McLamore THIS JOURNAL, **73**, 2221 (1951).

(5) Since both 2-cyclohexyl- and 2-(4'-cyclohexylbutyl)-3-hydroxynaphthoquinone were relatively potent drugs (ref. 2), most of the benzoquinones prepared for testing contained either a cyclohexyl or a 4-cyclohexylbutyl substituent.

(6) Ref. 2, p. 3171.

(7) U. S. Patent 2,125,810 (1938); *C. A.*, **32**, 7478 (1938).

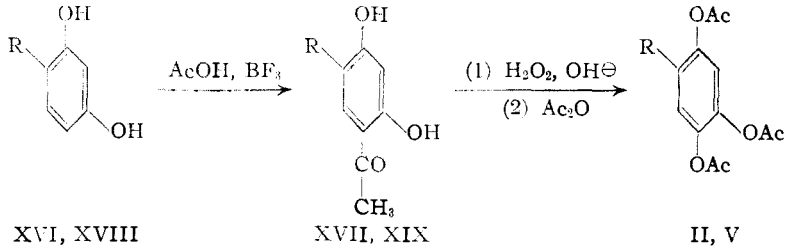
(8) Baker, *J. Chem. Soc.*, 1681 (1934).



I, IV, VII, X, XIII — II, V, VIII, XI, XIV — III, VI, IX, XII, XV

I, II, III: R_1 = *p*-cyclohexyl, $R_2 = R_3 = H$
IV, V, VI: $R_1 = -(CH_2)_4$-cyclohexyl, $R_2 = R_3 = H$
VII, VIII, IX: $R_2 = -(CH_2)_4$-cyclohexyl, $R_3 = -CH_3$, $R_1 = H$
X, XI, XII: $R_2 = -(CH_2)_4$-cyclohexyl, $R_1 = R_3 = -CH_3$
XIII, XIV, XV: $R_3 = -(CH_2)_4$-cyclohexyl, $R_1 = R_2 = -CH_3$

as the triacetate. The triacetate obtained in this way was identical with the triacetate II from the Thiele reaction on cyclohexylbenzoquinone.



XVI, XVIII — XVII, XIX — II, V

XVI, XVII: R = *p*-cyclohexyl; XVIII, XIX: R = $-(CH_2)_4$-cyclohexyl

The second proof of structure for the quinone III proceeded through preparation and oxidation of 4-cyclohexyl-6-aminoresorcinol. This aminoresorcinol could not be obtained by the well-known procedure of coupling with a diazonium salt, followed by reduction of the azo dye in solution[9]; when this procedure was applied to XVI the only product obtained was an air-sensitive, amorphous material insoluble in dilute hydrochloric acid. However, XVI was smoothly nitrosated in alcohol solution with nitrous acid, and the nitroso compound readily reduced to the amine by alkaline hydrosulfite. Oxidation of acidic solutions of the aminoresorcinol led to small amounts of the quinone III. Oxidation of 4-cyclohexyl-6-acetylaminoresorcinol, obtained by catalytic reduction of the nitroso compound in acetic anhydride, gave still smaller yields of III. Finally, direct hydrolysis of the nitrosoresorcinol (as its quinone oxime tautomer[10,4]) gave III in relatively high yield. This latter method, because of the ready availability of 4-alkylresorcinols and because of the good yields obtained here in the two subsequent steps, appears to offer a promising new route to quinones of this type.

The acid-catalyzed addition of acetic anhydride to 2-(4′-cyclohexylbutyl)-benzoquinone[4] (IV) proceeded rapidly and completely. The product was a mixture of solids from which a single triacetate (V) was readily obtained in good yield. A second compound was isolated in small amount; its analysis indicates that it is not an isomeric triacetate, and it was not characterized further. The structure of the triacetate V was established by acetylation of 4-(4′-cyclohexylbutyl)-resorcinol (XVIII) and Dakin oxidation of the resulting 6-acetyl-4-(4′-cyclohexylbutyl)-resorcinol (XIX). From the reaction product, after acetylation, 2-hydroxy-5-(4′-cyclohexylbutyl)-hydroquinone triacetate was obtained in very small amount and proved to be identical with the triacetate V from the Thiele reaction. Hydrolysis of V and oxidation of the resulting hydroquinone gave the hydroxyquinone VI.

Unlike 2-alkylnaphthoquinones, which do not undergo the Thiele reaction, alkylbenzoquinones are known in a few cases to add acetic anhydride at the position adjacent to an alkyl substituent.[11] Both 2-methyl-5-(4′-cyclohexylbutyl)-benzoquinone[4] (VII) and 2,6-dimethyl-3-(4′-cyclohexylbutyl)-benzoquinone[4] (X) reacted readily with acetic anhydride containing a little sulfuric acid. Quinone VII reacted with surprising rapidity to give, however, only a moderate yield of a pure triacetate (VIII); whereas X reacted slowly but gave an excellent yield of the single possible triacetate (XI). These triacetates, VIII and XI, afforded, respectively, the quinones IX and XII. The structure of IX was established by its conversion to XII on peroxide methylation.[12] As expected on steric grounds, the acetoxyl group had entered the molecule at the position adjacent to the relatively small methyl group. No other pure product could be isolated from the reaction. The more hindered quinone, 2,3-dimethyl-5-(4′-cyclohexylbutyl)-benzoquinone[4] (XIII) accordingly reacted very slowly with acetic anhydride to give in low yield the triacetate XIV, from which quinone XV was obtained. And a 2-cyclohexyl-?-(4′-cyclohexylbutyl)-benzoquinone[4] failed to undergo the Thiele reaction at an appreciable rate. Finally, although di-*t*-butylbenzoquinone[13] reacted very slowly with acetic anhydride under forcing conditions, in the only product that could be isolated one of the *t*-butyl substituents had been eliminated.

The Thiele reaction on 2,5-dimethylbenzoquinone (2,5-xyloquinone) produced the known[14] triacetate; hydrolysis and oxidation readily gave 2-hydroxy-3,6-dimethylbenzoquinone. Peroxide alkylation[12,2] of this quinone with di-(4′-cyclohexylbutyryl)-peroxide and with commercial lauroyl peroxide[15] afforded, respectively, 2-hydroxy-3,6-dimethyl-5-(3′-cyclohexylpropyl)-benzoquinone (XX) and 2-hydroxy-3,6-dimethyl-5-undecylbenzoquinone (XXI).

Antimalarial Activity.—None of the hydroxy alkylbenzoquinones III, VI, IX, XII, XV, XX or XXI was active in inhibiting the respiration of parasitized red blood cells obtained from ducks infected with *P. lophurae*—the preliminary, *in*

(9) Fieser, "Org. Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 39.
(10) Sumerford and Dalton, THIS JOURNAL, **66**, 1330 (1944).
(11) Raistrick, *Chem. and Ind.*, **16**, 293 (1938).
(12) Fieser and Oxford, THIS JOURNAL, **64**, 2060 (1942).
(13) I am indebted to the Tennessee Eastman Corporation for a generous supply of this quinone.
(14) Asahina and Ishibashi, *Ber.*, **62**, 1207 (1929).
(15) "Alperox C" from the Lucidol Corporation.

vitro test used extensively for screening 2-alkyl-3-hydroxynaphthoquinones.[2,16]

Acknowledgment.—I am greatly indebted to Prof. Louis F. Fieser for suggesting this problem and for his interest and advice during the investigation.

Experimental[17]

2-Hydroxy-5-cyclohexylhydroquinone Triacetate (II).—The Thiele addition of acetic anhydride (30 cc., containing a little 96% sulfuric acid) to cyclohexylbenzoquinone (4.5 g., 0.0236 mole) was incomplete after 27 days (positive test for quinone[18]). Excess acetic anhydride was hydrolyzed in a large volume of water and the product extracted with ether. The ether residue crystallized from benzene–ligroin as clusters of slightly discolored, heavy prisms; yield 4.55 g. (57.7%). After two recrystallizations from benzene–ligroin with the aid of Darco, the compound formed colorless prisms of m.p. 117.8–118.2°.[19]

Anal. Calcd. for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.80; H, 6.91.

2-Hydroxy-5-cyclohexylbenzoquinone (III).—The triacetate II (1.67 g., 0.005 mole) was dissolved in 15 cc. of ethanol, the solution flushed with purified nitrogen, and 1.5 g. of sodium hydroxide in 10 cc. of water (flushed with nitrogen) added. The hydrolysis was completed by warming for one-half hour on a steam-bath, and the light-green solution acidified by adding 8 cc. of 1:1 hydrochloric acid. The solution was cooled and treated with 5.4 g. (0.02 mole) of ferric chloride hexahydrate dissolved in 20 cc. of dilute hydrochloric acid. The quinone separated at once as yellow needles; yield 0.86 g. (84.0%). The quinone was sensitive to all solvents and was best purified by sublimation. Two sublimations at 65–75° (0.1 mm.) afforded the pure quinone as a micro-crystalline yellow solid of m.p. 89.5–91.5°. The yield of fully purified material was 0.79 g. (76.8%). Alkaline solutions of the quinone are red, and the color is not changed on addition of ethyl cyanoacetate (Craven test[18]). The quinone dissolves in concd. sulfuric acid to an orange solution, and it stains the skin a deep blue.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.12; H, 6.88.

4-Cyclohexylresorcinol (XVI).—Resorcinol (22.0 g., 0.20 mole) and cyclohexanol (22.0 g., 0.22 mole) were mixed with 2.0 g. of Superfiltrol X-365D and heated with stirring until a mixture of water and cyclohexene began to distil (flask temperature of about 135°). Water was separated and the organic layer returned to the flask until 3.5 cc. of water (approximately 0.2 mole) had been collected and the flask temperature had risen to 175°. Benzene was added to the cooled reaction mixture, the catalyst filtered, and the benzene residue distilled to give 35.5 g. of light-yellow oil that slowly solidified. It crystallized from benzene–ligroin as 32.5 g. (84.5% yield) of white leaflets; m.p. 122–124°. After two recrystallizations from benzene–ligroin, a sample formed shining white plates of m.p. 123.5–125.5°.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 74.85; H, 8.42.

4-Cyclohexyl-6-acetylresorcinol (XVII).—Boron fluoride (1.5 g., 0.022 mole) acetylation[4] (60 g. of glacial acetic acid, 1.0 mole) of 4-cyclohexylresorcinol (3.85 g., 0.02 mole) overnight and for 3 hours on a steam-bath afforded 3.96 g. (84.5%) of reddish solid that crystallized from methanol as salmon-colored prisms. On recrystallization from benzene–ligroin, the compound formed small, white needles, m.p. 143–144°; yield 3.67 g. (78.3%). Two more recrystallizations from benzene–ligroin afforded fine, white needles of m.p. 144.5–145.2°.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.52; H, 7.80.

2-Hydroxy-5-cyclohexylhydroquinone Triacetate (II) from **4-Cyclohexyl-6-acetylresorcinol** (**XVII**).—To a solution of 2.34 g. (0.01 mole) of XVII in 20 cc. of 1 *N* NaOH (0.02 mole), flushed with purified nitrogen, was added 21.2 cc. (0.015 mole) of 0.71 *M* hydrogen peroxide.[8] The solution darkened slightly and evolved some heat. After 1 hour at room temperature, the solution was warmed briefly, cooled, and acidified. Some insoluble material, probably XVII, was filtered. Two ether extracts afforded a small residue of dark oil that did not crystallize. Acetylation of the material in the presence of a little zinc dust afforded a small amount of solid; white prisms from benzene–ligroin, m.p. 116–117.5°. When mixed with the Thiele triacetate II (m.p. 117.8–118.2°), the melting point was 117–118°.

6-Nitroso-4-cyclohexylresorcinol.—To a stirred and cooled (−5–5°) solution of 9.61 g. (0.05 mole) of XVI in 175 ml. of 95% ethanol containing 58.5 g. (1.6 moles) of hydrogen chloride was slowly added 3.6 g. (0.05 mole) of sodium nitrite in 20 cc. of water. After 1.5 hours, dilution of the reaction mixture with 1 liter of water afforded 11.46 g. of finely divided, light-orange solid. This sparingly soluble compound crystallized from a mixture of acetone and ethyl acetate as golden-orange needles; yield 8.98 g. (81.3%). A sample, recrystallized from acetone, formed bright yellow needles, dec. 195°.

Anal. Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83. Found: C, 65.10; H, 6.70.

6-Amino-4-cyclohexylresorcinol.—Small portions of solid sodium hydrosulfite were added to a solution of 1.1 g. (0.005 mole) of 6-nitroso-4-cyclohexylresorcinol in 50 cc. of 0.5 *N* NaOH until the red color was discharged. A white solid was present, and the amount was increased by neutralization of excess sodium hydroxide with acetic acid. The aminoresorcinol was filtered, washed with a little fresh, dilute sodium hydrosulfite solution, and dissolved quickly in 40 cc. of dilute hydrochloric acid containing a little stannous chloride. Filtration of the greenish solution over a pad of Darco gave a colorless solution that failed to yield the crystalline hydrochloride when treated with some concd. hydrochloric acid and cooled. The solution was used as such for oxidation experiments.

6-Acetylamino-4-cyclohexylresorcinol.—Hydrogenation of 1.1 g. (0.005 mole) of 6-nitroso-4-cyclohexylresorcinol in a mixture of acetic acid and acetic anhydride in the presence of 70 mg. of presaturated platinum oxide was complete within 20 minutes and afforded (from chloroform) a microcrystalline white solid of m.p. 199.7–201.2°; yield 0.8 g. (64.0%). Two recrystallizations from chloroform gave small, white needles, m.p. 204.2–205.2°. The compound was freely soluble in dilute sodium hydroxide and was reprecipitated by acid.

Anal. Calcd. for $C_{14}H_{19}O_3N$: C, 67.45; H, 7.68. Found: C, 67.53; H, 7.82.

2-Hydroxy-5-cyclohexylbenzoquinone (III). (a) **From 6-Amino-4-cyclohexylresorcinol.**—Small test-experiments indicated that the best conditions for the oxidation consisted of the addition of ferric chloride to a warm solution of the hydrochloride. When 30 cc. of a solution containing 0.003 mole of the hydrochloride was oxidized in this manner, the quinone separated as a greenish-yellow oil. Extraction with ether led to a dark gum that afforded only 0.03 g. (4.8% yield) of quinone III (m.p. 84–87°) on sublimation at 0.2 mm. pressure.

(b) **From 6-Acetylamino-4-cyclohexylresorcinol.**—Oxidation of 6-acetylamino-4-cyclohexylresorcinol in acetic acid solution with excess ferric chloride gave a dark, gummy solid. Ether extraction, followed by sublimation at 90° (0.2 mm.), led to a trace of III, m.p. 88.5–90°, undepressed by admixture of authentic III (m.p. 89–91°). No quinone could be isolated from oxidation of 6-acetylamino-4-cyclohexylresorcinol with nitric acid or with chromic acid.

(c) **From 6-Nitroso-4-cyclohexylresorcinol.**—Direct hydrolysis of the nitroso compound (as the quinone monoxime) was accomplished by heating it (0.73 g., 0.0033 mole) to reflux for a few minutes in 10 cc. of dioxane with 0.5 cc. of acetone, 0.5 g. of cuprous oxide, and 1.6 cc. of hydrochloric acid diluted with 2.0 cc. of water.[10] Dilution of the deep-red reaction mixture gave a dark-red solid. This was dried and sublimed at 80° (0.2 mm.) to give bright-yellow quinone, m.p. 87.5–89.5°; yield 0.30 g. (44.0%).

2-Hydroxy-5-(4′-cyclohexylbutyl)-hydroquinone Triacetate (V).—A solution of 1.23 g. (0.005 mole) of 2-(4′-cyclo-

(16) Fieser and Heymann, *J. Biol. Chem.*, **176**, 1363 (1948).

(17) All melting points are corrected.

(18) Craven, *J. Chem. Soc.*, 1605 (1931).

(19) From this same reaction Fieser reported (ref. 6) a triacetate melting at 92–93°. A sample of Fieser's material (kindly supplied by Prof. Fieser), when heated very slowly, was found to melt incompletely at 92–93°, solidify, and remelt at 117–118°. The two substances are apparently polymorphic modifications of the same compound.

hexylbutyl)-benzoquinone (IV) in 20 cc. of acetic anhydride containing a little sulfuric acid gave a negative quinone test[18] after 24 hours at room temperature. The reaction mixture was stirred with water and the resulting granular white solid filtered and dried; 1.95 g. (100%). Two recrystallizations from ligroin gave 1.2 g. (61.5% yield) of essentially pure V, m.p. 74–76.5°. A sample, after another recrystallization from ligroin or dilute alcohol, formed fine white needles, m.p. 77.0–77.7°.

Anal. Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.75. Found: C, 67.92; H, 7.50.

The filtrate from V, on concentration, deposited several crops of impure V and eventually a second solid, which was further purified by chromatography on acid-washed alumina and recrystallization from ligroin. It formed small white leaflets of m.p. 62–63°, gave a negative test for halogen, and did not correspond in analysis to an isomeric triacetate. It was insoluble in base, but an alkaline alcoholic solution, on shaking in air, developed a red color, characteristic of alkaline solutions of hydroxyquinones. Its structure was not elucidated.

Anal. Found: C, 69.48, 69.65; H, 7.79, 7.87.

2-Hydroxy-5-(4′-cyclohexylbutyl)-benzoquinone (VI).—The triacetate V (1.95 g., 0.005 mole) was dissolved in ethanol and hydrolyzed by heating for one-half hour (in an atmosphere of nitrogen) with dilute sodium hydroxide. The solution was acidified and cooled; sufficient ethanol was added to dissolve the oily hydroxyhydroquinone, and excess alcoholic ferric chloride solution added. The oily quinone that separated was collected, dried, and sublimed at 60° (0.1 mm.) to give 0.83 g. (63.4% yield) of yellow, microcrystalline solid, m.p. 102.5–104.5°. Resublimation afforded pure quinone, m.p. 103.5–105.5°. The hydroxyquinone VI dissolves in dilute sodium hydroxide to a red solution; it gives no Craven test,[18] dissolves in concentrated sulfuric acid to a yellow solution, and stains the skin a deep blue.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.46. Found: C, 73.40; H, 8.59.

4-(4′-Cyclohexylbutyryl)-resorcinol.—Decomposition with sodium acetate of the red complex[4] formed by resorcinol (22.0 g., 0.20 mole), 4-cyclohexylbutyric acid (42.5 g., 0.25 mole) and boron fluoride[20] (20.2 g., 0.30 mole) during 12 hours at room temperature and 3 hours on a steam-bath left an oily white solid, which was washed with water and petroleum ether, and dried; yield 43.4 g. (83.1%); m.p. 96–106°. Two recrystallizations from benzene–ligroin gave white needles of m.p. 98–107°.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.46. Found: C, 73.49; H, 8.51.

Numerous recrystallizations from benzene–ligroin or dilute alcohol failed to give material of sharper melting point; fractionation on a column of acid-washed alumina was likewise ineffective. Moreover, the compound, on treatment with acetic anhydride and sodium acetate, gave a diacetate of m.p. 82.2–83.2° (dilute alcohol); and hydrolysis of this sharply melting diacetate gave material of the same unsharp melting point.

Diacetate.—*Anal.* Calcd. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.21; H, 7.68.

4-(4′-Cyclohexylbutyl)-resorcinol (XVIII).—Reduction of 4-(4′-cyclohexylbutyryl)-resorcinol (26.2 g., 0.10 mole) by the Clemmensen–Martin procedure with efficient stirring[21] was complete within 8 hours and afforded a viscous, almost colorless oil of b.p. 160–170° (0.2 mm.) that rapidly solidified; yield 22.9 g. (92.4%). Crystallization from benzene–ligroin gave 21.1 g. (85.2% yield) of small white leaflets, m.p. 83–86°. A sample, recrystallized twice from benzene–ligroin, formed gleaming white plates of m.p. 83.5–84.5°.

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.17; H, 10.02.

The diacetate, prepared in the usual way, formed small white needles from dilute alcohol, m.p. 58.0–58.6°.

Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.39; H, 8.57.

4-(4′-Cyclohexylbutyl)-6-acetylresorcinol (XIX).—Boron fluoride acetylation of XVIII (5.0 g., 0.02 mole) by the procedure described for preparation of XVII gave a yellowish-white solid (5.35 g., 92% yield) that crystallized from benzene–ligroin as minute white needles of m.p. 70–71°; yield 4.73 g. (81.2%). Two more recrystallizations raised the melting point to 71.5–72.2°.

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.55; H, 8.99.

The diacetate, prepared in the usual way, formed small white needles of m.p. 45.7–46.7°.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.54; H, 8.12.

2-Hydroxy-5-(4′-cyclohexylbutyl)-hydroquinone Triacetate (V) from 4-(4′-Cyclohexylbutyl)-6-acetylresorcinol (XIX).—The modified Dakin oxidation[8] of XIX (2.9 g., 0.01 mole) as described for XVII led to a dark oil that did not crystallize. Acetylation in the presence of a little zinc dust afforded a very small amount of crystalline solid, which after recrystallization formed white needles, m.p. 76.0–77.2°. This material did not depress the melting point of the Thiele triacetate V, and hence the structure of the Thiele product is established as 2-hydroxy-5-(4′-cyclohexylbutyl)-hydroquinone triacetate.

2-Hydroxy-3-methyl-6-(4′-cyclohexylbutyl)-hydroquinone Triacetate (VIII).—Addition of acetic anhydride (35 g., containing 2% of sulfuric acid) to the quinone VII (3.9 g., 0.015 mole) was complete within 1 hour.[18] After 12 hours, the mixture afforded 2.96 g. (48.8%) of small prisms (from petroleum ether). A sample recrystallized from ligroin as small white needles of m.p. 83.0–83.5°.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.98. Found: C, 68.11; H, 8.00.

Yields of triacetate in two other experiments were 34.0 and 42.6%, respectively. The combined filtrates from several experiments left a dark-yellow, viscous oil. This failed to crystallize even after evaporative distillation at 170° (0.3 mm.).

2-Hydroxy-3-methyl-6-(4′-cyclohexylbutyl)-hydroquinone.—Alkaline hydrolysis of the triacetate VIII (1.25 g., 0.0031 mole) under nitrogen in the usual way, followed by dilution and acidification gave the crude hydroquinone in quantitative yield. It crystallized from benzene–ligroin as fine, yellowish needles of m.p. 106–108°; yield 0.80 g. (92.6%). A sample, recrystallized from benzene–ligroin with the aid of Darco, formed fine white needles, m.p. 106–107° (brown melt).

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.42. Found: C, 73.35; H, 9.50.

2-Hydroxy-3-methyl-6-(4′-cyclohexylbutyl)-benzoquinone (IX).—Oxidation of 2-hydroxy-3-methyl-6-(4′-cyclohexylbutyl)-hydroquinone (0.49 g., 0.00176 mole) in 15 cc. of 95% ethanol with excess alcoholic ferric chloride gave IX as yellow needles, which were collected and dried; yield 0.43 g. (88.4%). Crystallization from petroleum ether with the aid of Darco afforded shining golden leaflets of m.p. 104–107°. Sublimation (slow) at 80° (0.1 mm.) gave short yellow needles of m.p. 109.5–111.5°.

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.70; H, 8.73.

Alkaline solutions of IX are violet; it is extracted from ether by 10% sodium carbonate but not by saturated sodium bicarbonate. The color with 96% sulfuric acid is reddish-brown; the quinone does not stain the skin.

Peroxide Methylation.—The structure of this quinone was established as IX by conversion to 2-hydroxy-3,5-dimethyl-6-(4′-cyclohexylbutyl)-benzoquinone (XII) and comparison with an authentic sample of the latter. To a solution of 0.56 g. (0.002 mole) of IX in acetic acid was added 8.0 cc. (0.0022 mole) of 0.28 *M* diacetyl peroxide in acetic acid.[12] The mixture was heated for 1 hour on a steam-bath, cooled, diluted, and the yellow oil extracted with ether. The ether residue dissolved in petroleum ether and slowly deposited some oily, crystalline solid, probably largely the sparingly soluble starting quinone. The filtrate from this material was evaporated and reductively acetylated with acetic anhydride, zinc dust, and a little sodium acetate. This procedure led to a small amount of light-yellow oil,

(20) The condensation was also effected by means of anhydrous zinc chloride, but the yield was lower, and the method required distillation of the product.

(21) Modification of Dr. C. S. Sherman, as employed by Fieser, Leffler and co-workers, THIS JOURNAL, 70, 3203 (1948).

which partially crystallized from ligroin–petroleum ether. After two recrystallizations from ligroin–petroleum ether and two from dilute alcohol, the crystalline material formed tiny white needles of m.p. 108.2–110.2°. A mixed melting point with an authentic sample of 2-hydroxy-3,5-dimethyl-6-(4′-cyclohexylbutyl)-hydroquinone triacetate (**XI**, m.p. 110.5–111.0) was 109.0–110.6°. Hydrolysis of this triacetate in the usual way, followed by oxidation and two recrystallizations of the quinone from dilute acetic acid, gave orange leaflets of m.p. 63.5–64.5°, not depressed by admixture of authentic **XII** (m.p. 65.0–65.5°).

2-Hydroxy-3,5-dimethyl-6-(4′-cyclohexylbutyl)-hydroquinone Triacetate (XI).—The quinone X (0.8 g., 0.0029 mole) slowly reacted with acetic anhydride (10 cc.) containing a few drops of sulfuric acid. After 44 hours, a quinone test[18] was negative; the reaction mixture was stirred with water, and the residual solid filtered and dried. It dissolved in hot ligroin on addition of a little benzene and crystallized as fine white needles of m.p. 109.5–110.5°; yield 1.17 g. (96.0%). After two recrystallizations from ligroin, a sample formed white needles of m.p. 110.5–111.0°.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.14; H, 8.43.

2-Hydroxy-3,5-dimethyl-6-(4′-cyclohexylbutyl)-hydroquinone.—Alkaline hydrolysis of the triacetate XI (4.18 g., 0.01 mole) under nitrogen in the usual way, followed by acidification, gave the hydroquinone as a granular yellow solid. It crystallized from benzene–ligroin with the aid of Darco as yellowish needles; yield 2.42 g. (82.9%). A sample recrystallized as small rosettes of yellowish-white needles; m.p. 115.0–115.6° (to an amber liquid).

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.74; H, 9.69.

2-Hydroxy-3,5-dimethyl-6-(4′-cyclohexylbutyl)-benzoquinone (XII).—The hydroquinone (2.0 g., 0.0068 mole) in acetic acid (15 cc.) was oxidized by addition of a solution of excess ferric chloride in acetic acid. The mixture was diluted, and the yellow-orange quinone filtered and dried (yield 1.97 g., 99.5%). The crude quinone crystallized from petroleum ether (b.p. 20–40°) as rosettes of orange needles; yield 1.73 g. (87.3%). It could be purified further either by recrystallization from dilute acetic acid or by sublimation (very slow) at 55–60° (0.07 mm.); the sublimed sample melted at 65.0–65.6°.

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.45; H, 9.03. Found: C, 74.61; H, 9.02.

Quinone XII was not extracted from ether by saturated sodium bicarbonate or by 10% sodium carbonate, but it was extracted by dilute sodium hydroxide as the sparingly soluble, violet sodium salt. The color with concentrated sulfuric acid was likewise deep violet. The quinone does not dye the skin.

2-Hydroxy-3-(4′-cyclohexylbutyl)-5,6-dimethylhydroquinone Triacetate (XIV).—The quinone XIII (2.74 g., 0.01 mole) reacted very slowly with acetic anhydride containing sulfuric acid; after 26 days quinone was still present.[18] The solution was stirred with water and the residual oil extracted with ether. The ether extracts left a dark gum that failed to crystallize. It was passed in ligroin solution through a 5-inch column of acid-washed alumina. Most of the dark impurities were retained near the top of the column, while the poorly adsorbed, unreacted quinone was rapidly eluted by ligroin (2.0 g. of orange, oily quinone was recovered). Further elution with mixtures of benzene and ligroin gave three small fractions of light-yellow gum, all of which crystallized from ligroin to furnish altogether 0.30 g. (7.2% yield; 26.6% yield based on recovered quinone) of XIV as yellowish-white needles. Recrystallization from ligroin gave clusters of compact white needles (0.28 g.), m.p. 74.5–75.5°.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.94; H, 8.32.

2-Hydroxy-3-(4′-cyclohexylbutyl)-5,6-dimethylbenzoquinone (XV).—The triacetate XIV (150 mg.) was dissolved in ethanol and hydrolyzed under nitrogen with dilute sodium hydroxide. Acidification produced the hydroquinone as an amber oil that rapidly solidified. It was filtered, dissolved in warm acetic acid and oxidized by addition of 1 g. of ferric chloride. The yellow-orange needles of XV were collected and dried; yield 105 mg. (100%). The quinone was best purified by sublimation (very slow) at 60° (0.2 mm.); it was obtained as a light-orange crystalline powder of m.p. 68.5–70.0°. Quinone XV formed a sparingly soluble, deep violet sodium salt; its solution in sulfuric acid was also deep violet in color.

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.45; H, 9.03. Found: C, 74.49; H, 9.16.

Thiele Reaction of 2,5-Di-*t*-butylbenzoquinone.—A suspension of 4.4 g. (0.02 mole) of 2,5-di-*t*-butylbenzoquinone in 40 cc. of acetic anhydride containing sulfuric acid was kept for 48 days with occasional brief periods of warming on a steam-bath. The dark mixture was stirred with water, and the semi-solid residue extracted with ether. Several recrystallizations from benzene–ligroin gave 3.2 g. of white prisms that melted 110–111°, resolidified at 115°, and remelted 121–122°.

Anal. Calcd. for $C_{30}H_{28}O_6$: C, 65.91; H, 7.74. Calcd. for $C_{16}H_{20}O_6$: C, 62.53; H, 6.23. Found: C, 62.85, 62.61; H, 6.39, 6.30.

2,5-Dimethylbenzoquinone (2,5-Xyloquinone).—A suspension of the diazonium salt from 52.5 g. (0.25 mole) of sulfanilic acid dihydrate[9] was added to a mixture of 200 g. of ice and an alkaline solution of 30.5 g. (0.25 mole) of 2,5-xylenol containing 55 g. (1.37 moles) of sodium hydroxide in 300 cc. of water. After 1.5 hours the deep-red solution was warmed to 40–50° and treated with a slight excess of technical sodium hydrosulfite. The cooled suspension was filtered, and the yellowish aminophenol washed with a little fresh, dilute sodium hydrosulfite solution. It was transferred at once to a mixture of 32 cc. of hydrochloric acid, 250 cc. of water and 1 g. of stannous chloride. The orange solution was heated to boiling, 50 cc. of hydrochloric acid added, the solution filtered over a pad of Darco, and the light-yellow filtrate treated with 100 cc. of hydrochloric acid. On cooling, 4-amino-2,5-dimethylphenol hydrochloride crystallized as white prisms; yield 32.9 g. (75.9%).

The hydrochloride (31.8 g., 0.183 mole) was dissolved in a solution of 50 cc. of sulfuric acid in 1000 cc. of water and added all at once to a solution of 35 g. (1.2 moles) of potassium dichromate in 500 cc. of water. The bright-yellow quinone that rapidly appeared on mixing was collected and dried; yield 23.5 g. (94.2%); m.p. 123–124° (lit.[22] 125°).

2-Hydroxy-3,6-dimethylhydroquinone Triacetate.—To a mixture of 100 g. of acetic anhydride and 3 g. of 96% sulfuric acid was added 13.6 g. (0.10 mole) of 2,5-dimethylbenzoquinone. Some cooling was required to keep the temperature at 40–50°. After 11 hours, the solution was only faintly yellow and gave a negative quinone test.[18] It was stirred with 600 cc. of water, and the residual white solid filtered and dried; m.p. 103–104.2° (lit.[14] 108°); yield 26.5 g. (94.7%). The material crystallized from benzene–ligroin as dense opaque prisms (25.0 g.) of m.p. 104–104.6°; a second recrystallization did not raise the melting point.

2-Hydroxy-3,6-dimethylbenzoquinone.—Fourteen grams (0.05 mole) of 2-hydroxy-3,6-dimethylhydroquinone triacetate was hydrolyzed under nitrogen in the usual way with 15 g. of sodium hydroxide in dilute alcoholic solution. Acidification and addition of more alcohol gave a clear light-yellow solution, to which was added 54 g. of ferric chloride hexahydrate in acidic ethanol. Dilution furnished the quinone as an orange, crystalline solid; yield 5.8 g. (76.4%). It was best purified by sublimation (rapid) at 80° (0.15 mm.), which afforded 5.7 g. (75.0% yield) of orange prisms, m.p. 102–104° dec. A sample resublimed as reddish-orange prisms, m.p. 102–104° dec.

Anal. Calcd. for $C_8H_8O_2$: C, 63.15; H, 5.30. Found: C, 63.23; H, 5.26.

2-Hydroxy-3,6-dimethyl-5-(3′-cyclohexylpropyl)-benzoquinone (XX).—A solution of 22.6 g. (0.12 mole) of 4-cyclohexylbutyryl chloride in 50 cc. of absolute ether was shaken with ice and a solution of sodium peroxide, freshly prepared from 17.2 cc. of "Superoxol" (0.132 mole by titration) and a dilute solution of 9.6 g. (0.24 mole) of sodium hydroxide.[2] Shaking was continued for 10 minutes with occasional additions of ice. The ether layer was separated, washed with saturated salt solution, dried over anhydrous magnesium sulfate, filtered, and diluted to 100 ml. with dry ether. A 1.0-ml. aliquot, titrated iodometrically, indicated the presence of 0.0405 mole (67.5% yield) of di-(4-cyclohexylbutyryl)-peroxide.

Alkylation[2] of freshly sublimed 2-hydroxy-3,6-dimethyl-

(22) Nietzski, *Ber.*, **13**, 472 (1880).

benzoquinone (4.56 g., 0.03 mole) in acetic acid (75 cc.) with this peroxide solution furnished a red oil, which was washed in ether with three portions of saturated sodium bicarbonate to remove unreacted 2-hydroxy-3,6-dimethylbenzoquinone as the deep-violet sodium salt. The ether residue crystallized from petroleum ether (b.p. 20–40°) at Dry Ice temperature to give 3.57 g. (43.0% yield) of orange quinone. Recrystallization from low-boiling petroleum ether afforded rosettes of light-orange needles, m.p. 79–80.5°; yield 2.62 g. (31.6%). Recrystallization of a sample once more from petroleum ether and once from dilute ethanol furnished yellow needles of m.p. 80.0–80.7°. The sparingly soluble, deep-violet sodium salt was formed on treatment of the quinone with sodium hydroxide.

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 74.02; H, 8.92.

2-Hydroxy-3,6-dimethyl-5-undecylbenzoquinone (XXI).—An acetic acid solution of 2-hydroxy-3,6-dimethylbenzoquinone (3.04 g., 0.02 mole) was heated for 1 hour on a steam-bath with 8.89 g. (0.022 mole) of commercial lauroyl peroxide.[15] Removal of acetic acid under reduced pressure left a partially crystalline residue. Unalkylated quinone was removed by extraction with bicarbonate and the residue crystallized from ligroin to give 2.68 g. (43.8% yield) of crude product. Recrystallization from ligroin and finally from dilute acetic acid gave cottony clusters of light-orange needles, m.p. 102.0–102.3°. The quinone was sparingly soluble in dilute sodium hydroxide as the deep violet salt.

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.33; H, 9.96.

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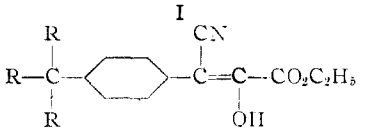
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

Alkyl-β-cyano-α-hydroxycinnamates and Pyrrolidinetriones[1]

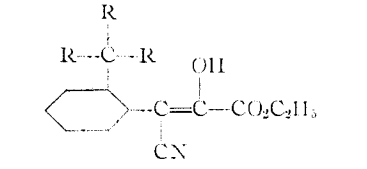
BY GLENN S. SKINNER, JULES A. GLADNER AND RICHARD F. HEITMILLER

The synthesis and separation of additional isomeric alkyl-β-cyano-α-hydroxycinnamates has been accomplished. Infrared absorption studies reveal that in the solid state these esters exist in the enol form. As more methyl groups are substituted for the hydrogen of an *o*-methyl group cyclization to a 4-alkylpyrrolidinetrione still takes place but the entry of bromine into the ring is hindered and there is alternation in the melting point. There is little or no evidence of alternation in the para series and bromine in no case enters the ring of the cyclicized product.

In a previous report[1e] it was shown that the blocking of the para position of ethyl β-cyano-α-hydroxycinnamate with a methyl group did not prevent cyclization by bromine and water to an arylpyrrolidinetrione, but that it did prevent the entry of bromine into the aromatic nucleus. The further introduction of the methyl group into all ortho and para positions caused the formation of an uncyclized product containing bromine in the side chain. It therefore seemed desirable to investigate the effect of methyl groups outside the nucleus as in (I) or (II) where the number of methyl groups (R–) is varied from zero to three.

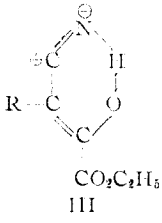


I



II

Customarily, compounds of this type have been called pyruvates. However, they yield ethers of the enol form which are therefore named as derivatives of β-cyano-α-hydroxycinnamic acid. The infrared spectrograms (Fig. 1) of the ethyl *o*- (A) and *p*-methyl-β-cyano-α-hydroxycinnamates (B) both show absorption for the ethylenic double bond (6.2μ) and one carbonyl group (5.8μ), in harmony with ethyl β-cyano-α-ethoxycinnamate. The ether (C) gives a very definite absorption for the nitrile group (4.6μ) which it is almost entirely absent for the cyanohydroxycinnamates. In the latter there is also indication of a bonded OH at 3.0μ. This behavior suggests that the enols may have the structure (III).



III

TABLE I

ALKYL β-CYANO-α-HYDROXYCINNAMATES

$[(CH_3)_mCH_n]-C_6H_4-C(OH)=C(CN)-CO_2C_2H_5$

Alkyl	*m*	*n*	M.p., °C.	Nitrogen, % Calcd.	Found
o-Methyl[1e]	0	3	115–117		
o-Ethyl	1	2	66–67	5.71	5.78
o-Isopropyl	2	1	115.5–116.5	5.41	5.36
p-Methyl[1e]	0	3	88–89		
p-Ethyl	1	2	82–83	5.71	5.81
p-Isopropyl	2	1	78–79	5.41	5.46
p-*t*-Butyl	3	0	74–75	5.13	5.06

The esters (Table I) decomposed to the pure nitriles (Table II) in fair yields when heated with an excess of dilute alkali to a temperature of 70–80°. The nitriles were identified by hydrolysis to the alkarylacetic acids (Table IV).

TABLE II

NITRILES $R-C_6H_4-CH_2CN$

R	B.p., °C. (5 mm.)	Yield, %	d^{25}_4	Nitrogen, % Calcd.	Found
o-C_2H_5–	95–97[a]	69		9.66	9.59
p-C_2H_5–	100–101	95	0.9775	9.66	9.72
p-iso-C_3H_7–	106–108	77	.9631	8.80	8.88
p-*t*-C_4H_9–	119–121	79	.9581	8.09	8.14

[a] B.p. at 2 mm.

(1) Previous reports in this series: THIS JOURNAL, (a) **55**, 2036 (1933); (b) **62**, 2882 (1940); (c) **64**, 2600 (1942); (d) **66**, 496 (1944); (e) **70**, 4011 (1948); (f) **72**, 5569 (1950).