[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Preparation of Some Alkylbenzoquinones

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Several new alkylated benzoquinones have been prepared by improved procedures that appear to be of general applicability. Hydroquinone (and 2-cyclohexylhydroquinone) was conveniently acylated in good yield by 4-cyclohexylbutyric acid and boron fluoride; the resulting ketone was smoothly reduced by low-pressure catalytic hydrogenation to the alkylhydroquinone, which was oxidized to the quinone in quantitative yield. *m*-Cresol, 3,5-xylenol and 2,3-xylenol were all acylated by 4-cyclohexylbutyric acid and boron fluoride; Clemmensen reduction of the resulting *o*-hydroxyketones, nitrosation of the alkylphenols, reduction of the *p*-nitrosophenols to the corresponding *p*-aminophenols, and oxidation of the latter led to the corresponding quinones in good over-all yields.

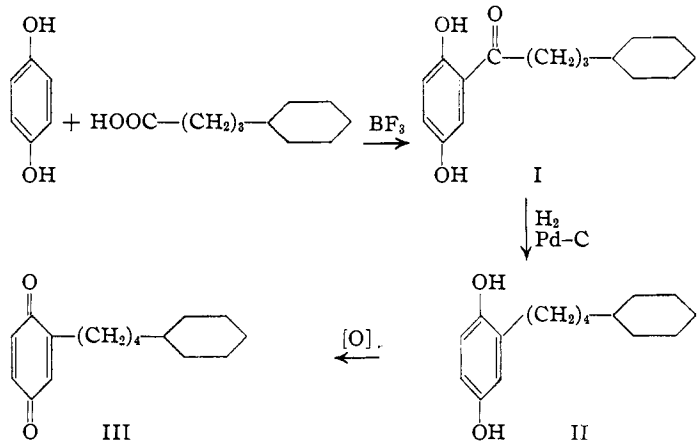
Alkylated 1,4-benzoquinones are most generally prepared by oxidation of the appropriate hydroquinones or *p*-aminophenols.[2] The object of the present paper is to report the preparation and oxidation of several new compounds of these latter types by improved procedures that promise to be of general applicability.

Direct alkylation of the hydroquinone nucleus is useful only for the introduction of one or more *s*- or *t*-alkyl substituents. Primary alkyl groups are usually introduced indirectly by means of the Friedel–Crafts or Fries acylation procedures, followed by Clemmensen reduction of the resulting ketones.[3,4] These methods leave much to be desired as regards yields and convenience of operation.

Although boron fluoride has been used in a few cases as catalyst for Friedel–Crafts type acylations,[5,6,7] it does not appear to have been applied to the acylation of polyhydric phenols.[8] Hydroquinone has now been condensed with 4-cyclohexylbutyric acid by means of boron fluoride to give 2-(4′-cyclohexylbutyryl)-hydroquinone (I) in good yield. With boron fluoride-etherate complex as catalyst, I was produced in low yield, along with considerable amounts of ethyl 4-cyclohexylbutyrate. Use of gaseous boron fluoride in excess, however, led to I in 74% yield. A small amount of tetrachloroethane was used as solvent, although the ketone was produced in comparable yield simply by use of a moderate excess of the low-melting 4-cyclohexylbutyric acid as solvent. This method has the considerable advantage of proceeding from hydroquinone itself and the free acid, and does not require protection of the hydroquinone nucleus or preparation of the acid chloride. The product crystallizes in good purity from the reaction mixture after destruction of the boron fluoride complex with sodium acetate.

Clemmensen reduction of the ketone I gave 2-(4′-cyclohexylbutyl)-hydroquinone (II) in low yield (30–35%) and produced considerable amounts of hydrocarbon by-products. Catalytic hydrogenation was more successful. High-pressure, high-temperature hydrogenation with a copper chromite catalyst gave somewhat impure II in 60–65% yield. The best result was obtained by low-pressure hydrogenation in absolute ethanol with palladium-on-charcoal as catalyst,[9] which afforded pure II in 86.5% yield. Oxidation of II with either sodium dichromate in acetic acid or with silver oxide in dry ether gave 2-(4′-cyclohexylbutyl)-benzoquinone (III) in quantitative yield.

Cyclohexylhydroquinone[10] was acylated in moderate yield by 4-cyclohexylbutyric acid and boron fluoride to give a single crystalline ketone (IV) of unknown orientation. Attempts to establish the structure of IV as the expected 2-cyclohexyl-5-(4′-cyclohexylbutyryl)-hydroquinone were unsuccessful; it was recovered unchanged from attempts to convert it to the known 2-hydroxy-5-cyclohexylhydroquinone[11] by means of the modified Dakin reaction.[12,13] The ketone IV was reduced in excellent yield by low-pressure catalytic hydrogenation to a dialkylhydroquinone (V), which was smoothly oxidized by ferric chloride to the corresponding benzoquinone (VI).



Both of the acylhydroquinones I and IV were oxidizable with some difficulty to the corresponding

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

(2) For a recent review, see Cason, in Adams, "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 305.

(3) Cruickshank and Robinson, *J. Chem. Soc.*, 2064 (1938).

(4) Cook, Heilbron and Lewis, *ibid.*, 659 (1942).

(5) Meerwein and Vossen, *J. prakt. Chem.*, **141**, 149 (1934).

(6) Kästner, in "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p. 249.

(7) Fawaz and Fieser, THIS JOURNAL, **72**, 996 (1950).

(8) After this work was completed, Killelea and Lindwall (*ibid.*, **70**, 428 (1948)) reported the synthesis of resacetophenone with boron fluoride as catalyst.

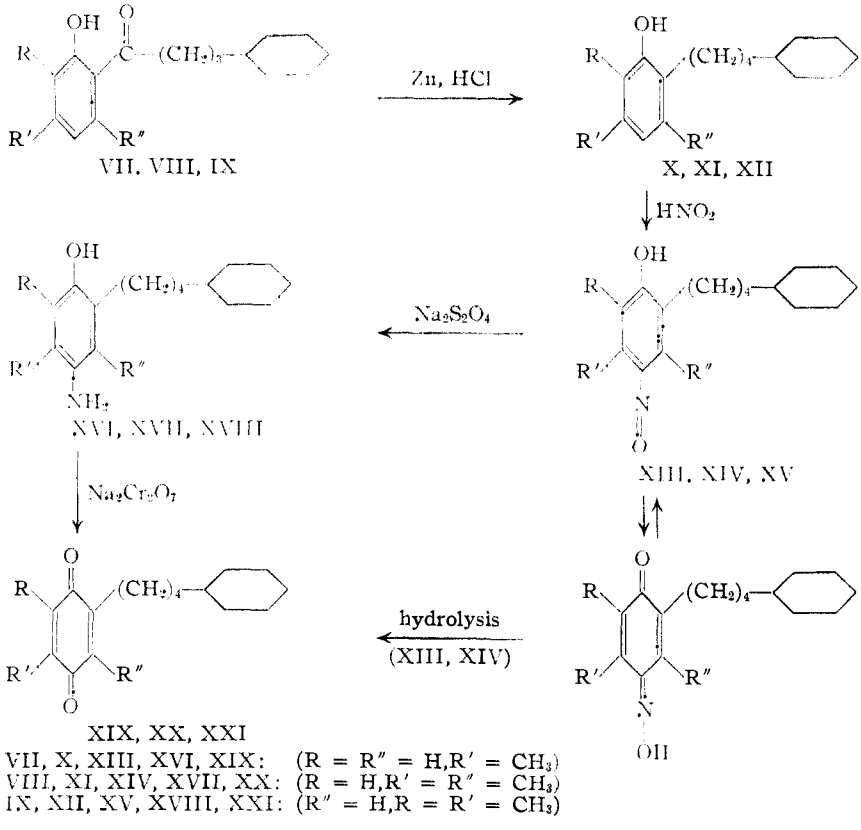
(9) Hartung and Crossley, *ibid.*, **56**, 158 (1934). In accord with Hartung's conclusion that similar hydrogenations do not proceed through the carbinol, there was no break in the hydrogenation curve, and the characteristic, greenish-yellow fluorescence of the phenolic ketone was present until all the hydrogen had been absorbed.

(10) Fieser, *ibid.*, **70**, 3171 (1948).

(11) McLamore, *ibid.*, **73**, 2225 (1951).

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

(13) Barger, *ibid.*, **113**, 218 (1918).



VII, X, XIII, XVI, XIX: (R = R″ = H,R′ = CH_3)
VIII, XI, XIV, XVII, XX: (R = H,R′ = R″ = CH_3)
IX, XII, XV, XVIII, XXI: (R″ = H,R = R′ = CH_3)

acylbenzoquinones. I was best oxidized with sodium dichromate in acetic acid and IV with silver oxide in dry ether. Both oxidations were complicated by the tendency of the quinone produced to combine with the remaining hydroquinone and form the sparingly soluble and deeply colored quinhydrone.

Each of the three phenols, *m*-cresol, 3,5-xylenol and 2,3-dimethylphenol[14] was acylated in good yield by 4-cyclohexylbutyric acid with boron fluoride to give the corresponding 6-(4′-cyclohexylbutyryl)-phenol (VII, VIII and IX, respectively). No 4-acylphenol was formed except in the case of 2,3-dimethylphenol; the small amount formed in this case was readily separated by virtue of its sparing solubility in cold petroleum ether. These acylphenols (VII, VIII, IX) were all readily reduced in good yield to the corresponding alkylphenols X, XI and XII, by means of the Clemmensen–Martin procedure, modified by efficient stirring,[15]

Inasmuch as these alkylated phenols were all insoluble in dilute aqueous alkali, they could not conveniently be converted to the corresponding aminophenols by the well-known procedure[16] involving coupling of the phenol in dilute alkaline solution with a diazonium salt. The phenols X, XI and XII were, however, all smoothly nitrosated by addition of sodium nitrite to a solution of the phenol in ethanol containing an excess of hydrogen chloride; the *p*-nitrosophenols, XIII, XIV and XV, respectively, were produced in good yields. Reduction of the nitrosophenols in alkaline solution with sodium hydrosulfite gave the desired *p*-aminophenols XVI, XVII and XVIII in excellent yields. These alkylated *p*-aminophenols were surprisingly stable and could easily be obtained analytically pure by recrystallization. They were, however, sufficiently pure as obtained from the reduction for oxidation to the corresponding benzoquinones (XIX, XX and XXI).

Alternatively, the nitrosophenols XIII and XIV could be hydrolyzed directly (as their benzoquinone monoxime tautomers) to the corresponding quinones by the method of Sumerford and Dalton.[17] This procedure was somewhat inferior as regards yields and purity of products to the two-step process described above.

I am deeply indebted to Professor Louis F. Fieser for his guidance and advice throughout the course of this investigation.

Experimental[18]

2-(4′-Cyclohexylbutyryl)-hydroquinone (I).—Boron fluoride from a cylinder was passed into a solution of 22.0 g. (0.2 mole) of hydroquinone and 50.0 g. (0.29 mole) of 4-cyclohexylbutyric acid in 50 cc. of tetrachloroethane until 22.7 g. (0.34 mole) had been absorbed. The dark red solution was heated on a steam-bath for 4 hours (during which it became turbid), cooled, and poured into 750 cc. of water containing 55 g. (0.67 mole) of sodium acetate. The red complex was decomposed, and addition of petroleum ether precipitated 33.5 g. of yellow solid. Concentration of the organic layer gave 5.3 g. more; yield 38.8 g. (74.0%); m.p. 107–109°. Recrystallization from benzene–ligroin or dilute alcohol gave light-yellow needles with a slight greenish fluorescence, m.p. 109–110°. An alcoholic solution of the compound gives a green color with ferric chloride.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.46. Found: C, 73.05; H, 8.71.

2-(4′-Cyclohexylbutyryl)-benzoquinone.—Oxidation of the hydroquinone I (2.62 g., 0.01 mole) in acetic acid solution with sodium dichromate (2.98 g. of the dihydrate, 0.01 mole) at room temperature led to 2.4 g. of a semi-crystalline, reddish-orange solid. Extraction of this material with petroleum ether (b.p. 30–60°) in a Soxhlet apparatus and crystallization of the extract furnished 1.65 g. (63.5% yield) of the quinone. It crystallized from petroleum ether as short, orange needles of m.p. 75–77°, but the purest sample was obtained by sublimation in vacuum, followed by crystallization from ligroin–petroleum ether; orange leaflets of m.p. 77.0–77.6°.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 74.09; H, 7.75.

(14) Smith and Opie, *J. Org. Chem.*, **6**, 427 (1941). In the preparation of this phenol by hydrolysis of the diazonium sulfate from 2,3-dimethylaniline, intramolecular reaction and coupling were minimized and the yield (80%) considerably improved by carrying out the hydrolysis in higher dilution and by continuously extracting the phenol into ether as it was formed.

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

(16) Fieser, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, 1943, p. 39.

(17) Sumerford and Dalton, THIS JOURNAL, **66**, 1330 (1944).

(18) All melting points are corrected.

2-(4'-Cyclohexylbutyl)-hydroquinone (II).—A solution of 13.1 g. (0.05 mole) of I in 100 cc. of absolute ethanol was shaken with hydrogen at 30 lb. pressure in the presence of 3.0 g. of a palladium-on-charcoal (1:6) catalyst.[9] One-tenth mole of hydrogen was absorbed within 2 hours, and no more was absorbed on longer shaking. The characteristic, greenish-yellow fluorescence of the hydroquinone persisted until hydrogenation was complete, when the solution became colorless. After filtration of the catalyst and removal of ethanol, the hydroquinone was crystallized from benzene–ligroin as a gel of fine white needles, m.p. 78–79°; yield 10.7 g. (86.5%). This material (which was susceptible to air oxidation), after two recrystallizations from benzene–ligroin, formed white needles of m.p. 79.0–79.6°.

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.32; H, 9.81.

Reduction by the Clemmensen–Martin method with stirring gave the compound in yields of 30–35%, while high-pressure, high-temperature hydrogenation in ethanol with a copper chromite catalyst led to a less pure material in 60–65% yield.

2-(4'-Cyclohexylbutyl)-benzoquinone (III).—Oxidation of II (4.97 g., 0.02 mole) in acetic acid with sodium dichromate (6.0 g. of the dihydrate, 0.02 mole) afforded, after dilution with water, 4.9 g. (100% yield) of light-yellow quinone, m.p. 59–62°. Recrystallization from dilute methanol or from petroleum ether was attended by considerable loss and little increase in purity.

Purer quinone was obtained by oxidation of the hydroquinone (1.24 g., 0.005 mole) in absolute ether with silver oxide (2.31 g., 6.01 mole) in the presence of anhydrous magnesium sulfate. The solution was filtered and evaporated to leave 1.28 g. (the theoretical yield is 1.23 g.) of rapidly crystallizing orange-yellow oil. Recrystallization from dilute acetic acid gave 0.95 g. (77.2% yield) of beautiful, lemon-yellow needles, m.p. 62.5–63.5°.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.09; H, 9.19.

2-Cyclohexyl-?-(4'-cyclohexylbutyryl)-hydroquinone (IV).—Cyclohexylhydroquinone[10] was obtained as a light amber-colored glass by alkylation of hydroquinone with cyclohexanol in the presence of "Superfiltrol X-365D"[19] and distillation of the product. Acylation of this material (34.5 g., 0.179 mole) with 4-cyclohexylbutyric acid (46.0 g., 0.27 mole) and boron fluoride (22 g., 0.32 mole) in tetrachloroethane (75 cc.) for 12 hours at room temperature and 6 hours on a steam-bath, followed by decomposition of the complex (as described in the preparation of I), and crystallization of the yellow solid from benzene–ligroin gave 31.7 g. (51.4% yield) of almost pure IV. Two recrystallizations from benzene–ligroin afforded yellow plates of m.p. 156.0–156.8°. Neither repeated recrystallization from benzene–ligroin or dilute alcohol nor chromatographic fractionation on acid-washed alumina gave samples of higher melting point, and none of these samples had quite the correct analysis. The purest specimen was obtained by reduction of a pure sample of the corresponding quinone (below); it formed pale-yellow needles (from benzene–ligroin) of m.p. 157.5–158.0°.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.37. Found: C, 77.06; H, 9.83.

The compound was recovered unchanged after treatment with alkaline hydrogen peroxide in either alcohol or pyridine solution.[12,13]

2-Cyclohexyl-?-(4'-cyclohexylbutyryl)-benzoquinone.—Oxidation of the hydroquinone IV (3.4 g.; 0.01 mole) was best carried out by slow extraction from a Soxhlet thimble into a boiling ether suspension of dry silver oxide (3.47 g., 0.015 mole) and anhydrous magnesium sulfate. This technique ensured solubility of the sparingly soluble (ether) hydroquinone and presence at all times of an excess of oxidizing agent, and thus prevented formation of the dark quinhydrone. Bumping of the solid suspension provided the necessary agitation. The reaction was complete within 1.25 hours. Solids were removed by filtration, the ether solution concentrated, and the residue of orange solid crystallized from ligroin–petroleum ether. The quinone was obtained as yellow to light-orange needles, m.p. 93.2–93.8°; yield 3.06 g. (89.4%). A sample recrystallized from ligroin as long, flattened, lemon-yellow needles of m.p. 93.5–93.8°.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 76.94; H, 8.89.

2-Cyclohexyl-?-(4'-cyclohexylbutyl)-hydroquinone (V).—An absolute ethanol solution of 1.71 g. (0.005 mole) of IV was shaken with hydrogen at atmospheric pressure in the presence of 0.5 g. of a palladium-on-charcoal (1:6) catalyst. Slightly more than 0.01 mole (265 cc. at 26°) was slowly absorbed during 24 hours. The catalyst was filtered, and the almost colorless filtrate diluted with water to give a granular white solid, m.p. 140–142°; yield 1.60 g. (97.0%). Three recrystallizations of a sample from benzene–ligroin gave small clumps of pearly-white leaflets, m.p. 143.2–143.7°.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.04; H, 10.10.

2-Cyclohexyl-?-(4'-cyclohexylbutyl)-benzoquinone (VI).—To a solution of 1.35 g. (0.004 mole) of the hydroquinone V in 25 cc. of ethanol was added 5.2 g. (0.02 mole) of ferric chloride hexahydrate dissolved in ethanol containing a little hydrochloric acid. The dark solution was warmed briefly, cooled, and diluted with water. The quinone separated as a granular yellow solid, m.p. 71.0–71.6°; yield 1.33 g. (99.3%). Two recrystallizations from ethanol afforded long, light-yellow needles of m.p. 71.0–71.8°.

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.53; H, 10.00.

3-Methyl-6-(4'-cyclohexylbutyryl)-phenol (VII).—A mixture of 102 g. (0.6 mole) of 4-cyclohexylbutyric acid, 43.2 g. (0.4 mole) of *m*-cresol, and 40.7 g. (0.61 mole) of boron fluoride was allowed to stand 15 hours at room temperature, and then heated on a steam-bath for 3 hours. Decomposition of the complex in the usual way, followed by distillation of the product afforded 90.0 g. (86.4% yield) of a light-yellow oil, b.p. 160° (0.2 mm.). It crystallized from light petroleum ether (b.p. 20–40°) at Dry Ice temperature to give 84.6 g. (81.2%) of white solid. A sample, recrystallized twice in the same manner, formed small white prisms of m.p. 29.5–30.0°. An alcoholic solution of the compound gives a red color with ferric chloride.

Anal. Calcd. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.63; H, 9.54.

3-Methyl-6-(4'-cyclohexylbutyl)-phenol (X).—Clemmensen–Martin reduction of the ketone VII (52.1 g., 0.2 mole) for 23 hours with efficient stirring afforded 46.7 g. (94.8%) of a colorless oil (b.p. 160–170° at 0.2 mm.) which solidified at room temperature. A sample, recrystallized twice from petroleum ether (b.p. 20–40°) at low temperature, gave fine white needles, m.p. 40.0–40.5°.

Anal. Calcd. for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.64; H, 10.72.

4-Nitroso-3-methyl-6-(4'-cyclohexylbutyl)-phenol (XIII).—Hydrogen chloride (cylinder) was passed into a solution of 24.6 g. (0.1 mole) of X in 400 cc. of 95% ethanol with stirring and cooling until 142 g. (3.9 moles) had been absorbed. To the stirred solution, cooled to 0–5°, was slowly added 11.9 g. (0.17 mole) of sodium nitrite dissolved in 40 cc. of water. A greenish solid soon appeared in the red solution. The mixture was stirred for 1 hour longer and then poured into 2.5 l. of water. The yellow solid was filtered, dried, and crystallized from benzene–ligroin as salmon-colored needles, m.p. 133.0–133.4°; yield 22.3 g. (81.0%). A sample, recrystallized from benzene–ligroin, formed yellow needles, m.p. 132.8–133.4°.

Anal. Calcd. for $C_{17}H_{25}O_2N$: C, 74.14; H, 9.15. Found: C, 74.01; H, 9.18.

4-Amino-3-methyl-6-(4'-cyclohexylbutyl)-phenol (XVI).—The nitrosophenol XIII (5.51 g., 0.02 mole) was dissolved in an excess of 2 *M* sodium hydroxide, and a solution of sodium hydrosulfite added until the clear, deep-red solution faded to colorless and deposited a light-colored solid. The aminophenol was collected, dried, and crystallized from benzene–ligroin to give pinkish-white leaflets of m.p. 159–160°; yield 4.92 g. (94.2%). A sample recrystallized from a mixture of benzene and ligroin as lustrous white leaflets, m.p. 160.5–161.5°.

Anal. Calcd. for $C_{17}H_{27}ON$: C, 78.11; H, 10.41. Found: C, 78.25; H, 10.39.

2-Methyl-5-(4'-cyclohexylbutyl)-benzoquinone (XIX). **Procedure A.**—Direct hydrolysis of the nitrosophenol XIII

(19) Dow Chemical Company, U. S. Patent 2,125,310 (1938); *C. A.*, **32**, 7478 (1938).

(quinone monoxime) was effected by refluxing it (5.51 g., 0.02 mole) for 45 minutes with 30 cc. of dioxane, 3.0 cc. of acetone, 2.8 g. of cuprous oxide and 9.4 cc. of hydrochloric acid diluted with 12 cc. of water.[17] The dark green solution was cooled, poured into water, and the precipitated granular quinone filtered. Crystallization from methanol gave, by successive concentration of the filtrates, 4.2 g. (81.5% yield) of somewhat impure quinone. Recrystallization of a sample from dilute methanol afforded fluffy, very light-yellow needles, m.p. 72.2–72.7°.

Anal. Calcd. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.17; H, 9.18.

Procedure B.—The aminophenol XVI obtained by reduction of 5.51 g. (0.02 mole) of XIII was, without drying or further purification, dissolved in 50 cc. of warm acetic acid, filtered through a pad of Darco, and oxidized by addition of 6 g. of sodium dichromate in slightly diluted acetic acid (25 cc.). The dark solution was cooled and slowly diluted, with stirring; the light-yellow needles were collected and dried to give 4.7 g. (90.4% over-all yield from the nitrosophenol) of almost pure quinone, m.p. 71.2–72.2°.

The hydroquinone was prepared by shaking an ether solution of the quinone with aqueous sodium hydrosulfite until the color was discharged. It formed minute white needles from benzene–ligroin, m.p. 136.8–137.2°.

Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99. Found: C, 77.97, 77.69; H, 9.83, 9.97.

3,5-Dimethyl-6-(4′-cyclohexylbutyryl)-phenol (VIII).—Acylation of 3,5-xylenol[20] (48.8 g., 0.4 mole) with 4-cyclohexylbutyric acid (102 g., 0.6 mole) and boron fluoride (41 g., 0.65 mole) for 13 hours at room temperature and 6 hours at 90–100° led to 71.0 g. (64.7%) of light-yellow oil, b.p. 160° at 0.2 mm. (the yield based on recovered starting materials was essentially quantitative). A portion, crystallized twice from petroleum ether (b.p. 20–40°) at Dry Ice temperature and twice from dilute ethanol, formed large white plates, m.p. 45.2–46.0°.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.75; H, 9.72.

3,5-Dimethyl-6-(4′-cyclohexylbutyl)-phenol (XI).—Clemmensen–Martin reduction of VIII (61.2 g., 0.223 mole) with stirring was complete within 24 hours. The product distilled as a colorless, viscous oil, b.p. 150° (0.2 mm.), which soon solidified; yield 54.1 g. (93.4%). Two recrystallizations of a sample from petroleum ether (b.p. 20–40°) afforded small white needles, m.p. 46–47°.

Anal. Calcd. for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 83.03; H, 10.94.

4-Nitroso-3,5-dimethyl-6-(4′-cyclohexylbutyl)-phenol (XIV).—Nitrosation of the phenol XI (26.0 g., 0.10 mole) was effected by the procedure described for the preparation of XIII. The fluffy yellow solid (28.9 g., 100%) was sufficiently pure for conversion to the quinone. A sample crystallized from acetone in 78% yield; recrystallization gave small, light-yellow needles, m.p. 202–203° dec.

Anal. Calcd. for $C_{18}H_{27}O_2N$: C, 74.70; H, 9.41. Found: C, 74.63; H, 9.49.

4-Amino-3,5-dimethyl-6-(4′-cyclohexylbutyl)-phenol (XVII).—The nitrosophenol XIV (1.55 g., 0.0054 mole) dissolved in 2 *M* sodium hydroxide on addition of some ethanol; the clear, dark-green solution rapidly became colorless on addition of excess sodium hydrosulfite, and deposited a silky, white solid (1.48 g., 100%), m.p. 176–177°. A sample, recrystallized twice from benzene with the aid of Darco, formed gleaming white leaflets of m.p. 176–177°.

Anal. Calcd. for $C_{18}H_{29}ON$: C, 78.49; H, 10.61. Found: C, 78.57; H, 10.63.

2,6-Dimethyl-3-(4′-cyclohexylbutyl)-benzoquinone (XX). Procedure A.—The nitrosophenol (quinone monoxime) XIV (2.89 g., 0.01 mole) was refluxed for 1 hour with a mixture of 25 cc. of dioxane, 1.5 cc. of acetone, 1.4 g. (0.01 mole) of cuprous oxide and 4.7 cc. of hydrochloric acid diluted with 10 cc. of water.[17] The sparingly soluble solid slowly disappeared and was replaced in the green solution by an upper layer of orange oil. When the mixture was poured into cold water, this oil soon solidified to an orange solid, which was collected and crystallized from methanol as yellow needles; yield 1.97 g. (72.0%). A sample was dissolved in petroleum ether, filtered from a trace of amorphous solid, evaporated, and the residue recrystallized twice from methanol; it formed lemon-yellow needles, m.p. 48.2–48.8°.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.50; H, 9.52. Found: C, 78.76; H, 9.42.

Procedure B.—Oxidation of the recrystallized aminophenol XVII (1.1 g., 0.004 mole) in 25 cc. of acetic acid with an excess of sodium dichromate gave 1.09 g. (100% yield, 94.8% over-all yield from XIV) of yellow quinone, m.p. 47.5–48.0°.

2,3-Dimethylphenol.—2,3-Dimethylphenol was prepared from 2,3-dimethylaniline by a modification of the method of Smith and Opie.[14] The method was modified by diazotization of the amine in more dilute solution to minimize intramolecular reaction, and by continuous ether extraction of the phenol as it was formed to prevent coupling. Freshly distilled 2,3-dimethylaniline (39.3 g., 0.324 mole) was dissolved in a boiling solution of 53.4 cc. of concentrated sulfuric acid in 500 cc. of water. The solution was cooled in ice, 400 g. of ice added, and the amine diazotized by addition of 23 g. (0.33 mole) of sodium nitrite in 105 cc. of water. An excess of nitrite was present as indicated by the starch–iodide test, and it was not entirely destroyed by addition of urea. After thirty minutes in an ice-bath, the solution was diluted to 1500 cc. and allowed to warm up to room temperature, when evolution of nitrogen began and a little insoluble oil appeared. The phenol was continuously extracted with ether overnight (12 hours) as the hydrolysis proceeded at room temperature. The aqueous layer was heated for 6 hours on a steam-bath to complete the reaction, cooled, and extracted again with ether. The ether extracts were combined and extracted with two portions of 2 *M* sodium hydroxide. The alkaline extracts were saturated with carbon dioxide, the reddish oil that separated extracted with ether, and, after removal of ether, distilled. The phenol distilled at 120° (20 mm.) as a light-yellow oil that rapidly solidified; yield 31.7 g. (80.1%). Smith and Opie report a yield of 52%. The ether layer from the alkaline extraction left a few grams of dark red oil that partially crystallized, presumably impure 4-methylindazole.

2,3-Dimethyl-6-(4′-cyclohexylbutyryl)-phenol (IX).—A mixture of 2,3-dimethylphenol (30.5 g., 0.25 mole), 4-cyclohexylbutyric acid (85 g., 0.5 mole), and boron fluoride (31.9 g., 0.47 mole) was kept for 13 hours at room temperature and warmed for 5 hours on a steam-bath. Decomposition of the complex and distillation of the product gave 59.1 g. (86.2%) of viscous, light-yellow oil, b.p. 160–165° at 0.4 mm., that solidified at Dry Ice temperature. Crystallization from petroleum ether (b.p. 20–40°) gave 12.4 g. of almost pure **2,3-dimethyl-4-(4′-cyclohexylbutyryl)-phenol**. Recrystallization from petroleum ether and finally from ethanol afforded large, irregular plates, m.p. 77.7–78.4°. This 4-isomer dissolved with difficulty in dilute alcohol on addition of 2 *M* sodium hydroxide to give a yellow solution; acidification discharged the color and reprecipitated the compound. An alcoholic solution of the substance instantly gave an intense deep-violet color with ferric chloride.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.50; H, 9.86.

The petroleum ether filtrate from the 4-isomer was freed of a little contaminating 4-cyclohexylbutyric acid by extraction with dilute sodium hydroxide. On further cooling, it then deposited a small fraction (3.9 g.) of mixed isomers; the residue of light-yellow oil (41.5 g., 60.5% yield) appeared to be essentially pure **2,3-dimethyl-6-(4′-cyclohexylbutyryl)-phenol (IX)**. It was a low-melting solid, but could be crystallized only with considerable loss, and was used as the oil. A sample, crystallized once from petroleum ether (b.p. 20–40°) and recrystallized twice from methanol, formed small, white leaflets, m.p. 38–40°. This 6-isomer dissolved readily in dilute alcohol on addition of 2 *M* sodium hydroxide. The solution was yellow; acidification discharged the color and reprecipitated the compound. An alcoholic solution of the material slowly developed a light violet color with ferric chloride.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.91; H, 9.37.

2,3-Dimethyl-6-(4′-cyclohexylbutyl)-phenol (XII).—Clemmensen–Martin reduction of IX (39.5 g., 0.144 mole)

(20) I am indebted to Shell Development Company for a generous gift of 3,5-xylenol.

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).