does not define the range of potency. A benzolog of the phenanthrenequinone series is completely inactive.

Transformation to Active Compounds in the Organism.—The observation that several precursors of vitamin K_1 or of 2-methyl-1,4-naphthoquinone are apparently converted efficiently into these antihemorrhagic substances in the animal body[4] suggested trial of comparable precursors of the naphthoquinone antimalarials. It appears, however, that the duck organism has relatively little power for effecting such biological transformations of orally administered materials. Thus even simple esters and hydroquinone triacetates of such active compounds as M-1916 showed at most feeble activity in oral assays. When given intramuscularly M-1916 propionate proved to be almost as active as the free hydroxy compound but the triacetate was only feebly active. In view of these findings it is hardly surprising that orally administered oxides and naphthoresorcinols showed no activity. Two of the compounds listed in Table XVIII are ketols that are readily transformed into hydroxyalkylnaphthoquinones by oxidation with copper sulfate and alkali (Paper XII) and the one of higher molecular weight showed signs of at least weak activity; this type of precursor is of interest by virtue of greatly increased water solubility.

(4) Fieser, Tishler and Sampson, *J. Biol. Chem.*, **137**, 659 (1941).

Summary

The results of this investigation are summarized in Paper I of the series.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Naphthoquinone Antimalarials. III. Diene Synthesis of 1,4-Naphthoquinones[1]

BY LOUIS F. FIESER

A reinvestigation of the reactions involved in the Diels–Alder synthesis of naphthoquinones and in the hydroxylation of the products has led to the development of shorter routes to several of the simple naphthoquinone intermediates that have been required for the synthetic program and has also provided a practical method of preparing certain hydroxyalkylnaphthoquinones that are difficultly accessible by peroxide alkylation.

In the procedure[2] heretofore usually followed the addition of butadiene to a benzoquinone is conducted in benzene, ligroin or alcohol at about 70° in a pressure vessel, the low-melting and highly soluble adduct (II) is isolated, isomerized to III, and this is oxidized with chromic acid to the naphthoquinone. It has now been found that the Diels–Alder addition can be conducted efficiently without the use of pressure equipment and at room temperature in glacial acetic acid, a solvent well adapted to use in the subsequent steps of isomerization and oxidation. The isolation of the adduct is unnecessary, for isomerization to III can be conducted by brief heating following the addition to the solution of a mineral acid and stannous chloride[3,4]; the parent substance separates in colorless needles of high purity in excellent yield. The direct oxidation of 5,8-dihydro-1,4-naphthohydroquinone (III, R = H) with chromic acid to α-naphthoquinone at first presented the difficulty that unless an excessive volume of acetic acid is employed an intermediate tar separates and does not fully redissolve. One solution is to add a dichromate–sulfuric acid mixture to the acetic acid solution of the adduct at 65–70°; the processes of isomerization and oxidation then proceed concurrently and the sparingly soluble component III never reaches a concentration high enough to cause tar formation. A still better laboratory procedure is based upon the finding that nitrous acid in acetic acid solution[5] is a specific reagent for oxidation to the dihydronaphthoquinone stage (V) and no further.[6] The reaction proceeds very readily without tar formation, and when chromic acid is subsequently added a smooth conversion to the naphthoquinone is realized.

The preparation of pure α-naphthoquinone by either procedure is far simpler than by the previous best method from α-naphthol[7] and the reactions can be applied on any scale. The compound thus becomes a practical intermediate. One use is in the preparation of 2-chloro- and 2,3-dichloro-1,4-naphthoquinone. Another application affords a better route to 2-hydroxy-1,4-naphthoquinone (VIII) than that from β-naphthol.[8] Boron fluoride (best as etherate) has been found a superior catalyst for the Thiele reaction[9] with acetic anhydride, and by a simple procedure pure 1,2,4-triacetoxynaphthalene (VII) can be prepared in quantity. A nearly quantitative conversion to pure 2-hy-

(1) See Paper I, Ref. 1, for acknowledgments to CMR and the Rockefeller Foundation.

(2) Diels and Alder, *Ber.*, **62**, 2362 (1929).

(3) Fieser, Tishler and Wendler, THIS JOURNAL, **62**, 2861 (1940).

(4) Fieser and Chang, *ibid.*, **64**, 2043 (1942).

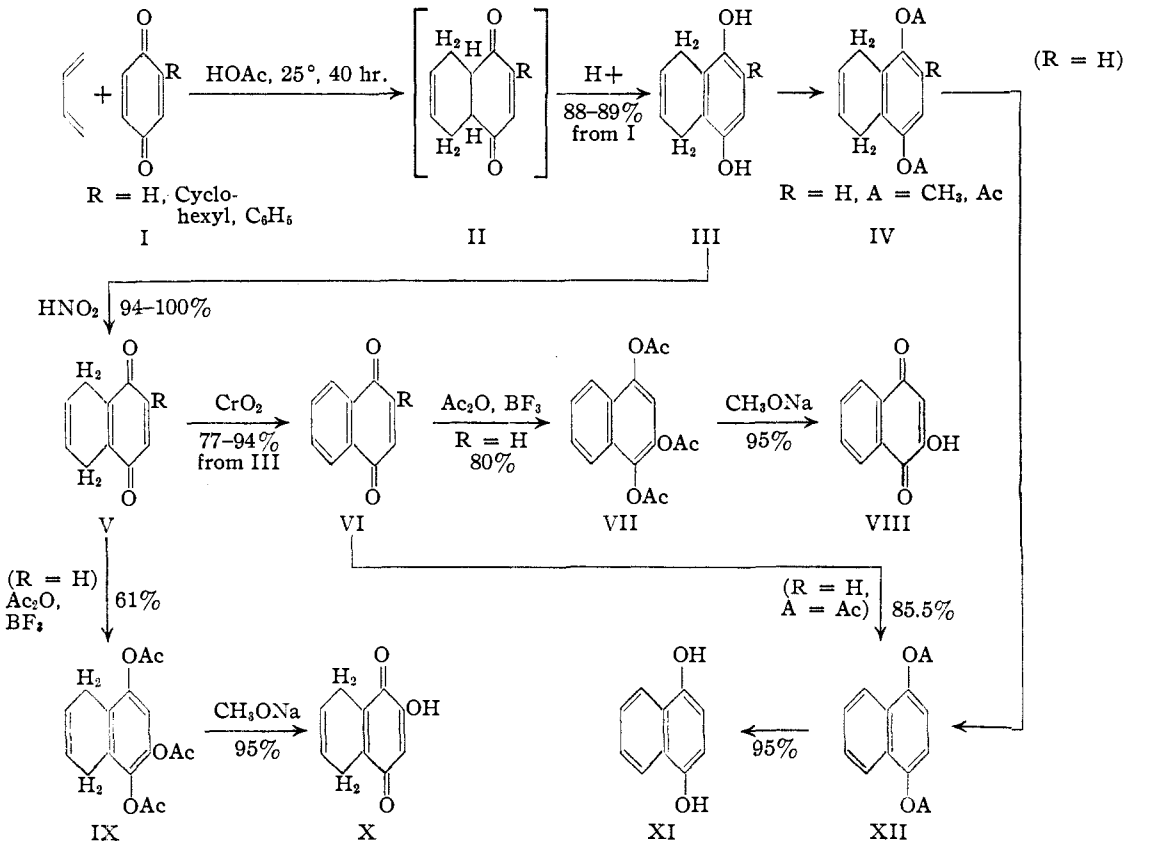
(5) Trial of this reagent was suggested by an observation by Fieser and Peters, THIS JOURNAL, **53**, 4083, 4090 (1931).

(6) A previous search for an oxidizing agent better than chromic acid led to the discovery of the alkylating action of lead tetraacetate; Fieser and Chang.[4]

(7) Fieser, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 383.

(8) Fieser and Martin, "Organic Syntheses," **21**, 56 (1941).

(9) Thiele and Winter, *Ann.*, **311**, 347 (1900).



droxy-1,4-naphthoquinone is accomplished by stirring a suspension of the triacetate in methanol with sodium methoxide in the presence of air. A route to α-naphthohydroquinone (XI) more reliable than direct reduction is by hydrolysis of the diacetate XII under nitrogen; the diacetate is obtained either by the sulfur dehydrogenation of its dihydride IV or by reductive acetylation of the quinone VI. α-Naphthohydroquinone reacts with methyl or ethyl alcohol in the presence of boron fluoride to give mixtures of the mono- and diethers. Boron fluoride is also an excellent catalyst for both the acetylation and the Fischer esterification of 2-hydroxy-1,4-naphthoquinone, and with its use the heretofore difficultly accessible allyl ether[10] can be prepared easily.

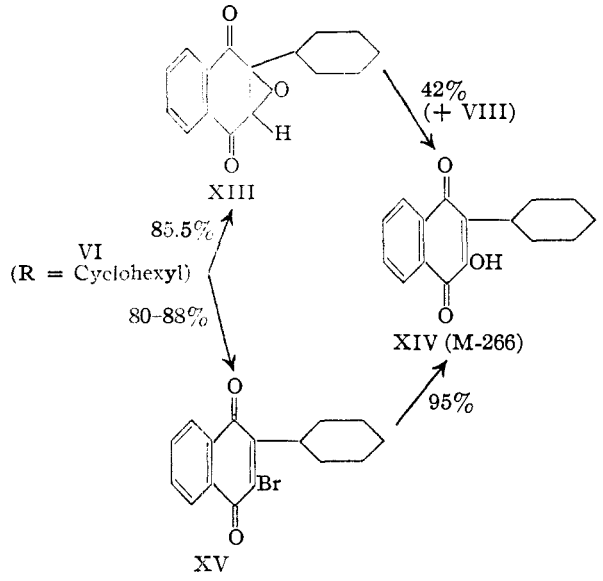
5,8-Dihydro-1,4-naphthoquinones (V), previously isolated in only a few instances[2,3,11] and little characterized, can be prepared readily by the nitrous acid oxidation reaction in high yield and purity. The unsubstituted quinone is extremely sensitive to light, but can be manipulated satisfactorily. The observation of the ability of boron fluoride to promote the Thiele reaction was the result of an experiment made to see if acetic anhydride under the influence of a catalyst would add to the quinonoid system or cause enolization of the bridgehead hydrogen atoms. Boron fluoride was tried as catalyst because sulfuric acid probably adds to the double bond. Actually the addition reaction proceeds slowly and enolization not at all, for the product is the triacetoxy derivative IX and it is convertible into the new 5,8-dihydro derivative of 2-hydroxy-1,4-naphthoquinone, X.

The 2-cyclohexyl and 2-phenyl derivatives of 1,4-naphthoquinone are obtainable from the benzoquinones by the procedures cited in even higher yields than the parent compound because they are less sensitive to overoxidation. A difficulty was encountered in the attempt to hydroxylate 2-cyclohexyl-1,4-naphthoquinone by a method that proceeds very smoothly with the methyl derivative.[12] The oxide XIII was obtained satisfactorily by the regular procedure, but on cleavage with either acid or base it yielded mixtures of the desired hydroxy compound XIV and 2-hydroxy-1,4-naphthoquinone and the yield of XIV was invariably low. The manner in which the alkyl group is lost was not studied because a satisfactory alternate route was found in bromination to XV and hydrolysis with methyl alcoholic potassium hydroxide. A point of general interest noted in the alkaline hydrolysis both of XV and of 1,2,4-triacetoxynaphthalene is that the reaction affords a much inferior product when ethanol is employed in place of methanol.

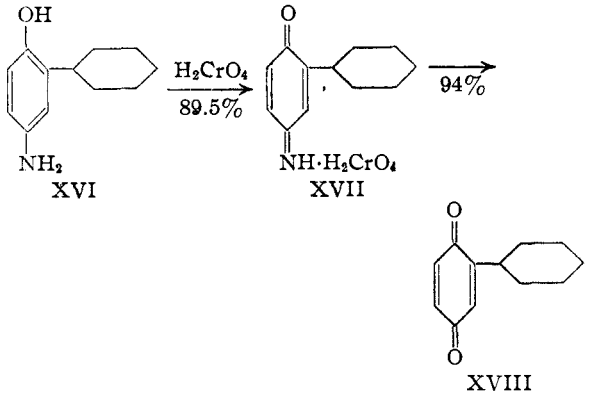
(10) Fieser, THIS JOURNAL, **48**, 3201 (1926).

(11) E. Bergmann and F. Bergmann, *J. Org. Chem.*, **3**, 125 (1938).

(12) Fieser, *J. Biol. Chem.*, **133**, 391 (1940).



An unusual behavior was also noted with one of the earlier intermediates in the cyclohexyl series. Commercially available *o*-cyclohexylphenol was converted readily by coupling and reduction into the *p*-amino derivative XVI, but attempts to oxidize this to the benzoquinone by ordinary methods led only to purple, intractable tars. A scheme of oxidation with nitrous acid followed by steam distillation was worked out that gave the quinone in 52–56% yield but it was tedious and of doubtful application to other quinones of higher molecular weight whose synthesis was at the time contemplated (*e. g.*, the 4′-cyclohexylcyclohexyl derivative M-2293). Further investigation then disclosed the difficulty: the initial product of oxidation, the quinonimine, is so unusually stable that when produced in solution by an added oxidant it can survive hydrolysis long enough to enter into condensations with the unchanged aminophenol. By the addition of the aminophenol all at once to a large excess of chromic acid it is possible to isolate a beautifully crystalline chromic acid salt of the quinonimine, XVII. This unusual substance, which decomposes slowly on storage even in the dark, reacts with many phenols and aromatic amines in either acetic acid or alcoholic sodium hydroxide solution to give products showing the color phenomena of indophenols; the chromic acid present in salt combination evidently serves as oxidant in an indophenol condensation. This quinonimine seems to be much more stable than those that have been characterized chemically[13] or by potentiometric titration,[14] but the ready separation of the chromate salt may be in large part due to its sparing solubility. The amine from *o*-phenylphenol gave a comparable salt but the more soluble amine from thymol did not. Cyclohexylbenzoquinone can be prepared satisfactorily through the chromate only on a small scale. However, a practical preparative procedure was worked out for preparing a solution of the quinonimine by oxidation with ferric chloride and for effecting hydrolysis by adding the solution to hot aqueous acid. Thus all six steps in the synthesis of M-266 from *o*-cyclohexylphenol are satisfactory and the over-all yield is 71%.



Since some of the methods developed in this research were employed in other work in this series, those of a general nature that have been adequately standardized and checked are designated "procedures."

Experimental Part

5,8-Dihydro-1,4-naphthohydroquinone, III. Procedure A.—A suspension of 108 g. of *p*-benzoquinone in 500 cc. of acetic acid in a 1-l. Erlenmeyer flask was chilled in ice until the solvent started to crystallize and 65 g. of liquid butadiene[15] was added. The flask was closed with a wired-on rubber stopper, placed in a pan of running water under a wet towel,[16] and shaken occasionally for a few hours until the quinone all went into solution. After a total of forty to forty-eight hours[17] the solution was filtered through an acetic acid-washed layer of Nuchar on a Büchner funnel. A total of 100 cc. of acetic acid was used for rinsing and washing and for transferring the filtrate to a beaker in which it was heated on the steam-bath to remove any remaining butadiene (exposure to strong light should be avoided). The hot solution was then treated with 500 cc. of distilled water containing 100 cc. of 36% hydrochloric acid and 15 g. of stannous chloride crystals and heated for fifteen minutes. Heavy needles of III separated within a few minutes and at the end of the heating period both crystals and liquor were colorless. After cooling, eventually in ice, the product was collected, washed with water, and dried in a vacuum oven. The yield of colorless, crystalline III, m. p. 208–209° was 143 g. (88%, consistently duplicated). The substance sometimes acquires a slight purplish tinge in drying.

(13) Willstätter and Mayer, *Ber.*, **37**, 1494 (1904); Willstätter and Pfannenstiel, *ibid.*, **37**, 3761 (1904).

(14) Fieser, THIS JOURNAL, **52**, 4915 (1930); Fieser and Fieser, *ibid.*, **56**, 1565 (1934).

(15) It is not safe to employ liquid drawn from an inverted tank because sometimes considerable polymer is present. The preferred procedure is to condense gas from a tank in a calibrated test-tube immersed in a Dry Ice-bath; the liquid is decanted from any ice that deposits on the walls of the container.

(16) If some cooling is not provided during the first eight to ten hours in a run of this size the solution may become warm enough to develop considerable pressure.

(17) In this period isomerization of the adduct to III occurs to only a negligible extent; when the period is extended to one to two weeks, crystals of III begin to separate and the presence of the bis-adduct is established by the isolation of a trace of anthraquinone in the final product of oxidation.

α-Naphthoquinone. Procedure B.—The filtered acetic acid solution of the addition product from 108 g. of quinone was transferred to a three-necked 5-l. flask equipped with a Hershberg stirrer and thermometer with provision for intermittent and very efficient cooling, and treated at 50° with a solution at 50° of 400 g. of sodium dichromate dihydrate and 20 cc. of 96% sulfuric acid in 250 cc. of water. The temperature rose to 65° in three minutes and was controlled to 65–68°; particular vigilance is required after about twenty minutes, when the product suddenly begins to crystallize with a surge of heat. In twenty-five minutes the main reaction was over; the mixture is then maintained at 65–70° for one-half hour and 1 kg. of ice and 1 l. of water are added. The yellow naphthoquinone was washed free from chromium salts and acetic acid and dried in vacuum at 60–80°; yield 125–135 g. (79–85%) of crude material, m. p. 120–122°, that darkens on the surface on exposure to light due to the presence of a trace of the dihydride V. The material was dissolved in 400 cc. of glacial acetic acid and heated on the steam-bath for fifteen minutes with 20 g. of sodium dichromate dihydrate in 20 cc. of water and the product was reprecipitated: yield 112–131 g. (71–83%), m. p. 122–124°; no darkening on exposure.

α-Naphthoquinone. Procedure C.—A 16.2-g. portion of the hydroquinone III was dissolved in 150 cc. of acetic acid at the boiling point in a flask equipped with a dropping funnel and a short condenser leading the escaping nitrous fumes to a hood or trap. The solution was allowed to cool to about 100°, a solution of 16 g. of sodium nitrite (more or less may be required according to the amount of gas lost) in 25 cc. of water was run in rapidly (five minutes) with swirling of the flask. Nitrous fumes were evolved and a green quinhydrone usually separated and formed a thick paste but then went into solution as more reagent was added. At the end of the addition a clear yellow solution resulted sometimes containing a few suspended particles of quinhydrone, but these disappear after a few minutes of shaking. The temperature was adjusted to 65°, and a warm (65°) solution of 16 g. of sodium dichromate dihydrate and 1 cc. of 96% sulfuric acid in 10 cc. of water was added. The temperature was controlled to 65–70° by intermittent cooling under the tap for the first fifteen minutes. After a total of forty-five minutes the product was precipitated by the addition of 75 g. each of ice and water, collected and thoroughly washed. The crude material melted at 123–124° and was bright yellow and darkened only very slightly on exposure to light; the yield was 13.9 g. (88%) of material satisfactory for most uses. Purification can be accomplished by treatment with charcoal in ether,[7] or as follows: a solution of the crude product (13.9 g.) in 30 cc. of acetic acid is heated on the steam-bath for fifteen minutes with a solution of 0.5 g. of sodium dichromate dihydrate in 1 cc. of water and the naphthoquinone is precipitated; m. p. 124.5–125.5°; yield 12.1 g. (77%).

1,2,4-Triacetoxynaphthalene. Procedure D.—A suspension of 15.8 g. of pure α-naphthoquinone in 40 cc. of acetic anhydride was treated with 2 cc. of boron fluoride etherate. The quinone slowly went into solution, with a slight temperature rise, and after one or two hours crystals of the triacetate began to separate. At this point the mixture was warmed gently to bring the rest of the quinone into solution and then allowed to stand, and after a few hours a large crop of crystalline product had separated from the dark brown solution. This was collected, washed with a little acetic acid and then, after removal of the filtrate, with a liberal amount of alcohol; the material was a crystalline, pure white solid weighing 19.40 g., m. p. 137–138°. The material precipitated by drowning the mother liquor and alcohol washings was a granular grey solid, and when this was crystallized from the minimum quantity of acetic acid (without charcoal treatment or filtration) the very dark solution again deposited crystalline material that when washed was completely colorless: 4.85 g., m. p. 136–137°; total yield 81%.

The addition was conducted with equal success with the crude quinone C in amounts up to 75 g.; the reaction proceeds best with precipitated material. In a comparison run with 1 cc. of 96% sulfuric acid as catalyst the total yield was 74.5% (compare Ref. 7).

2-Hydroxy-1,4-naphthoquinone. Procedure E.—A suspension of 12.5 g. of commercial sodium methoxide in 125 cc. of methanol was stirred mechanically in a flask immersed in an ice-bath, 15.1 g. of 1,2,4-triacetoxynaphthalene was added and the mixture stirred for one hour, when the bright red sodium salt of hydroxynaphthoquinone formed a thick paste. The salt was collected and washed with methanol; more salt often separates when the mother liquor is shaken with air. The moist salt was dissolved in about 350 cc. of hot water and the solution filtered and acidified with hydrochloric acid. The hydroxynaphthoquinone collected after ice-cooling was pure yellow in color and melted at 195–196°, dec.; yield 8.2 g. (95%). The product was of quality equal to that obtained by hydrolysis of the methyl ether.[8] Crystallization from acetic acid (4–5 cc. per g.) gave bright yellow prisms of the same melting point with a recovery of 90–93%. An alternate procedure is to dissolve the sodium salt in 250 cc. each of water and methanol and acidify the filtered solution at the boiling point; a clear yellow solution results and deposits fine yellow needles of hydroxynaphthoquinone on cooling; yield 7.65 g. (88%).

With ethanol as solvent, the final product was orange or orange-yellow when the sodium methoxide was added last, or when the alkoxide was added to a hot solution of the triacetate. When methanol was used there is less tendency for the formation of material of an off-color.

Procedure F. Hydrolysis under Nitrogen, Oxidation with Ferric Chloride.[7]—The reaction was carried out in a three-necked flask with a gas inlet tube in the central tube extending to the bottom, a separatory funnel, and a gas-exit tube connected to a water bubbler. A suspension of 30.2 g. of 1,2,4-triacetoxynaphthalene in 200 cc. of alcohol was swept with oxygen-free nitrogen, and the exit gas was bubbled through 70 cc. of 25% aqueous sodium hydroxide placed in the separatory funnel and covered with a layer of ligroin. After one-half hour the alkali was run in; a deep yellow solution soon resulted and after twenty minutes it was acidified with 65 cc. of 36% hydrochloric acid in 150 cc. of water added from the funnel. The flask was opened and the weakly tan-colored solution of the hydroquinone warmed to 85° and treated with a hot, filtered solution of 65 g. of ferric chloride hexahydrate and 22 cc. of 36% hydrochloric acid in 100 cc. of water. The hydroxynaphthoquinone collected after ice cooling consisted of slightly dull yellow needles, m. p. 190–192°; yield 16.83 g. (97%).

Hydrolysis in a purely aqueous medium was conducted in the same way with a charge of 30.2 g. of triacetate suspended in 425 cc. of water; the mixture was heated to promote hydrolysis, the acidification was done with undiluted 36% acid, and the solution was filtered prior to oxidation; yield 96.5%, pure yellow; m. p. 191–192°.

5,8-Dihydro-1,4-naphthoquinone.[2]—One-tenth mole of III was oxidized according to C except that the nitrite solution was added in a period of about one-half minute; the yellow solution was diluted with 150 cc. of water and cooled in ice; these operations must be conducted in a well-darkened room. The quinone separated in bright yellow needles, and was collected, washed well, and dried in vacuum at room temperature in the dark; yield 14.5–15.5 g. (91–97%).

The substance is readily soluble in hot methanol and separates on cooling in lemon-yellow needles. A sample crystallized for analysis twice in a darkened room darkened slightly at about 90° and melted at 105.5–106.5°.

Anal. Calcd. for $C_{10}H_8O_2$: C, 75.00; H, 5.04. Found: C, 75.17; H, 5.26.

On brief exposure to light the yellow quinone rapidly turns brown and then black; the solutions in methanol or acetic acid appear to be more stable. A solution in concentrated sulfuric acid is initially brown and slowly changes to a bright cherry red. The quinone slowly

imparts a pink coloration to cold dilute alkali, and in time the solution becomes brown; it dissolves in aqueous sodium bisulfite to give a completely colorless solution. The yellow solution in methanol shows no immediate change on the introduction of boron fluoride.

1,2,4-Triacetoxy-5,8-dihydronaphthalene (IX).—Since there is danger of damage to the sensitive quinone in the process of drying it as a solid, the material is best dried in ether and the solvent removed at reduced pressure. The reaction of 0.1 mole of product with acetic anhydride and boron fluoride was conducted as in D except that the amount of catalyst was doubled and a period of twenty-eight hours was allowed for the addition (in the dark). The resulting weakly reddish yellow solution was poured into water and gave a granular yellowish solid. In one experiment crystallization from methanol gave two crops of colorless triacetate: 21.2 g., m. p. 125.5–126.5°; 0.7 g., m. p. 124–125°; total yield 72%. In another, by Dr. D. Curtin, the product was crystallized from 60 cc. of preheated *n*-butanol (charcoal) diluted with 25 cc. of 90–120° ligroin (yield 58%).

The triacetate is very readily soluble in methanol but separates from a concentrated solution in colorless plates. It is much more soluble than the aromatic triacetoxy compound. Crystallization from 90–120° ligroin (moderately soluble) gives a granular microcrystalline powder. The best samples melted at 125–126°.

Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.47; H, 5.33.

2-Hydroxy-5,8-dihydro-1,4-naphthoquinone (X).—Fifteen grams of IX was processed according to F except that the oxidation with ferric chloride was conducted in the cold. The yield of deep yellow product, m. p. 150–155°, dec., was 8.25 g. (95%).

The dihydro derivative is distinctly less soluble in alcohol or acetic acid than hydroxynaphthoquinone. The substance undergoes rather rapid alteration in hot acetic acid or *o*-dichlorobenzene but can be crystallized from preheated tetrachloroethane (15 cc. per g.). It is moderately soluble in alcohol and separates in deep yellow prisms. It is rather sparingly soluble in benzene and separates in yellow or orange-yellow prisms that occlude some solvent. The best samples melted at 162–163°, dec.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 68.40; H, 4.65.

An attempted alkylation of this quinone with the peroxide from γ-cyclohexylbutyric acid conducted by Dr. Curtin gave the aromatized M-1916 as the only identified product.

α-Naphthohydroquinone Diacetate: (a) By **Reductive Acetylation.**—When the procedure developed for the reductive acetylation of 2-methyl-1,4-naphthoquinone[18] is applied to the parent substance there is some danger that the reaction may proceed so rapidly as to get out of hand. Five grams of powdered naphthoquinone together with 2.5 g. of zinc dust was covered with 20 cc. of acetic anhydride, and two drops of triethylamine was added. The mixture was kept at about 25° by swirling in a pan of cold water and was worked with a stirring rod. In about twenty minutes the yellow quinone had been converted into a thick, tan paste of the diacetate. When no further change was apparent, 0.5 g. of fresh zinc dust was added and the mixture was warmed briefly on the steam-bath until the liquor was at most light yellow. It was then cooled, water was added, and the flask was stoppered and shaken until a granular light grey-white solid was obtained. This was collected, dried (9.1 g.) and extracted with excess alcohol (60 cc.); the solution was clarified with charcoal, evaporated to a small volume (15–20 cc.) and allowed to cool. The diacetate separated as large colorless plates, m. p. 130–131°; yield 6.70 g. (85.5%).

(b) **From III by Dehydrogenation.**—5,8-Dihydro-1,4-naphthohydroquinone diacetate,[2] m. p. 133–133.5°, was obtained in 80% yield by acetylation of III with a drop of sulfuric acid as catalyst. When the diacetate was heated with palladium charcoal in boiling mesitylene it appeared to undergo disproportionation (tetrahydride[2] isolated). However, dehydrogenation was accomplished readily as follows.[19] A mixture of 70.5 g. of the diacetate and 9.2 g. of sulfur was heated in a two-bulb distilling flask in a bath at 180° and dry nitrogen was bubbled through the melt to agitate the globule of sulfur and eliminate hydrogen sulfide (the results were much poorer without this expedient). The bath temperature was raised to 250° in about one-half hour, and by that time the evolution of gas had ceased. About 0.25 g. of zinc dust was added and the product was distilled at 11 mm. and crystallized once from alcohol: colorless plates, m. p. 128–129°; yield 53.5 g. (76.5%).

α-Naphthohydroquinone.—Attempts to develop a satisfactory procedure for the reduction of naphthoquinone with stannous chloride in water, alcohol, or acetic acid, or with hydrosulfite in an ether–water mixture were not successful, but the following longer route through the diacetate is fully reliable.

The hydrolysis of 24.4 g. of α-naphthohydroquinone diacetate was conducted according to F except that only 100 cc. of alcohol was used. The solution was acidified as in F, treated with 2.5 g. of stannous chloride in 2.5 cc. of 36% hydrochloric acid, heated to the boiling point, and filtered by suction from a trace of residue. α-Naphthohydroquinone separated in large, colorless or faintly pink blades, which were collected after ice cooling; yield 15.1 g. (95%), m. p. 187–189°, dec.

Derivatives of α-Naphthohydroquinone.—The **dibenzyl ether of the 5,8-dihydride** was prepared from III, benzyl chloride, and potassium carbonate in acetone; it formed a mesh of slender white needles from methanol, m. p. 82–83°. The substance decomposed on attempted dehydrogenation with sulfur.

Anal. Calcd. for $C_{24}H_{22}O_2$: C, 84.18; H, 6.48. Found: C, 84.39; H, 6.76.

α-Naphthohydroquinone dibenzoate, prepared by reductive benzoylation, formed long colorless spars from benzene–ligroin, m. p. 169–169.5°.

Anal. Calcd. for $C_{24}H_{16}O_4$: C, 78.26; H, 4.38. Found: C, 78.39; H, 4.68.

When a solution of α-naphthohydroquinone (2 g.) in methanol (20 cc.) was treated with boron fluoride gas until warm (1–2 g.) and refluxed for five hours there resulted a mixture of the **monomethyl ether**[20] (long, fine needles from 90–100° ligroin, m. p. 131–132°) and the **dimethyl ether**[20] (white blades from methanol, m. p. 87–88°). Alkylation under more moderate conditions appears useful as a method of preparing the monoether, but the diether is better prepared by methylation of III with dimethyl sulfate in the presence of hydrosulfite (79% yield, distilled) and dehydrogenation with sulfur (m. p. 86–87°; yield without nitrogen sweeping, 59%).

1,2,4-Trihydroxynaphthalene.—This substance is too soluble in water to be obtainable by the method given for α-naphthohydroquinone but it can be prepared readily by shaking 2-hydroxy-1,4-naphthoquinone (15.0 g.) with ether and hydrosulfite solution,[21] washing the ethereal solution with brine containing hydrosulfite, and recovering the air-sensitive hydroquinone as follows. The funnel is mounted to deliver into a second funnel containing ether-washed Drierite supported on glass wool and this in turn delivers into a flask heated on the steam-bath; the drying flask and the receiver are both flushed with nitrogen and the ethereal solution is run through the train and the solvent removed by flash distillation. The product was white, yield 13.9 g. (93%).

Ethers of 2-Hydroxy-1,4-naphthoquinone.—For success in conducting boron trifluoride etherifications with allyl or isopropyl alcohol it is imperative that overheating

(18) Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath, New York, N. Y., 1941.

(19) Experiment by Frederic C. Merriam.

(20) Russig, *J. prakt. Chem.*, [2] **62**, 51 (1900).

(21) Fieser and Gates, THIS JOURNAL, **63**, 2951 (1941).

be avoided and that the hydroxyquinone be of highest purity (a concentrated solution in dioxane should be pure yellow). If gaseous catalyst is used this must first be absorbed slowly in ice-cold allyl alcohol (without bubbling the gas through the liquid) or else darkening will occur; when the quinone is then added, undue time is required for its solution and some decomposition occurs. It is much better to dissolve the quinone first and then add the much less destructive boron fluoride etherate.

Allyl Ether.[10]—One gram of pure hydroxynaphthoquinone was dissolved in 20 cc. of allyl alcohol and the solution placed in a pan of water maintained at 70° and allowed to come to the bath temperature (no crystallization occurs), when 2 cc. of boron fluoride etherate was added. After five hours at 70°, during which time little darkening had occurred, the solution was cooled, diluted with 80 cc. of water, and cooled in ice. The solid that separated was collected on a filter, washed with dilute bicarbonate as long as any red color was noted, and dried. The residual ether consisted of pale yellow needles, m. p. 100–101° (lit.[10] 97.5°); yield 0.73 g. (59%). The bicarbonate wash on acidification gave 0.22 g. (22%) of yellow hydroxynaphthoquinone, m. p. 187–189°; crystallized from acetic acid, 0.15 g., m. p. 195–196°. The yield was 10% lower when half the amount of catalyst was used. When three-fourths of the allyl alcohol was replaced by dioxane the yield (not allowing for recovery) was 39% in a seven-hour run; in a fifteen-hour run the crude product was very dark and the yield of satisfactory crystallized product was 40%. *t*-Butyl alcohol was tried as solvent but no etherification occurred.

The **isopropyl ether** was obtained by the same procedure (1 g. of quinone, 20 cc. of alcohol, 2 cc. of catalyst, seven hours) as light yellow needles, m. p. 113–114°; yield 0.89 g. (72%); starting material 0.16 g. Recrystallizations from dilute methanol gave flat, glistening yellow needles of the same m. p.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.17; H, 5.60. Found: C, 72.27; H, 5.75.

The **methyl ether**[22] was obtained by heating 1 g. of quinone, 20 cc. of methanol, and 2 cc. of catalyst in the 70° bath for two hours, when much of the product had crystallized; yield of ether, m. p. 182–183° (lit. 183.5°), 0.90 g. (83%); in a one-hour run the yield was 69%.

2-Chloro-1,4-naphthoquinone.[23]—A solution of 15.8 g. of α-naphthoquinone in 100 cc. of acetic acid was kept at about 25° by cooling while chlorine was passed in in excess (10 g.); the dichloride[23] that soon began to separate was collected after the mixture had stood for one-half hour and after cooling and amounted to 20.0 g. (87%) of nearly white product, m. p. 182–183°, dec. This was dissolved in 200 cc. of acetic acid, 10 g. of anhydrous sodium acetate was added, and the mixture was boiled for a few minutes, diluted with water until saturated at the boiling point and let cool. The chloro quinone separated in golden yellow needles, m. p. 117–118°; yield 14.4 g. (75% over-all).

2,3-Dichloro-1,4-naphthoquinone.—Chlorination of chloronaphthoquinone[23] in acetic acid, either alone or with a chlorination catalyst, often leads either to considerable darkening or to the formation of a nearly colorless substance, m. p. 109–111° (C, 42.21, 42.14; H, 1.49, 1.58). The difficulty is obviated by the use of one equivalent of sodium acetate; in the following procedure the monochloro quinone is not isolated. A mixture of 22.9 g. (0.1 mole) of crude naphthoquinone dichloride and 16.4 g. (0.2 mole) of anhydrous sodium acetate was covered with 250 cc. of acetic acid and chlorine bubbled in through an addition tube inserted through a short reflux condenser. The mixture was heated and chlorinated at the boiling point for about two hours and the end-point determined either from the gain in weight or from the melting point of a precipitated test portion (no danger of over-chlorination). The mixture was poured into water and the bright yellow product collected; yield 19.5 g. (86%), m. p. 193–194°. One crystallization from acetic acid raised the m. p. to 194–195° (94% recovery). Chlorination of chloronaphthoquinone in the same way but at room temperature took about seven days.

α-Naphthoquinone Oxide.—The oxide is so much more sensitive than those of substituted naphthoquinones that the peroxide–soda method of preparation[24] is not applicable. The best results in the application of Zincke's procedure[25] on a large scale were obtained as follows. Crude naphthoquinone C (100 g.) was treated with chromate solution, reprecipitated as a fine powder, and this was washed free of acetic acid and stirred to a fine slurry with 1 l. of water to which 100 g. of sodium bicarbonate was added. The hypochlorite solution from 80 g. of chlorine, 100 g. of sodium hydroxide in 140 cc. of water (cooled) and 640 g. of ice was added and the mixture stirred in ice for a total of about one-half hour, when the conversion seemed complete. The cream-colored product was collected (100 g., m. p. 129–131°), stirred with 750 cc. of alcohol, and collected and dried; the yield of light grey product, m. p. 132–133°, was 91.5 g. (83%).

Oxide that has been fully purified by crystallization from ether is transformed readily by sodium methoxide in methanol to a sodium salt that affords very pure hydroxynaphthoquinone in 92% yield, but the crude oxide gives material contaminated with a persistent, salmon red impurity.

Cyclohexyl Derivatives of Benzo- and Naphthoquinone

2-Cyclohexyl-4-aminophenol Hydrochloride.—The coupling of commercial *o*-cyclohexylphenol (0.5 mole) with diazotized sulfanilic acid and the reduction of the dye with hydrosulfite was conducted by the procedure described for α-naphthol.[26] The amine separated as an oil or semisolid but became solid on cooling and was collected and washed with hydrosulfite solution. The moist solid was dissolved in a solution of 55 cc. of 36% hydrochloric acid and 3 g. of stannous chloride in 250–300 cc. of water and the hot solution was filtered by suction, cooled, and treated slowly with excess acid (100 cc.), when the hydrochloride separated as a light tan, granular solid; yield crude, 113.9 g. (theory 113.0 g.). Coupling was also conducted satisfactorily with a solution of 0.5 mole of *o*-cyclohexylphenol in a mixture of 800 cc. of alcohol and a solution of 110 g. of sodium hydroxide in 100 cc. of water.

A sample for analysis was dissolved in a little acetic acid and the pink solution was treated with a few drops of stannous chloride to discharge the color, filtered, treated at the boiling point with excess hydrochloric acid, and allowed to cool. The hydrochloride separated as large colorless prisms. Crystallization of the salt on a large scale was attended with considerable losses.

Anal. Calcd. for $C_{12}H_{18}ONCl$: C, 63.28: H, 7.96. Found: C, 63.33; H, 7.72.

The **diacetate** was prepared by brief warming with acetic anhydride and sodium acetate and crystallized from methanol. It was obtained as a microcrystalline white solid, m. p. 135–136°; the substance is readily soluble in alcohol or benzene, sparingly soluble in 90–120° ligroin.

Anal. Calcd. for $C_{16}H_{21}O_3N$: C, 69.79; H, 7.69. Found: C, 69.55; H, 7.60.

For preparation of the **free amine** 0.50 g. of the hydrochloride was dissolved in 7.5 cc. each of acetone and water in the cold, a few drops of hydrosulfite solution were added to discharge the pink or purple color, an aqueous solution of 0.25 g. of sodium bicarbonate was added, and the mixture stirred in an ice-bath and diluted. A white solid separated and was washed with hydrosulfite solution and when dried it was light tan or light grey. The yield of fully dried product was 0.46 g. (theory 0.42 g.). The

(22) Fieser, THIS JOURNAL, **48**, 2992 (1926).

(23) Zincke and Schmidt, *Ber.*, **27**, 2757 (1894).

(24) Tishler, Fieser and Wendler, THIS JOURNAL, **62**, 2869 (1940).

(25) Zincke, *Ber.*, **25**, 3602 (1892).

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

conversion from the hemisulfate also gave about 10% excess material, and in the conversion to the quinonimine chromate the crude amine gave 12% less material than its salts; hence the amine is hydrated. The crude amine begins to soften and turn red at about 138° and melts at 146°. The substance is very readily soluble in alcohol, acetone or acetic acid, readily soluble in benzene, and sparingly soluble in ligroin, and tends to turn pink in all these solvents.

The amine appears to form both a **hemisulfate** ($ArNH_2 \cdot 0.5H_2SO_4$, less soluble) and a **sulfate** ($ArNH_2 \cdot H_2SO_4$, more soluble), but neither was obtained crystalline. The more soluble salt was obtained as an amorphous pink-grey solid by heating the amine with water containing excess acid and adding still more acid to the filtered solution. When this salt was dissolved in acetone–water and the solution decolorized with hydrosulfite and treated with sodium acetate solution, the less soluble hemisulfate separated as a light tan solid in close to the calculated yield; this salt in turn afforded the expected amount of free amine when treated with bicarbonate in acetone–water solution.

2-*o*-Cyclohexyl-1,4-benzoquinone. Nitrous Acid Method.—The following procedure is based on the method described[27] for aminothymol, modified to take account of the lesser solubility of the salt in question. Crude 2-cyclohexyl-4-aminophenol hydrochloride (1.5 g.) in 15 cc. of hot acetic acid was cooled in ice and treated with 3 cc. of 36% hydrochloric acid; a solution of 2.5 g. of sodium nitrite in 10 cc. of water was then added by drops with stirring. After five minutes the solution was diluted with 40 cc. of water and heated for ten minutes on the steam-bath and then steam distilled. The quinone separates from the distillate as a bright yellow solid of high purity (m. p. 51–53°); yield 0.71 g. (56.5%). The procedure outlined was applied to two 37.5-g. lots of amine hydrochloride and the yield was 52.5%.

A sample of the quinone for analysis was crystallized from dilute methanol and separated as shimmering, bright yellow plates, m. p. 53.5–54.5°.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.41; H, 7.18.

The hydroquinone, obtained by reduction with aqueous hydrosulfite in alcoholic solution and extraction with ether, did not crystallize on long standing either as such or in solvents. The hydroquinone **diacetate** crystallized from methanol in colorless aggregates and melted at 72–73°.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.62; H, 7.30.

2-Cyclohexyl-1,4-benzoquinone-4-imine Chromate, XVII.—When chromic acid is added dropwise to an acetic acid solution of 2-cyclohexyl-4-aminophenol, as free base or salt, a purple coloration is produced and dark intractable material results on dilution.

A 1.00-g. portion of 2-cyclohexyl-4-aminophenol hydrochloride was dissolved by warming in the major part of a mixture of 5 cc. of 10% sulfuric acid and 5 cc. of acetic acid and the solution was cooled and transferred to a separatory funnel with use of the rest of the solvent mixture. A solution of 3.0 g. of chromic anhydride in 5 cc. of 20% sulfuric acid was diluted with 5 cc. of acetic acid and swirled in an ice-bath while the other solution was run in by drops directed to the body of the solution. The clear red-yellow solution was at once diluted with 100 cc. of water, when shimmering, thin, golden yellow plates of the chromate separated almost at once and appeared to fill the flask. The mixture was cooled in ice and the product collected (slow filtration), washed with water, and dried to constant weight under complete exclusion of light at room temperature; yield 1.21 g. (89.5%). The filtrate deposited 0.07 g. (7%) of cyclohexylquinone. The free amine, sulfate, or hemisulfate, can be substituted. It is essential that the reaction mixture be diluted immediately after completion of the addition; otherwise, quinone of poor quality slowly separates. When the reaction mixture was diluted with a solution of 1–5 cc. of 96% sulfuric acid in 50 cc. of water, quinone was slowly deposited in yield of 31–36%.

The quinonimine chromate is not appreciably soluble in water or ether and undergoes extensive decomposition in alcohol, acetic acid or acetone. The substance is very sensitive to light, and samples could not be kept in the dark for more than about twenty-four hours before showing signs of darkening.

Anal. Calcd. for $C_{12}H_{17}O_5NCr$: Cr, 16.93. Found: Cr, 16.87, 16.98.

Cyclohexylquinonimine chromate reacts readily with many amines and phenols in acetic acid solution. When a mixture of equivalent amounts of the chromate (1 g.) and α-naphthol (0.47 g.) was stirred with acetic acid (20 cc.) the components dissolved in a minute or two to a deep purple-red solution that soon changed to intense purple. Ready reactions in acetic acid solution were noted also with phenol, thymol, *o*- and *p*-cresol, dimethylaniline, α-naphthylamine, N,N-dimethyl-α-naphthylamine. The quinonimine chromate also reacts with phenols in alcoholic solution containing sodium hydroxide. When 1 g. of chromate was added to a solution of 0.63 g. of anthrone in 25 cc. of alcohol containing 2 cc. of 25% sodium hydroxide the solution became blue-green at once and then pure blue, and the product that separated on dilution and neutralization with acetic acid was a brick-red solid (1.30 g.). On attempted crystallization from acetic acid, cleavage occurred to anthraquinone. Thymol and α-naphthol gave a blue color in the alkaline test, and it was noted that a positive test could be obtained on adding the phenol after the alcoholic alkaline solution of the quinonimine had been boiled.

2-Cyclohexyl-1,4-benzoquinone from the Quinonimine.—One gram of the freshly prepared chromate salt was stirred for a minute or two with a mixture of 7 cc. of acetic acid and 7 cc. of 50% sulfuric acid until the crystals had all dissolved to a deep yellow solution, and 200 cc. of water was then added. With a few seconds the yellow solution became cloudy, and within five to ten minutes the emulsion gave rise to yellow crystals of the quinone. Light yellow crystalline material (m. p. 52.5–53.5°) was obtained; yield 0.58 g. (94%).

Oxidation of 2-Cyclohexyl-4-aminophenol to Cyclohexylbenzoquinone.—A mixture of 195 g. of ferric chloride hexahydrate, 300 cc. of acetic acid, and 150 cc. of 36% hydrochloric acid was stirred and warmed to 45° to bring the solid into solution and 68.3 g. (0.3 mole) of 2-cyclohexyl-4-aminophenol hydrochloride was added. The mixture was stirred and warmed to 55°, and within a few minutes the salt dissolved to a deep reddish yellow solution containing the quinonimine. This was poured into a solution at 90° of 60 g. of chromic anhydride and 200 cc. of 96% sulfuric acid in 4 liters of water. After five minutes the mixture was cooled to about 15°, when a yellow oil that had separated solidified to a somewhat dark yellow solid. The yield of crude cyclohexylquinone, m. p. 51.5–53°, was 52.0 g. (91%). Bright yellow material can be obtained by charcoal treatment in ether or by distillation (b. p. 115–120° at 1 mm.). The yield and quality of the product were the same when either crude or pure hydrochloride was employed; the omission of the chromic anhydride resulted in a very inferior product.

2,?,5-Triacetoxycyclohexylbenzene.—A Thiele addition to cyclohexylbenzoquinone conducted as in Procedure D gave in 97% yield a weakly yellowish oil that appeared to be an isomer mixture. One component was isolated in about 30% yield by slow crystallization from methanol (very soluble). The substance then crystallized from ligroin in clusters of small prisms, m. p. 92–93°.

Anal. Calcd. for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.90; H, 6.77.

2-Cyclohexyl-5,8-dihydro-1,4-naphthohydroquinone.—The addition of butadiene (11 g.) to cyclohexylbenzoquinone (32.0 g.) was conducted in acetic acid (84 cc.) at room temperature for four days. The solution (un-

(27) Kremers, Wakeman and Hixon, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1941, p. 511.

filtered) was heated to expel butadiene and then warmed on the steam-bath for forty-five minutes with 15 cc. of 36% hydrochloric acid and 2.5 g. of stannous chloride in 100 cc. of water. The oily product that separated solidified on cooling and rubbing and the yield of light tan granular material, m. p. 142–144°, was 37.54 g. (90.2%).

A sample for analysis crystallized from 90–120° ligroin (moderately soluble) as colorless blades, m. p. 147–148°.

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.47; H, 8.07.

2-Cyclohexyl-5,8-dihydro-1,4-naphthoquinone.—A mixture of 5 g. of cyclohexylbenzoquinone, 5 g. of butadiene and 40 cc. of acetic acid was heated in an Erlenmeyer flask with a wired-on rubber stopper in an oven at 80° for fifteen hours. The resulting pale tan solution was heated on the steam-bath for a few minutes to drive off excess butadiene and treated, while hot, with a solution of 5 g. of sodium nitrite in the minimum amount of water (or with solid sodium nitrite). The resulting yellow solution was cooled in ice and diluted slowly with successive portions of water, when the dihydronaphthoquinone separated as a granular, bright yellow solid; yield quantitative. The quinone dissolves readily in hot methanol and is deposited as either plates or large prismatic spars; a recrystallized sample melted at 82.5–83.5°.

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.29, 79.17; H, 7.35, 7.62.

The pure quinone is bright yellow and is much less sensitive to heat and light than the parent quinone; it does darken slightly on exposure to direct sunlight.

2-Cyclohexyl-1,4-naphthoquinone.—The oxidation of the dihydrohydroquinone proceeds less vigorously than in the case of the unsubstituted dihydronaphthohydroquinone, and a higher reaction temperature can be maintained without danger of destroying the product. Thus Procedure B was applied with minor modifications: 32.22 g. of crude product in 380 cc. of acetic acid was treated at 50° with 21 g. of sodium nitrite in 30 cc. of water; the second step was conducted with 30.5 g. of sodium dichromate and 1.5 cc. of 96% sulfuric acid in 15 cc. of water at the steam-bath temperature for forty-five minutes. The yield of crystalline, pure yellow, light-stable cyclohexylnaphthoquinone, m. p. 84–86°, was 29.74 g. (93.5%). A sample crystallized from methanol melted at 87–88°.

The naphthoquinone was also obtained by processes requiring only mild conditions in the final oxidation, namely, by an isomerization of the dihydronaphthoquinone to the naphthohydroquinone. In one experiment a solution of 0.5 g. of material and three drops of triethylamine in 5 cc. of alcohol was heated on the steam-bath for two hours and the resulting reddish solution was treated with 2 g. of ferric chloride and 1 cc. of concentrated hydrochloric acid in 5 cc. of water. The light yellow precipitate (0.5 g., m. p. 82–84°) on crystallization from alcohol gave 0.35 g. of cyclohexylnaphthoquinone, m. p. 85–86°. In another trial 0.5 g. was heated on the steam-bath for two hours with 5 cc. of acetic acid containing 0.5 cc. of 36% hydrochloric acid and oxidation was accomplished at 25–40° with 1 g. of chromic anhydride in 1 cc. of water. Recrystallization of the crude product (0.5 g., m. p. 80–85°) gave 0.35 g. of material m. p. 85–86°.

The simplest procedure for the preparation of the naphthoquinone consists in heating the benzoquinone with butadiene in acetic acid at 80° and treating the resulting solution with sodium nitrite and then with chromic anhydride; the yield of purified product (m. p. 87–88°) from 1 g. of the benzoquinone was 0.66 g.

2-Cyclohexyl-1,4-naphthohydroquinone diacetate was obtained by the reductive acetylation procedure described above as a white powder, m. p. 118–119°, in 75% yield. It crystallized well from 70–90° ligroin in clusters of silken needles, m. p. 120–121°.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.59; H, 6.80. Found: C, 73.72; H, 6.76.

The diacetate was also obtained by heating the dihydronaphthoquinone with acetic anhydride and a trace of triethylamine on the steam-bath for two hours.

2-Cyclohexyl-1,4-naphthoquinone Oxide.—Solutions of 1 cc. of perhydrol and 0.2 g. of sodium carbonate in 5 cc. of water and of 1 g. of the quinone in 20 cc. of alcohol were mixed and the solution diluted with water; on cooling the emulsion set to a paste of white oxide; 1.0 g. (85.5%), m. p. 79–80°. Crystallization from methanol gave fibrous masses, then dense clusters of small needles, m. p. 79.5–80.5°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.24; H, 6.63.

A solution of 1 g. of the oxide in 25 cc. of alcohol was warmed with 1 g. of sodium methoxide for a minute or two, when the solution began to turn red, and let stand with occasional shaking for one day. The deep red solution, containing some suspended red solid, was diluted with water, acidified, and extracted with ether. Extraction with bicarbonate removed a total of 0.23 g. of hydroxynaphthoquinone (methyl ether, m. p. and mixed m. p. 183–184°). The ethereal solution was then extracted further with sodium hydroxide and the extracted material crystallized from 90–120° ligroin to give 0.20 g. of yellow plates of 2-hydroxy-3-cyclohexyl-1,4-naphthoquinone, m. p. 133–134° (mixed m. p.). In an experiment with sodium methoxide conducted in an oxygen-free atmosphere for two days, the yield of the hydroxycyclohexyl compound was better; 0.36 g. (42%) from 0.85 g. of oxide.

Cleavage of the oxide with 96% sulfuric acid at room temperature was tried on a micro scale and the amounts of bicarbonate-extracted and alkali-extracted products determined colorimetrically as 13 and 27%, respectively.

2-Bromo-3-cyclohexyl-1,4-naphthoquinone.—The most reliable bromination procedure found was as follows.[28] A suspension 12.0 g. of cyclohexylnaphthoquinone and 12 g. of anhydrous sodium acetate in 100 cc. of acetic acid in a glass-stoppered flask was treated with 8.8 g. of bromine and the flask was shaken occasionally at the start. Some warming occurred and after the first day the sodium acetate had all dissolved; after three days the bromo compound began to deposit in shiny leaflets. After seven days at room temperature an equal volume of water was added and the product collected (15.5 g. crude). Crystallization from 350 cc. of methanol gave a first crop of 10.0 g., m. p. 103–105°, and a second crop (3.5 g., m. p. 95–98°) that on recrystallization gave 2.5 g. of product, m. p. 101–103°; total yield of satisfactory material, 12.8 g. (80%). A recrystallized sample melted at 105–106°.

Anal. Calcd. for $C_{16}H_{15}O_2Br$: C, 60.20; H, 4.74. Found: C, 60.00; H, 4.73.

The following shorter procedure (L. F. F.) gave satisfactory results in several experiments but not in all. A solution of 12.0 g. of 2-cyclohexyl-1,4-naphthoquinone in 80 cc. of acetic acid was treated at 25° with 8.9 g. of bromine and 5 cc. of boron fluoride etherate. After forty-four hours the resulting stiff crystalline paste was treated with 80 cc. of water and homogenized with a stirring rod and the crystalline yellow solid was collected, washed with water, and dried to constant weight at 80°; yield of crude material, m. p. 102–103.5°, 15.51 g. (97%). Crystallization from 400 cc. of methanol gave a first crop of 13.25 g. of material that softened at 95° and melted at 105–106°, and a second crop of 0.78 g. of satisfactory product, m. p. 102.5–104°. In some experiments the solution darkened badly and the entire batch was ruined.

The bromo compound usually crystallized from methanol or ethanol in thin, lustrous yellow plates and the best samples melt at 105–106° without previous softening. Slightly less pure, but still satisfactory, crystallizates often melt or soften at 95–96°, resolidify, and remelt at 105–106°. In the crystallization of one large batch from methanol a crop of heavy, prismatic needles first separated and then the characteristic thin plates began to appear. The plates were dissolved by warming and the needles were separated and recrystallized from ethanol. Large,

(28) Experiments by Drs. F. C. Chang and C. Heidelberger.

prismatic needles again separated; they melted at 105–106°, showed no depression when mixed with the plate-form, and gave M-266 on hydrolysis. When a sample of the needle form was recrystallized once more from ethanol, the plate form separated.

2-Hydroxy-3-cyclohexyl-1,4-naphthoquinone (M-266).[29]—A mixture of 15.95 g. of 2-bromo-3-cyclohexyl-1,4-naphthoquinone (m. p. 105–106°), 16 g. of sodium hydroxide pellets, and 650 cc. of methanol was refluxed gently for one hour and the deep red solution was acidified while hot by the gradual addition of a mixture of 33 cc. of concentrated hydrochloric acid and 200 cc. of water. The resulting light yellow solution on cooling deposited bright yellow needles of the hydroxy compound of highest purity, yield 12.19 g. (95%), m. p. 135–136°.

When the hydrolysis was carried out in exactly the same manner except for the substitution of absolute ethanol for methanol the product was dark and tarry and afforded satisfactory M-266 only after much processing and in low yield. An ethereal solution of the gummy material when shaken with bicarbonate solution afforded a dirty orange extract suggestive of the presence of hydroxynaphthoquinone. A likewise poor product resulted from a trial hydrolysis with ethanol and 25% sodium hydroxide. Hydrolysis in methanol solution gave a bright yellow product of exceptionally fine quality in every experiment conducted with the pure bromo derivative.

Phenylbenzoquinone. Preparation.—4-Amino-2-phenylphenol hydrochloride was obtained from *o*-phenylphenol through the *p*-sulfobenzeneazo derivative[26] as a granular white solid in 78% yield. Hill and Hale[30] oxidized this substance with chromic acid as Borsche[31] had done and stated that it was necessary to warm the mixture on the steam-bath to start the reaction. Actually warming is required not for the oxidation but for the hydrolysis of a quinonimine chromate. Thus when a solution of the hydrochloride was added to a chromic acid solution as in the preparation of XVII, the diluted solution in a few moments began to deposit an orange microcrystalline solid. This substance is light-sensitive, insoluble in ether, hydrolyzable to the quinone, and gives the indophenol reaction, but it does not crystallize as well as the cyclohexyl derivative (Cr calcd., 17.3; found, 16.1).

For the preparation of the quinone a solution of 5 g. of the hydrochloride in 35 cc. of water was added dropwise to 15 g. of chromic anhydride in a mixture of 15 cc. of water, 50 cc. of acetic acid and 5 cc. of 96% sulfuric acid, when the chromate soon began to separate. A solution at 80° of 10 cc. of 96% sulfuric acid in 200 cc. of water was added, when the salt dissolved and the quinone soon began to crystallize. The golden-yellow product, collected after ice cooling, weighed 3.06 g. (65%), m. p. 113.5–114.5°.

Diene Synthesis.—A mixture of 1 g. of phenylbenzoquinone, 1 g. of butadiene and 20 cc. of acetic acid was heated at 80° for fifteen hours and the filtered solution was warmed for one-half hour on the steam-bath with 2 g. of chromic anhydride in 2 cc. of water. On gradual addition of water and cooling, **2-phenyl-1,4-naphthoquinone**[32] separated in bright yellow needles, m. p. 112–113° (yield good).

2,?,5-Triacetoxydiphenyl.—A suspension of 12.0 g. of phenylbenzoquinone in 40 cc. of acetic anhydride and 2 cc. of boron fluoride etherate was warmed briefly until the quinone had dissolved, allowed to stand for one hour (Craven test negative), and poured into water. After hydrolysis of the excess anhydride the oily product was extracted with equal parts of ether and benzene and the solution clarified, dried, and evaporated. A solution of the residue in 100 cc. of dry ether on standing a few hours deposited one component of the mixture in a hard crystalline cake, m. p. 135–138°, yield 8.88 g. (41%). No further crystalline material could be secured; the residual oil amounted to 12.28 g. (57%). Recrystallization from 85 cc. of alcohol gave 8.46 g. of colorless material, m. p. 141–142°, and a sample purified further melted at the same temperature and formed aggregates of short prismatic needles.

Anal. Calcd. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91. Found: C, 65.97; H, 4.98.

?-Hydroxy-2-phenyl-1,4-benzoquinone.—Hydrolysis of 8.46 g. of the triacetate under nitrogen and oxidation with ferric chloride (Procedure F) gave 4.90 g. (95%) of deep orange-yellow needles. A sample crystallized twice from benzene (moderately soluble) formed short, prismatic orange needles that decomposed at 167–170°.

Anal. Calcd. for $C_{12}H_8O_3$: C, 72.00; H, 4.03. Found: C, 72.09; H, 4.16.

The hydroxyquinone is very readily soluble in alcohol or acetic acid and in small tests it crystallizes in beautiful needles on dilution of solutions in either of these solvents. However, when attempts were made to prepare material suitable for analysis by crystallization from dilute alcohol or acetic acid the product decomposed extensively. The substance seems to be completely stable in benzene solution, or in solution in absolute ethanol or glacial acetic acid.

The **methyl ether** was obtained by esterification with methanol and boron fluoride etherate. The substance is sparingly soluble in methanol and crystallizes in the form of yellow blades, m. p. 199–200°.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 73.10; H, 4.84.

The **acetate**, prepared by the action of acetic anhydride catalyzed by boron fluoride etherate, crystallized from 70–90° ligroin, in which it is only moderately soluble, in the form of long, slender, yellow blades, m. p. 112–113°.

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.62; H, 4.26.

The **allyl ether** was prepared by heating a suspension of the hydroxyquinone (0.5 g.) in allyl alcohol (2 cc.) with boron fluoride etherate (0.5 cc.) at 60° for one hour and adding a little water to the solution. A somewhat sticky product separated, but two crystallizations from alcohol gave golden-yellow blades, m. p. 162.5–163.5° (0.35 g.).

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.98; H, 5.07. Found: C, 75.20; H, 5.10.

Oxidation of Aminothymol Hydrochloride.—The salt (2.0 g.), obtained as large colorless spars in 85.7% yield from thymol by the coupling procedure,[26] when treated exactly as in the preparation of XVII gave no quinonimine chromate but instead, within about one minute, thymolquinone began to crystallize (m. p. 46–47°, yield 1.0 g.). However, when chromic acid solution was added quickly to an iced solution of the salt in dilute sulfuric acid an oily orange tar precipitated. A part of this adhered to the flask and could be washed with water; it was found to be insoluble in ether and to give a blue indophenol color with α-naphthol in alcoholic alkali and hence it must be the quinonimine chromate.

Summary

Improved procedures have been worked out for the preparation of α-naphthoquinone from benzoquinone and butadiene and for its conversion into various naphthalene derivatives that are useful as synthetic intermediates. The diene synthesis has been found applicable also to the quantity production of an antimalarial (M-266) of a type difficultly obtainable by peroxide alkylation. An interesting intermediate is the crystalline chromic acid salt of 2-cyclohexyl-1,4-naphthoquinone-4-imine.

(29) This procedure is based upon one developed by F. C. Chang.

(30) Hill and Hale, *Am. Chem. J.*, **33**, 11 (1905).

(31) Borsche, *Ber.*, **32**, 2937 (1899); *Ann.*, **312**, 220 (1900).

(32) Breuer and Zincke, *Ber.*, **11**, 1404 (1878).

Developments of perhaps general application are: use of acetic acid as solvent in the diene synthesis: use of boron fluoride etherate as catalyst in the Thiele reaction, in acylations, and in the Fischer esterification of hydroxynaphthoquinone with allyl or isopropyl alcohol; use of nitrous acid in acetic acid solution for the quantitative oxidation of 5,8-dihydro-1,4-naphthohydroquinones to the dihydronaphthoquinones.

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Naphthoquinone Antimalarials. IV–XI. Synthesis[1]

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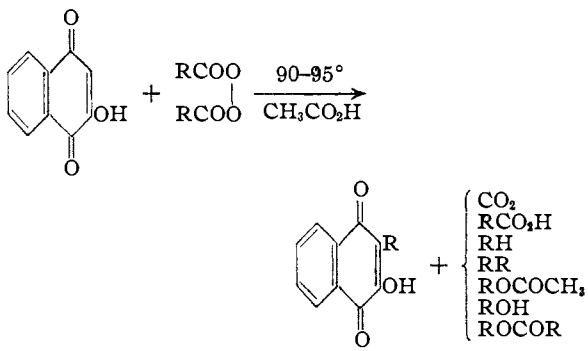
The synthesis of 3-alkyl or aralkyl derivatives of 2-hydroxy-1,4-naphthoquinone has been accomplished by condensation of the hydroxyquinone with an aldehyde and hydrogenation of the resulting 3-α-alkenyl derivative,[2] by the action of an allylic or benzyl halide on the hydroxyquinone silver salt to produce 3-derivatives either by direct C-alkylation or by rearrangement of an allylic ether,[3,4] and, in a few special cases, by condensation of the hydroxyquinone with a polyaryl carbinol.[3,5] A synthesis of long-chain 3-β-alkenyl derivatives consists in the condensation of 1,2,3,4-tetrahydroxynaphthalene with a higher allylic alcohol.[6] A novel synthesis of 2-hydroxy-3-diphenylmethyl-1,4-naphthoquinone from α-naphthoquinone and diphenyldiazomethane[7] has not been explored for generality of application because of the inaccessibility of higher diazoalkanes. Other recently developed syntheses proceed through a non-naphthalenoid intermediate. One is from a 2-alkylindanedione-1,3,[8] another is from a 3-alkyltetralone-1 by treatment either with *p*-nitrosodimethylaniline[9] or with selenium dioxide,[10] and a third involves a ring closure to a 2-alkyl-1,3-dihydroxynaphthalene and oxidation.[11] The combination of the diene synthesis and hydroxylation[12] is the subject of Paper III. The other methods mentioned have been tried or considered in the present work with but little favorable outcome. However, the great majority of the compounds sought have been readily obtainable by another method consisting in the alkylation of hydroxynaphthoquinone by a diacyl peroxide.[13] Although this and other applications of a general alkylation process[14] probably proceed through a free radical intermediate, the yields are usually adequate, pure products are readily isolated, the reaction is of wide application, and the entire synthesis from an acid through the acid chloride and peroxide is essentially a one-step process. The observations to date concerning the nature of the reaction are merely incidental and preliminary, but some of the by-products characterized are indicated in the formulation (see Paper V).



The acid by-product predominates, and considerable satisfactory starting acid is recoverable in some cases, but not in others.

One limitation in the application of the peroxide alkylation reaction to the purpose at hand is that the yields are very poor with α-branched acids and with cycloalkane carboxylic acids. In these instances it has frequently been found expedient to synthesize the next higher homolog and apply the remarkable Hooker oxidation reaction[15] whereby a methylene group is eliminated from either a saturated or unsaturated side chain. An example is in the synthesis of M-2293, illustrated in the formulas. It also is sometimes more con-

(1) See Paper I for acknowledgments to CMR and the Rockefeller Foundation.

(2) Hooker, THIS JOURNAL, **58**, 1163 (1936).

(3) Fieser, *ibid.*, **48**, 3201 (1926).

(4) Fieser, *ibid.*, **49**, 857 (1927).

(5) Möhlau and Klopfer, *Ber.*, **32**, 2146 (1899).

(6) Fieser and Gates, THIS JOURNAL, **63**, 2948 (1941).

(7) Fieser and Peters, *ibid.*, **53**, 4080 (1931).

(8) Koelsch and Byers, THIS JOURNAL, **62**, 560 (1940).

(9) Buu-Hoi and Cagniant, *Compt. rend.*, **214**, 87 (1942).

(10) Weygand and Schröder, *Ber.*, **74**, 1844 (1941).

(11) Soliman and West, *J. Chem. Soc.*, 53 (1944); Soliman and Latif, *ibid.*, 55 (1944).

(12) E. Bergmann and F. Bergmann, *J. Org. Chem.*, **3**, 125 (1938).

(13) Fieser and Oxford, THIS JOURNAL, **64**, 2060 (1942).

(14) Fieser and Chang, *ibid.*, **64**, 2043 (1942); Fieser, Clapp and Daudt, *ibid.*, **64**, 2052 (1942); Fieser and Turner, *ibid.*, **69**, 2338 (1947).

(15) Hooker, THIS JOURNAL, **58**, 1168, 1174, 1179 (1936).