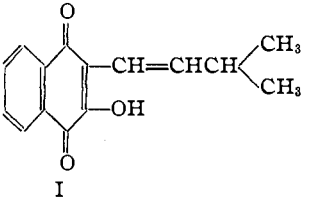
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

THE ALKYLATION OF HYDROXYNAPHTHOQUINONE. III. A SYNTHESIS OF LAPACHOL

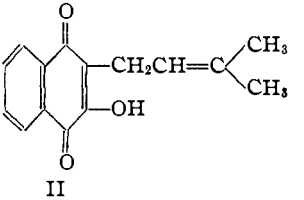
BY LOUIS F. FIESER

RECEIVED DECEMBER 21, 1926 PUBLISHED MARCH 9, 1927

Lapachol, a yellow coloring matter which occurs in the grain of a number of woods,[1] was shown by Paternò[2] to have the structure of an amylene hydroxynaphthoquinone with both substituent groups in the quinone ring. After Hooker[3] had presented convincing reasons for regarding the substance as a derivative of α-naphthoquinone, Paternò's formula (I) remained uncertain only in respect to the position of the double bond in the side chain. Hooker[4] then carried out a synthesis of the compound corresponding to I by the condensation of *iso*valeraldehyde with hydroxynaphthoquinone and obtained an isomer of lapachol which, however, was regarded as the *o*-quinone isomer of I ("*iso*-β-lapachol") on account of its red color. Since the difference between the synthetic and the natural products extended to their hydroquinones, Formula I could no longer be ascribed to lapachol. Of the remaining possibilities, Formula II was given preference by Hooker, after finding that both lapachol and *iso*-β-



I



II

lapachol may be converted into the same hydroxy compound, having the grouping $-CH{=}C(OH)CH(CH_3)_2$.

Hooker's formula for lapachol (II) was thus largely influenced by the structure assigned to *iso*-β-lapachol, and this cannot be regarded as established with certainty. Indeed, Dr. Hooker has expressed to me his opinion that the problem of the structure of lapachol should not be regarded as an entirely settled matter. In consequence, I have undertaken a synthesis

[1] The Taigu wood of Paraguay [Arnoudon, *Compt. rend.*, **41**, 1152 (1857)]; the Surinam Greenheart [Stein, *J. prakt. Chem.*, [1] **99**, 1 (1867)]; the Lapacho wood of South America [Paternò, *Gazz. chim. ital.*, **9**, 506 (1879)]; the Bethabarra wood of the West Coast of Africa [Greene and Hooker, *Am. Chem. J.*, **11**, 267 (1889)]; various Ipè woods [Oesterle, *Arch. Pharm.*, **251**, 301 (1913)]; the *Avicennia tomentosa* wood [Bournot, *ibid.*, **251**, 351 (1913)]; the Moah and the *Tecoma araliacea* woods [Matthes and Schreiber, *Ber. pharm. Ges.*, **24**, 385 (1914)].

[2] Paternò, *Gazz. chim. ital.*, **12**, 337 (1882).

[3] Hooker, *J. Chem. Soc.*, **61**, 611 (1892).

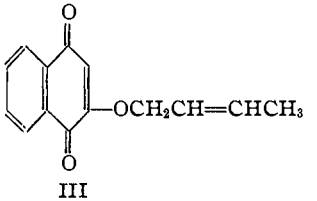
[4] Hooker, *ibid.*, **69**, 1355 (1896).

of the compound corresponding to II by a method suggested by the recent discovery that alkyl hydroxynaphthoquinones are formed in the reaction of the silver salt of hydroxynaphthoquinone with various β,γ-unsaturated alkyl halides.[5]

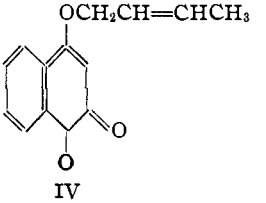
It was found that γ,γ-dimethylallyl bromide (isoprene hydrobromide),[6] $(CH_3)_2C{=}CHCH_2Br$, reacts with the silver salt in question with great rapidity at 0° in ethereal suspension. Though the greater part of the silver salt was converted into hydroxynaphthoquinone, a small amount of the normal alkylation product, the 2-alkoxy-1,4-naphthoquinone, was produced together with a small amount of an acidic isomer to which Formula II must be assigned. The latter substance, 2-(γ,γ-dimethylallyl)-3-hydroxy-1,4-naphthoquinone, was found to be identical with lapachol by direct comparison with a sample of the natural substance which was kindly furnished by Dr. Hooker.

In view of the results of similar alkylation experiments[5] there is little reason to question the validity of this synthesis. It is at least conceivable, however, that the lapachol obtained in the manner described was the product of rearrangement of one of the possible O-ethers. Since only one of these ethers was produced, and that in only 3% yield, it appeared impractical to attempt to test out this point in the lapachol series. Consequently the crotylation of hydroxynaphthoquinone was studied in the expectation that the crotyl derivatives would be formed in better yield and would lend themselves equally well to a comparison of the C-alkylation product and the rearrangement product.

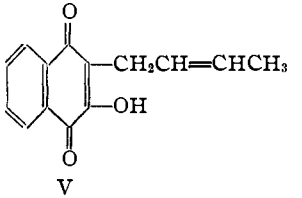
By the action of crotyl bromide on the silver salt of hydroxynaphthoquinone the two O-ethers, III and IV, and an acidic isomer were produced



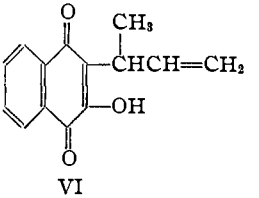
III



IV



V



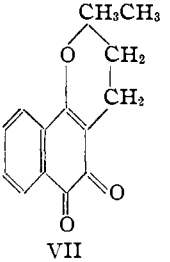
VI

[5] Fieser, THIS JOURNAL, **48**, 3201 (1926).

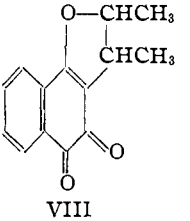
[6] (a) Claisen, *J. prakt. Chem.*, [2] **105**, 76 (1922). (b) Staudinger, Kreis and Schilt, *Helvetica chim. Acta*, **5**, 743 (1922).

in 11, 15 and 32% yields, respectively.[7] If the acidic substance is the product of direct C-alkylation it must have the structure of V. If, on the other hand, a Claisen rearrangement has taken place, such a rearrangement would give rise to VI, for Claisen and Tietze have recently shown[8] that it is the γ- and not the α-carbon atom of the crotyl group which becomes attached to the nucleus in the rearrangement of phenolcrotyl ethers.

On examination of the O-ethers III and IV, it was found that they both undergo rearrangement and yield the same substance, VI. This proved to be isomeric with the alkylation product, which can thus be regarded as V. The possibility of stereo-isomerism is excluded by the fact that V and VI yield different products in the presence of acidic condensing agents. Thus, concd. sulfuric acid converts V into a mixture of the methyl *o*-chromane quinone (VII) and the *p*-quinone isomer, while the *sec.*-crotyl



VII



VIII

derivative (VI) is converted under similar conditions into the dimethyl *o*-coumarane quinone (VIII).

Since the C-alkyl derivative produced in the reaction with crotyl bromide is the product of direct C-alkylation, it is extremely probable that the lapachol formed in the course of a reaction which was carried out at a much lower temperature is also the normal product and is not formed by

TABLE I

MELTING POINTS OF ALLYL HYDROXYNAPHTHOQUINONES AND OF THEIR DERIVATIVES

Side chain	M. p. of hydroxy compound, °C.	M. p. of heterocyclic isomers, °C. *o*-Quinone	*p*-Quinone	
$-CH_2CH=CH_2$[a]	116	133.5	166–167	Coumaranes
$-CH(CH_3)CH=CH_2$	69	109–110	...	
$-CH_2CH=CHCH_3$	132–133	164	122.5	Chromanes
$-CH_2CH=C(CH_3)_2$[b]	139.5–140.5	154	117	

[a] Ref. 5.
[b] Ref. 3.

[7] These results confirm the previous observation (Ref. 5) that an increase in the reactivity of the alkyl halide causes an increased yield of the C-alkylation product. Crotyl bromide is much more reactive than allyl bromide and it yields about twice as much of the C-alkyl derivative.

[8] Claisen and Tietze, *Ber.*, **59**, 2344 (1926).

a Claisen rearrangement. The physical properties of the several compounds confirm this point of view; the melting points of allyl- (γ-methylallyl)- and (γ,γ-dimethylallyl)-hydroxynaphthoquinone fall into a regular series, while relationships between the melting points of the heterocyclic derivatives of both the coumarane-quinone and the chromane-quinone type are apparent.

The structure assigned to lapachol by Hooker in 1896 thus receives considerable support from the present synthesis.

Experimental Part

1. Alkylation with γ,γ-Dimethylallyl Bromide (Isoprene Hydrobromide).—Isoprene (b. p., 35–37°) was prepared from limonene by the method of Harries and Gottlob[9] and converted into the hydrobromide essentially according to Claisen,[10] somewhat less than the theoretical amount of hydrogen bromide being employed in order to avoid reaction with the trimethyl ethylene probably present in the isoprene used.[11] A freshly distilled hydrobromide fraction boiling at 64–66° at 67 mm. was employed in the following experiments.

A suspension of 20 g. of the silver salt of hydroxynaphthoquinone in 150 cc. of absolute ether was stirred mechanically in an ice-bath while 12 g. of isoprene hydrobromide was slowly added. The mixture became completely yellow almost as soon as all of the bromide had been added. The solution was then filtered by suction and the residue was washed out with 400 cc. of ether. The residue still contained a considerable quantity of hydroxynaphthoquinone, which was recovered by extraction with sodium carbonate solution. The ethereal solution, after extraction with ammonia solution, was found to be free of any bisulfite-soluble compounds. On evaporation of the dried ethereal solution under diminished pressure a crystalline compound was obtained from the resulting oil by trituration with petroleum ether. After washing the product with ether, it was obtained in nearly pure condition and proved to be the alkoxy-α-naphthoquinone. The remaining mother liquor yielded only a heavy oil which decomposed on distillation.

From the ammonia extract there was obtained a mixture of hydroxynaphthoquinone and the C-alkyl derivative. In order to effect a separation of the two, the mixture was warmed with a quantity of ligroin insufficient for the complete solution of the material. The C-alkyl derivative was completely removed by this extraction, but it was contaminated with a small quantity of hydroxynaphthoquinone. The latter was removed by taking advantage of its greater solubility in bisulfite solution; the crude product was precipitated from a solution of the ammonium salt, bisulfite solution was added to the fine suspension, the mixture stirred for a short time, and the product collected. The hydroxynaphthoquinone was then recovered from the solution by acidification. The yields were: hydroxynaphthoquinone, 9.6 g. (77%); m. p., 186–188°, with decomposition; alkoxy-α-naphthoquinone, 0.5 g. (3%); m. p., 143–146°; C-alkyl derivative, 0.8 g. (5%); m. p., 136°.

An adequate interpretation of the formation of such a large quantity

[9] Harries and Gottlob, *Ann.*, **383**, 228 (1911).

[10] Ref. 6 a, p. 65.

[11] Staudinger and Klever, *Ber.*, **44**, 2213 (1911).

of hydroxynaphthoquinone in this reaction, or indeed of the production of the same compound in the course of the reaction with methyl iodide,[12] cannot be given at the present time. Reaction of the halide with water, or the hydrolysis of an O-ether by the action of traces of hydrogen bromide, are both out of the question in the present case because precautions were taken to exclude even traces of moisture. The application of Nef's mechanism of the alkylation of aceto-acetic ester,[13] which involves the reaction $-CBr(ONa)CHR- \longrightarrow -C(ONa)=CR- + HBr$, encounters the same obstacle which is met in an attempt to apply this hypothesis to the dialkylation of aceto-acetic ester; while Michael's suggestion[14] that there is an equilibrium between the alkylated and unalkylated hydroxy compounds and their salts is not only improbable in the present instance but is inconsistent with the relative yields of the products obtained. The only alternative is to consider that hydrogen bromide, which can react with the silver salt, is in some way directly eliminated from the alkyl halide during the course of the reaction, though the precise mechanism is not yet clear.

2-(γ,γ-Dimethylalloxy)-1,4-naphthoquinone.—The crude material was crystallized from ligroin, in which it is moderately soluble, and was obtained in the form of pale yellow needles; m. p., 149–150°. It is hydrolyzed by aqueous alkali less readily than the saturated ethers of this series; hydroxynaphthoquinone was most easily identified by hydrolysis of the ether with aqueous alcoholic sodium hydroxide solution. Being insoluble in bisulfite solution, the compound is clearly a *p*-quinone.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.35; H, 5.85. Found: C, 74.05; H, 5.71.

2-(γ,γ-Dimethylallyl)-3-hydroxy-1,4-naphthoquinone (Lapachol, II).—The reaction product, crystallized from dil. alcohol, dil. acetic acid and from glacial acetic acid, formed lustrous, yellow plates; m. p., 139–140°.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.35; H, 5.83. Found: C, 74.11; H, 5.65.

No depression of the melting point was produced on admixture with a sample of natural lapachol, m. p. 139–140°, while conversion of the substance into β-lapachone, m. p. 153°, which was compared by a mixed-melting-point determination with a sample of pure β-lapachone, m. p. 154°, for which I am also indebted to Dr. Hooker, served to prove the identity of the synthetic and the natural products.

2. Alkylation with Crotyl Bromide.—Croton alcohol, b. p. 118–122°, was prepared by reduction of the aldehyde with magnesium chloro-alcoholate according to the convenient method of Meerwein and Schmidt[15] and converted into the bromide by shaking with four parts of 48% hydrobromic acid at room temperature. After allowing the mixture to stand for several hours, the bromide layer was separated, dried in ethereal solution and distilled; the fraction boiling at 103–105° was employed in the following experiments.

On adding 16 g. of crotyl bromide to a suspension of 30 g. of hydroxynaphthoquinone silver salt in 150 cc. of ether, a rapid exothermic reaction took place. To insure com-

[12] Fieser, THIS JOURNAL, **48**, 2922 (1926).

[13] Nef, *Ann.*, **266**, 60 (1891); **276**, 210 (1893).

[14] Michael, *J. prakt. Chem.*, [2] **46**, 191 (1892).

[15] Meerwein and Schmidt, *Ann.*, **444**, 237 (1925).

pletion of the reaction, the mixture was then shaken mechanically for one hour. The various products were isolated by extraction of the ethereal solution with ammonia solution and then with bisulfite solution and by concentration of the mother liquor in the usual manner, the yields being: crotyl hydroxynaphthoquinone, 7.7 g.; alkoxy-β-naphthoquinone, 3.7 g.; alkoxy-α-naphthoquinone, 2.6 g.

2-(γ-Methylalloxy)-1,4-naphthoquinone (III).—This substance is sparingly soluble in petroleum ether, moderately soluble in ligroin, and readily soluble in benzene or alcohol. It separates from ligroin solution in the form of long, thick, pale yellow needles; m. p., 137°. Certain crude samples were colored deep red by traces of by-products; the color was completely removed by crystallization from benzene but persisted after numerous crystallizations from ligroin. Like its analog, the ether is hydrolyzed only slowly by boiling sodium hydroxide solution and the hydroxynaphthoquinone produced was contaminated by decomposition products. It was identified by conversion into the pure methyl *p*-quinone ether. The methylallyl ether was further identified by conversion into *p*-toluidino-α-naphthoquinone.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.66; H, 5.30. Found: C, 73.76; H, 5.30.

4-(γ-Methylalloxy)-1,2-naphthoquinone (IV).—After purification through its bisulfite addition compound, the substance was crystallized from dil. alcohol and from ligroin; m. p., 120°. It forms hair-like, orange-yellow needles.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.66; H, 5.30. Found: C, 73.68; H, 5.21.

This ether is more readily hydrolyzed by alkalies than the isomer, but the hydrolysis is somewhat slower than in the case of the saturated *o*-quinone ethers. It is somewhat unusual that the melting point should be lower than that of the *p*-quinone isomer, though this same relationship was observed in the case of the *n*-butyl ethers.[12]

2-(γ-Methylallyl)-3-hydroxy-1,4-naphthoquinone (Crotyl Hydroxynaphthoquinone, V).—As stated above, this substance was isolated from the alkylation mixture by extraction with ammonia solution. The precipitated material, however, was very dark in color and it was consequently treated with ammonia solution in order to effect a further purification. A considerable quantity of a dark red substance, possibly a chemical individual, failed to redissolve, although it was soluble in alcoholic alkali. As decomposition occurred on all attempts at crystallization, the nature of the material was not determined. When freed from the by-product in this way, the crotyl hydroxynaphthoquinone was readily obtained in pure condition by repeated crystallization from alcohol, as yellow plates; m. p., 132–133°. The compound is very sparingly soluble in water or petroleum ether, and very readily soluble in alcohol or glacial acetic acid. It dissolves in solutions of alkalies or alkali carbonates with the development of a deep red color, and is but sparingly soluble in bisulfite solution.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.66; H, 5.30. Found: C, 73.64; H, 5.36.

By the action of concd. sulfuric acid the substance is converted into a mixture of about equal parts of an orange and a yellow isomer which may be separated by taking advantage of the fact that the orange isomer alone is soluble in bisulfite solution. This distinction serves to indicate the quinone groupings present in each compound, and the fact that they are both insoluble in alkali is evidence of a chromane or a coumarane structure. Since Claisen and Tietze have proved[8] that *o*-crotyl phenol yields methyl chromane and not ethyl coumarane on acid condensation, the chromane structure can be attributed to the above compounds with assurance.

Two g. of crotyl hydroxynaphthoquinone was slowly stirred into 10 cc. of concd. sulfuric acid and the dark red solution, after standing for one hour, was poured into 300 cc. of water. After standing for one hour in the ice chest, a mass of fine, orange crystals had deposited. On triturating the material with bisulfite solution the yellow *p*-chromane

quinone (0.8 g.) remained undissolved, while the isomer (0.9 g.) was recovered from the solution by the addition of sodium carbonate.

2-Methyl-7,8-benzo-5,6-chromane-quinone (VII).—The bisulfite-soluble isomer was crystallized repeatedly from methyl alcohol and obtained in the form of slender, orange needles; m. p., 164°. It dissolves very readily in benzene, readily in alcohol, and is sparingly soluble in water. The behavior of the substance towards alkali corresponds precisely to that of β-lapachone, as described by Hooker:[3] it is insoluble in cold, dil. alkali but is slowly dissolved on warming with the production of a claret-red solution. Neutralization of the solution with acetic acid, or with just the required amount of hydrochloric acid, causes the separation of a dark oil which slowly solidifies to a mass of yellow, alkali-soluble needles. If the alkaline solution is acidified with hydrochloric acid in large excess, orange crystals of the *o*-chromane-quinone soon develop in the yellow emulsion. The reactions are no doubt similar to those of β-lapachone, which Hooker has shown to involve ring fission by alkali followed by ring closure in the presence of mineral acids.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.66; H, 5.30. Found: C, 73.40; H, 5.28.

2-Methyl-6,7-benzo-5,8-chromane-quinone.—The yellow material undissolved by bisulfite solution was crystallized from methyl alcohol and thus obtained in the form of fine, yellow needles; m. p., 122.5°.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.66; H, 5.30. Found: C, 73.51; H, 5.30.

The compound may be recovered unchanged from its solution in concd. sulfuric acid. This solution is a much deeper shade of red than the sulfuric acid solution of the isomer. It is dissolved slowly by boiling sodium hydroxide solution, and the claret colored solution apparently contains the same substance as may be obtained from the isomer, for a yellow oil is precipitated on addition of acetic acid, while acidification with hydrochloric acid in excess results in the formation of the *o*-chromane-quinone.

3. **Rearrangement of the Crotyl Ethers.**—Rearrangement of each ether took place at a temperature slightly above the melting point and the yields were quantitative. Thus, the *o*-quinone ether (m. p., 120°) was heated in an oil-bath maintained at 125°, while the temperature was raised to 140° for the rearrangement of the *p*-quinone ether (m. p., 137°). In each case the temperature of the melt rapidly rose and air cooling was necessary. In 20 to 30 minutes (for 1 to 2 g.) the reaction was complete. The same substance, *2-(α-methylallyl)-3-hydroxy-1,4-naphthoquinone* (VI), was formed in each case. It was best purified, after collecting the crude melt by extraction with petroleum ether, by crystallization from dil. methyl alcohol. When the solution is allowed to cool very slowly, thick, yellow needles are obtained; m. p., 69°.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.66; H, 5.30. Found: C, 73.60; H, 5.25.

The substance dissolves very readily in the usual solvents and is somewhat soluble in water. The alkaline solution is deep red.

1,2-Dimethyl-5,6-benzo-3,4-coumarane-quinone (VIII).—This was prepared by dissolving the *sec.*-crotyl compound in concd. sulfuric acid and pouring the dark red solution into water. A fiery-red product was precipitated in crystalline condition. The substance forms a soluble bisulfite addition compound, is readily soluble in the usual solvents and is somewhat soluble in water. It crystallizes from methyl alcohol in the form of long, heavy, red needles; m. p., 109–110°.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.66; H, 5.30. Found: C, 73.83; H, 5.35.

The compound dissolves in cold, concd. hydrochloric acid, apparently without change while, like the methyl benzo-*o*-coumarane-quinone previously described,[5] it dissolves slowly in dil. alkali in the cold and a yellow oil is precipitated on acidifying the solution.

Summary

C-alkyl derivatives of hydroxynaphthoquinone are produced, together with the isomeric O-ethers, by the action of γ-methyl- and γ,γ-dimethylallyl bromide on the silver salt of hydroxynaphthoquinone. Since the crotyl derivative formed in the first case is not identical with the product of rearrangement of either of the crotyl O-ethers, it can only be 2-(γ-methylallyl)-3-hydroxy-1,4-naphthoquinone. It is inferred that the acidic substance produced in the second reaction is 2-(γ,γ-dimethylallyl)-3-hydroxy-1,4-naphthoquinone. The identity of the compound with lapachol furnishes additional evidence in support of Hooker's formula for this natural coloring matter.

BRYN MAWR, PENNSYLVANIA

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

THE REDUCING ACTION OF SODIUM METHYLATE

BY H. SHIPLEY FRY AND JESSIE LOUISE CAMERON[1]

RECEIVED DECEMBER 29, 1926 PUBLISHED MARCH 9, 1927

Introduction

There are numerous references in the literature relative to the reducing action of sodium methylate upon aromatic nitro compounds. The most common example is the reduction of nitrobenzene to azoxybenzene according to the equation

$$4C_6H_5NO_2 + 3CH_3ONa \longrightarrow 2(C_6H_5N)_2O + 3HCOONa + 3H_2O \quad (1)$$

This equation was postulated by Klinger[2] but neither he nor subsequent investigators, as far as we know, have attempted to check quantitatively the amount of azoxybenzene formed with the amount of sodium methylate oxidized to sodium formate or, in other words, to establish the stoichiometrical ratio $2(C_6H_5N)_2O:3HCOONa$ indicated in Klinger's equation.

This reaction is effected by heating a solution of nitrobenzene and sodium methylate in methyl alcohol. The sodium methylate is prepared by dissolving either sodium (Equation 2) or sodium hydroxide (Equation 3)[3] in methyl alcohol.

$$2Na + 2CH_3OH \longrightarrow 2CH_3ONa + H_2 \quad (2)$$

$$NaOH + CH_3OH \longrightarrow CH_3ONa + H_2O \quad (3)$$

The yield of azoxybenzene is usually between 80 and 90% of that calculated by Equation 1.

It should be noted that water is not only a product of Reaction 1, but

[1] A synopsis of a thesis presented to the Faculty of the Graduate School, University of Cincinnati, by Jessie Louise Cameron in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Klinger, *Ber.*, **15**, 866 (1882).

[3] Zinin, *J. prakt. Chem.*, **36**, 98 (1845).