## Summary

The preparation of some γ-ketosulfones by means of the 1,4-addition of sulfinic acids to chalcones is described. Some new α,β-unsaturated ketones and sulfinic acids prepared as intermediate compounds in these reactions are reported.


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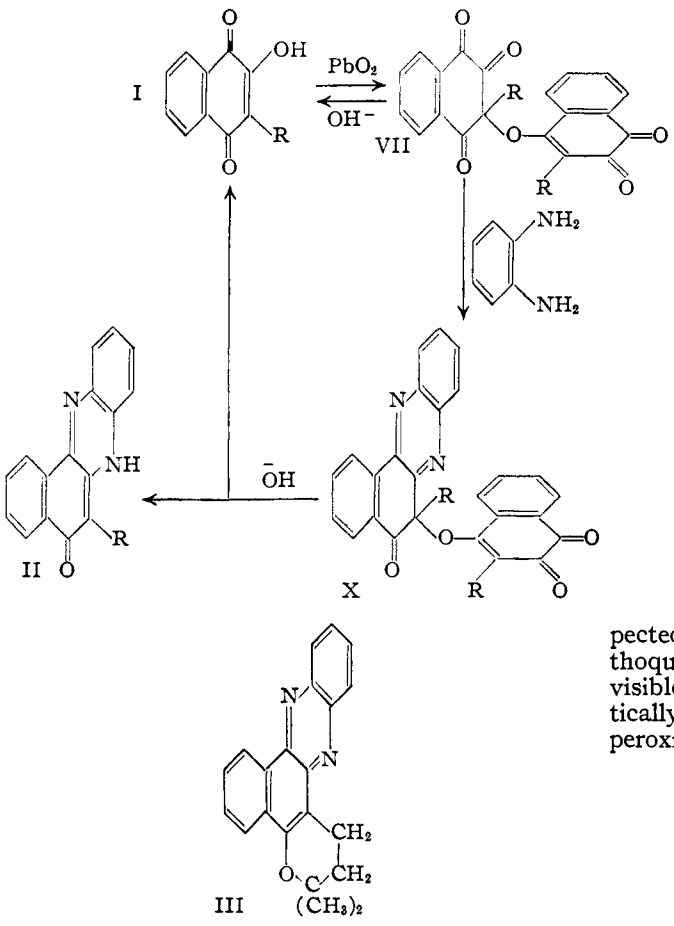
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

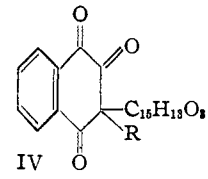
# Hydroxynaphthoquinones. III. The Structure of Lapachol Peroxide

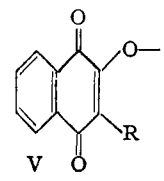
BY MARTIN G. ETTLINGER[1]

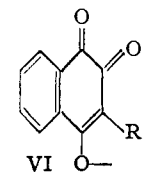
During studies on the natural pigment lapachol (I, R = $CH_2CH{=}C(CH_3)_2$), Hooker discovered[2] that this substance was oxidized by lead dioxide in acetic acid to a neutral, yellow compound of molecular formula $C_{30}H_{26}O_6$ equivalent to two molecules of lapachol less two atoms of hydrogen, which was named lapachol peroxide. A similar, unanalyzed product was obtained from 2-hydroxy-3-*n*-amyl-1,4-naphthoquinone (I, R = $(CH_2)_4CH_3$). Hooker observed that lapachol peroxide was reconverted to lapachol by alkaline hydrolysis in a molar yield of 1.6, but examined the peroxide no further and merely represented it graphically as containing an oxygen–oxygen bond.

In the present investigation, it was found that lapachol peroxide reacted easily with *o*-phenylenediamine in acetic acid to form a yellow, sparingly soluble *monophenazine*, $C_{36}H_{30}O_4N_2$, m. p. 185–186° (dec.). The monophenazine is cleaved by zinc and alkali to lapachol and lapeurhodone[3] (II, R = $CH_2CH{=}C(CH_3)_2$). The ultraviolet absorption spectrum (Fig. 1) of the phenazine resembles that of the peroxide (Fig. 2) and entirely lacks the intense bands at 305 mμ and 410–440 mμ in the spectrum (Fig. 1) of lapazine[3] (III). Therefore, one of the lapachol residues in the peroxide must contain a non-quinonoid 1,2-diketone group, which is possible in stable form only in the partial formula IV (R = $CH_2CH{=}CH(CH_3)_2$). Inasmuch as the peroxide is readily hydrolyzed in high yield to lapachol, the residues must be united by a carbon–oxygen bond and the group $C_{15}H_{13}O_3$ in IV is V or VI (R = $CH_2CH{=}C(CH_3)_2$). Since the 1,2,4-triketotetralin group in IV may be expected, similarly to benzil[4] or 2-methyl-1,4-naphthoquinone oxide,[5] to absorb only weakly in the visible, the band beyond 400 mμ that occurs practically identically in the spectra of lapachol peroxide and its phenazine must belong to V or VI.



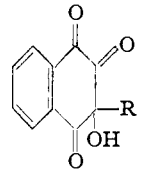



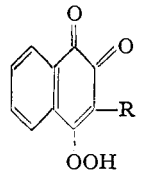

(1) Member of the Society of Fellows, Harvard University.
(2) Hooker, THIS JOURNAL, **58**, 1168 (1936).
(3) Hooker, *ibid.*, **58**, 1190 (1936).
(4) Leonard and Blout, *ibid.*, **72**, 484 (1950).
(5) Fieser and Fieser, *ibid.*, **70**, 3215 (1948).

However, the absorption of 2-alkoxy-3-alkyl-1,4-naphthoquinones[6,7] decreases too rapidly in the visible to allow attribution of the peroxide band to V. On the other hand, 4-alkoxy-3-alkyl-1,2-naphthoquinones,[6,7] models of VI, possess a maximum near 430 mμ, log $\epsilon \cong 3.25$, which agrees closely with the value log $\epsilon = 3.2$ at 430 mμ for lapachol peroxide and its phenazine. The circumstance that the last two compounds are yellow and absorb less beyond 450 mμ than common *o*-quinones may be ascribed[8,9] to the attachment of the electron withdrawing triketotetralin group to the quinone. The structure of lapachol peroxide is hence established as VII (R = $CH_2CH{=}C(CH_3)_2$).

In repetition of the hydrolysis to lapachol, the peroxide was found to be unusually sensitive to base. Judged by the apparition of the red color of the anion of lapachol, cleavage of the peroxide in dilute alcoholic alkali was complete almost instantaneously, whereas hydrolysis of lapachol methyl ether[10] under the same conditions required roughly an hour. Even sodium bicarbonate attacked the peroxide in a minute. Since *o* and *p*-quinone ethers of 2-hydroxy-1,4-naphthoquinone do not differ greatly in ease of alkaline hydrolysis,[11] it seems unlikely that the rapid cleavage of lapachol peroxide follows a comparable course. Instead, attack of hydroxide ion on the peroxide may occur by displacement at the 3-carbon of the triketotetralin unit to furnish VIII (R = $CH_2CH{=}C(CH_3)_2$) and the anion of lapachol, or at

VIII 

the oxygen linking the rings to produce the anion of lapachol, from the trione portion, and the intermediate IX (R = $CH_2CH{=}C(CH_3)_2$), which would hydrolyze to hydrogen peroxide and lapachol. The lability of the lapachol peroxide sys-

IX 

tem is perhaps the reason why it forms only the monophenazine X (R = $CH_2CH{=}C(CH_3)_2$) and not a diazine. The only isolable reaction product of X, which is a sterically hindered quinone, and excess *o*-phenylenediamine was lapeurhodone.

(6) Cooke, Macbeth and Winzor, *J. Chem. Soc.*, 878 (1939).
(7) Ettlinger, THIS JOURNAL, **72**, 3090 (1950).
(8) Hooker and Steyermark, *ibid.*, **58**, 1207 (1936).
(9) Ettlinger, *ibid.*, **72**, 3085 (1950).
(10) Fieser, *ibid.*, **50**, 439 (1928).
(11) Fieser, *ibid.*, **48**, 2922 (1926).

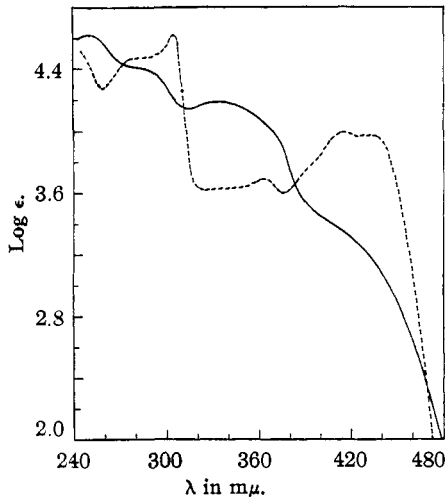



Fig. 1.—Absorption spectra in chloroform: —, lapachol peroxide monophenazine (X, R = $CH_2CH{=}C(CH_3)_2$); . . ., lapazine (III).

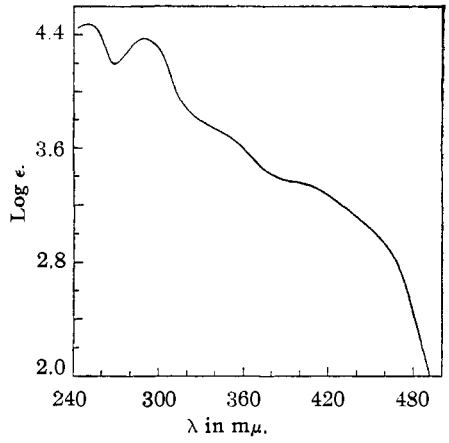
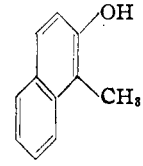
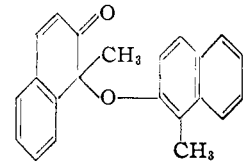



Fig. 2.—Absorption spectrum of lapachol peroxide (VII, R = $CH_2CH{=}C(CH_3)_2$) in chloroform.

Close analogs of lapachol peroxide are dehydrobis-1-methyl-2-naphthol[12,13] (XI), obtained by oxidation of 1-methyl-2-naphthol (XII) with nitrous acid, ferric chloride, or alkaline ferricyanide,

XII  XI 

and the structurally similar dehydro derivatives of 1-methylene-di-2-naphthol[12,14] and 1-ethylene-di-2-naphthol.[15] Dehydrobis-1-methyl-2-naphthol is notably reactive, liberates iodine from acidic iodide solutions and is reduced to XII by stannous

(12) Pummerer and Cherbuliez, *Ber.*, **47**, 2957 (1914).
(13) Pummerer, *ibid.*, **52**, 1403 (1919); Fries and Schimmelschmidt, *Ann.*, **484**, 245 (1931).
(14) Shearing and Smiles, *J. Chem. Soc.*, 1931 (1937).
(15) Pummerer and Cherbuliez, *Ber.*, **52**, 1392 (1919).

chloride or zinc in acetic acid, hydroquinone, or phenylhydrazine. Except for the tautomerism that enables lapachol, like 2-hydroxy-1,4-naphthoquinone, to form two kinds of ethers, the oxidations of XII to XI and lapachol to lapachol peroxide are identical.

## Experimental

**Absorption Spectra.**—Measurements were made in U. S. P. chloroform solution with a Beckman Spectrophotometer, Model DU, used by courtesy of Dr. I. H. Scheinberg. The positions and intensities of maxima were: lapachol peroxide, 250 mμ (log ε 4.48), 289 (4.37), 340 (3.73) (inflection), 400 (3.36) (inflection); lapachol peroxide monophenazine, 249 (4.61), 290 (4.39) (inflection), 332 (4.19), 410 (3.39) (inflection); lapazine, 280 (4.46) (inflection), 305 (4.61), 362 (3.69), 415 (4.00), 435 (3.97) (inflection).

**Sensitivity to Alkali.**—A solution of lapachol peroxide in chloroform or ether imparted no color to 0.1 *N* sodium hydroxide, but if alcohol or dioxane was added to the mixture, a deep red color appeared within a second. Under the same conditions, 2-methoxy-1,4-naphthoquinone required roughly a minute for hydrolysis, lapachol peroxide monophenazine two minutes, and lapachol methyl ether an hour.

A chloroform solution of lapachol peroxide, treated with an equal amount of 2% sodium bicarbonate and sufficient alcohol (two volumes) to homogenize the mixture, developed a strong red color in a minute. No instantaneous color appeared if a solution of the peroxide in aqueous alcohol–chloroform was treated with bicarbonate after standing five minutes.

**Lapachol Peroxide Monophenazine.**—A mixture of 0.5 g. of lapachol peroxide, 0.25 g. of *o*-phenylenediamine, and 10 cc. of acetic acid was heated on the steam-bath for half an hour, cooled, and filtered. The solid, crystallized from acetic acid (100 cc. per g.), afforded 0.45 g. (78%) of small, bright yellow needles of lapachol peroxide monophenazine, m. p. 184–185° (dec.). The analytical sample darkened at 182° and melted at 185–186° (dec.) (bath preheated to 175°).

*Anal.* Calcd. for $C_{26}H_{30}O_4N_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.18; H, 5.12; N, 5.31.

Lapachol peroxide monophenazine is sparingly soluble in cold acetone, alcohol, or ether, readily in chloroform and hot benzene or dioxane. In concentrated sulfuric acid it forms an orange-yellow solution that darkens rapidly to blackish green. If a solution of the phenazine in aqueous dioxane is treated with sodium bisulfite, the color immediately deepens toward orange, possibly because of cleavage to lapeurhodone.

After a mixture of 0.1 g. of lapachol peroxide, 0.1 g. of *o*-phenylenediamine and 10 cc. of acetic acid was refluxed for ten minutes, cooled and diluted with 3 cc. of water, the precipitated oil soon solidified and yielded 0.09 g. of recrystallized monophenazine. Further dilution of the mother liquor with water afforded 0.01 g. of crude lapeurhodone.

**Hydrolysis of Monophenazine.**—A mixture of 0.2 g. each of lapachol peroxide monophenazine and zinc dust was heated under reflux for fifteen minutes with a solution of 1 g. of potassium hydroxide pellets in 5 cc. of water and 20 cc. of alcohol, cooled and filtered, and the intensely crimson filtrate poured into excess dilute acid and extracted with ether. The ether solution was extracted with 5% sodium carbonate, washed with water, dried and evaporated, and the residue crystallized from 2 cc. of alcohol. There was obtained 92 mg., m. p. 158–162°, of dark red crystals contaminated with a yellow solid, possibly dehydrolapazine,[3] a known reaction product of alkali and lapeurhodone. Recrystallization from 5 cc. of alcohol afforded 63 mg. (56%) of dark red, hexagonal tablets of lapeurhodone, m. p. 165.5–167°, which gave a deep green solution in concentrated sulfuric acid and did not depress the melting point of an authentic sample.

The sodium carbonate extracts were washed judiciously with ether, acidified hot, chilled, and filtered. The precipitate, crystallized from 1 cc. of alcohol, furnished 75 mg. (86%) of golden plates of lapachol, m. p. 141–142.5°, which did not depress the melting point of the genuine substance.

## Summary

The structure of lapachol peroxide, a derivative of 1,2,4-triketotetralin and an *o*-quinonoid ether of lapachol, is elucidated.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMICAL ENGINEERING, UNIVERSITY OF TORONTO, AND THE DOMINION RUBBER COMPANY, RESEARCH LABORATORIES]

# Separation of the Acids of Hog Bile

BY E. BRUCE TRICKEY[1]

Although the composition of the bile acid mixtures from other commonly available animals is well-known, that of the hog is a notable exception.

Numerous preliminary experiments led to the development of a chromatographic method for the separation of the hog bile acids. Whole hog bile was subjected to an alkaline hydrolysis to release the unconjugated acids which were recovered as a dark-brown resinous mixture in 7.85% yield based on the starting weight of the whole bile. This material was called the "crude bile acids" and served as the starting point in our attempts at separation. Percentage yields of products reported in this paper are calculated on the basis of the weight of "crude bile acids." This product was subjected to an acid hydrolysis, followed by a partial removal of the keto acids with hydrazinobenzoic acid. The dry residue deposited hyodesoxycholic acid in 22.4% yield from ethyl acetate. The amorphous fraction was converted to the acid chlorides of the bile acid formates and reacted with aminoazobenzene to obtain the azoyl amide formates. On deformylation and chromatographing over alumina four main products were obtained which were numbered in the order of their appearance in the filtrate. Band I was found to be derived from 3-hydroxy-6-keto-*allo*cholanic acid. Band II an-

(1) This paper comprises a portion of a thesis presented by E. Bruce Trickey in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemical Engineering, University of Toronto. Present address: Ardentown, Delaware.