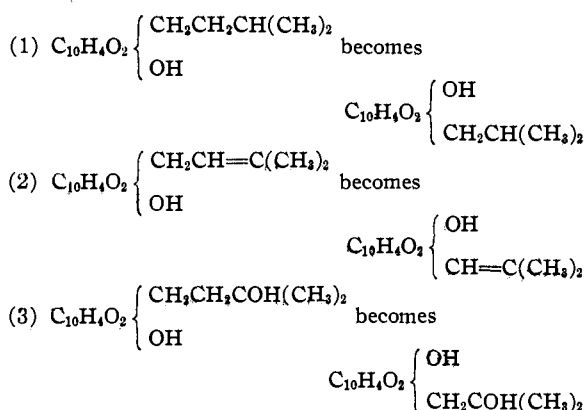


## On the Oxidation of 2-Hydroxy-1,4-naphthoquinone Derivatives with Alkaline Potassium Permanganate<sup>1,2</sup>

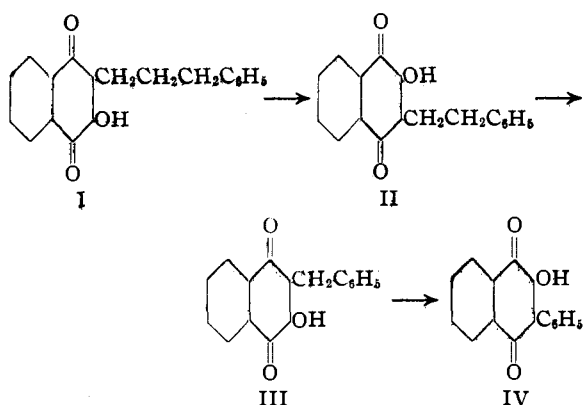
BY SAMUEL C. HOOKER

I have shown in a recent paper<sup>3</sup> on the constitution of lapachol that the following extraordinary changes are brought about by oxidation with alkaline potassium permanganate:



The full discussion of the mechanism involved I have reserved for the present paper.

In view of the varied chains from which  $\text{CH}_2$  was eliminated as shown in the above examples, the conclusion seemed inevitable that the reaction would prove to be a general one, and further study has fully confirmed this anticipation. Thus through successive oxidations the following compounds have been prepared from 2- $\gamma$ -phenylpropyl-3-hydroxy-1,4-naphthoquinone:



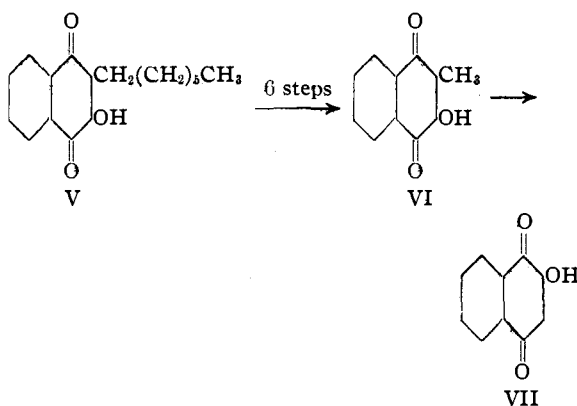
(1) See Editor's note (1), *THIS JOURNAL*, **58**, 1163 (1936).

(2) The theoretical part of this paper, the summary, and the last section of the experimental part are reproduced essentially as they were written by Dr. Hooker in 1934, although it has seemed expedient to rearrange some of the material. The experiments were carried out largely by Dr. A. Steyermark, who has been of great assistance in collecting the data. Dr. C. A. Lear also contributed to the experimental work, and the analyses were all done by Dr. D. Price of Columbia University.—L. F. FIESER.

(3) Hooker, *THIS JOURNAL*, **58**, 1168 (1936).

The starting material (I) was prepared by the hydrogenation of the condensation product of hydrocinnamaldehyde with hydroxynaphthoquinone, and the first oxidation product (II) proved to be identical with the quinone similarly obtained<sup>4</sup> from the condensation product from phenylacetaldehyde. The product of the second oxidation (III) was compared directly and found to be identical with 2-benzyl-3-hydroxy-1,4-naphthoquinone,<sup>5</sup> kindly sent to me by Dr. L. F. Fieser. The final product (IV) is undoubtedly identical with " $\beta$ -phenylhydroxynaphthoquinone" of Zincke.<sup>6</sup>

In another series of experiments starting with *n*-heptylhydroxynaphthoquinone (V)  $\text{CH}_2$  has been removed step by step passing through hexyl-, pentyl-, butyl-, propyl-, ethyl-, and methylhydroxynaphthoquinone until finally hydroxynaphthoquinone itself has been reached. This series of oxidations has yielded substances which with



the exception of the hexyl and ethyl compounds have been compared with those having the same number of carbon atoms, prepared<sup>4</sup> by the aldehyde synthesis and hydrogenation. They proved to be identical in every instance. Comparison was not made in the case of the hexyl compound because hexyl aldehyde was not commercially available, and, as it was not possible to obtain a condensation product of the required type with acetaldehyde, comparison was made with the ethyl product prepared by the hydrogenation of

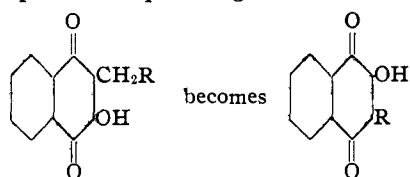
(4) Hooker, *ibid.*, **58**, 1163 (1936).

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

(6) Zincke and Breuer, *Ann.*, **226**, 32 (1884); Zincke, *ibid.*, **240**, 140 (1887).

the vinyl compound<sup>7</sup> resulting from the oxidation of 2-allyl-3-hydroxy-1,4-naphthoquinone. The next to last oxidation product, 2-methyl-3-hydroxy-1,4-naphthoquinone (VI), was compared directly and found to be identical with synthetic phthiocol,<sup>8</sup> kindly sent to me by Professor R. J. Anderson. The final product of the reaction was fully identified as 2-hydroxy-1,4-naphthoquinone, a result which shows clearly that the new reaction can be extended for the purpose of eliminating completely a saturated radical attached to the quinone group.

Stated generally, by suitable oxidation with alkaline potassium permanganate



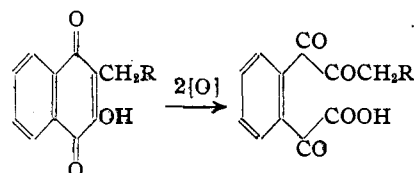
The conditions most suitable for bringing about the transformation are more clearly defined in the experimental part of the present paper. For the oxidation of quinones having saturated side chains a rather strongly alkaline solution is required and the reaction is conducted at 0–5°. The quantity of permanganate used is sufficient to supply two atoms of oxygen to the molecule of the hydroxyquinone plus 5%. In carrying out the reaction, solutions of the hydroxyquinone in 1% alkali and of the permanganate in 10% alkali are cooled in ice and quickly mixed. In the course of the reaction the crimson solution of the sodium salt of the hydroxynaphthoquinone derivative becomes *almost colorless* as manganese dioxide is being deposited. In a short time, varying somewhat with the substance oxidized, sometimes very rapidly, *the solution again becomes more or less intensely crimson*. On acidification of the filtered solution the oxidation product is obtained in a crystalline, usually yellow condition. The purity of the oxidation product is excellent and the yield generally ranges from 70 to over 80% of the weight of the material taken. It has been found in some cases that still better yields may be obtained by increasing the concentration of alkali, and conversely a decrease in the alkalinity may result in diminished yields.

(7) Details of experiments conducted in conjunction with Dr. Al Steyermark will be recorded in another paper describing the formation of this compound by permanganate oxidation of the allyl derivative.

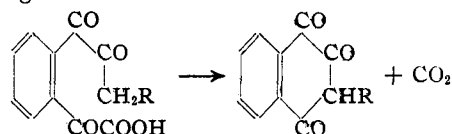
(8) Anderson and Newman, *J. Biol. Chem.*, **103**, 197, 405 (1933); Anderson, Crowder and Newman, *ibid.*, **105**, 279 (1934).

The above remarks and method of procedure apply to derivatives with saturated chains. In oxidizing those with a double bond in the chain it has proved desirable to use a much less strongly alkaline medium. In this case the permanganate is dissolved in water containing no alkali and in other respects the procedure is the same. The yields are considerably less, ranging from 35–40% of the material oxidized as a maximum in the substances examined, and may be much smaller. If the double bond now occupies the  $\alpha,\beta$ -position the substance obtained varies in color from deep orange to red instead of being yellow.

The oxidation appears to take place in at least three stages, as follows: (1) The hydroxyquinone ring probably is split thus:

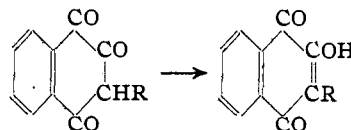


(2) A six-membered ring is again formed, the carbon originally attached to hydroxyl, however, being eliminated as carbon dioxide and the carbon in the  $\alpha$ -position in the chain entering into the ring:



The ring as first formed probably has no double bonds, as the compound appears to be colorless, or nearly so. Whether the carbon dioxide is eliminated at the time of the formation of the ring or before or subsequent to its formation can only be surmised, as it has not yet been possible to isolate the intermediate compound or compounds.

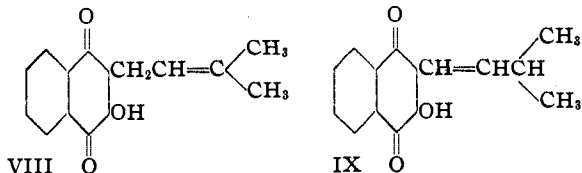
(3) By tautomeric change the colorless compound becomes a hydroxynaphthoquinone derivative:



As the oxygen supplied by the permanganate up to the formation of manganese dioxide is sufficient only for the opening of the ring, it was originally thought that the oxidation is effected first by the oxygen derived from the permanganate and then, corresponding to the reddening of the



formula (VIII) was confirmed by Fieser by synthesis many years later.<sup>10</sup> Now in view of my



more recent experiments, as lapachol is *yellow* it could not have the formula IX for the position of the double bond in this case would require the substance to be *red* or *orange-red*. Synthesis of IX has substantiated this; it is *red*.<sup>9</sup> On oxidation lapachol loses  $\text{CH}_2$  and the resulting hydroxynaphthoquinone derivative is *red*. The bond therefore has moved one step to the left as the result of the removal of  $\text{CH}_2$  and lapachol therefore has the side chain  $-\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$  and not

$-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}_2$ . I have proved independently<sup>3</sup> that the substance resulting from the oxidation actually has the chain  $-\text{CH}=\text{C}(\text{CH}_3)_2$  which the above considerations would require.

As Fieser has shown<sup>11</sup> that the chemistry of polycyclic  $\beta$ -hydroxy- $\alpha$ -quinones closely follows in a number of respects that of 2-hydroxy-1,4-naphthoquinone, it is not unreasonable to expect that they too would be subject to the aldehyde synthesis and their derivatives to the permanganate oxidation described in this and preceding papers.

## Experimental Part

### Potassium Permanganate Oxidations

The amounts of materials oxidized in the different experiments and the quantities of potassium permanganate and of alkali employed are indicated in Table I, which records also the yields, properties and analyses of the oxidation products. It is evident from the results that the yield is improved by using a rather strongly alkaline solution. The alkali is added to the permanganate solution rather than to the solution containing the hydroxynaphthoquinone because the troublesome separation of the sodium salt is in this way avoided. Generally very satisfactory results are obtained by operating in the following manner.

**General Procedure.**—For the oxidation of an alkylhydroxynaphthoquinone, for example of the molecular weight 230, 1 g. of the material is dissolved in 100 cc. of 0.5% sodium hydroxide solution and the crimson solution is cooled in ice water. The second solution is prepared by dissolving 0.96 g. of potassium permanganate, an amount sufficient to furnish two atoms of oxygen plus 5% in excess, in 100 cc. of 10% sodium hydroxide, and

this is likewise cooled in ice water. The two solutions are mixed rapidly in one operation and kept in ice water until manganese dioxide separates, the crimson solution of the hydroxynaphthoquinone derivative on the addition of the permanganate usually becoming successively bright green, olive green, brown, and as the manganese dioxide separates almost colorless. In order that the manganese dioxide may be completely deposited it is well to allow the solution to stand for several hours at room temperature, during which time a crimson color develops at a rate varying with the substance oxidized.<sup>12</sup> The manganese dioxide is filtered off and thoroughly washed so as to redissolve any sodium salt of the new product which may have crystallized from the alkaline solution. The addition of dilute hydrochloric acid precipitates the new substance, which may separate as an emulsion but is soon obtained well crystallized, usually in small, bright yellow needles. The products usually crystallize well from either alcohol or petroleum ether.

Of the entire list of products, only two are described for the first time, namely, 2-*n*-hexyl- and 2-ethyl-3-hydroxy-1,4-naphthoquinone. Samples of all of the other compounds, with the exception of 2-phenyl-3-hydroxy-1,4-naphthoquinone, were available for comparison and mixed melting point determinations with the substances prepared by other methods showed no depressions. Microscopic examinations further established the identity of the oxidation products.

**The Effect of Oxygen.**—In special experiments the oxidation of 2-*n*-butyl-, 2-*n*-heptyl- and 2-*n*-hexyl-3-hydroxy-1,4-naphthoquinone was conducted in the absence of oxygen. The solutions of the quinone and of the permanganate were boiled to expel air and placed in vessels connected in a train whereby the system could be evacuated thoroughly and filled with nitrogen. The cooled solutions were mixed by forcing the permanganate solution into the quinone solution under nitrogen pressure. The oxidations proceeded exactly as when carried out with free access of air and no significant differences were noted.

**Attempts to Arrest the Reaction.**—Noting that the changes occur more slowly in a weakly alkaline medium, some attempts were made to isolate intermediate compounds under these conditions. 2- $\beta$ -Phenylethyl-3-hydroxy-1,4-naphthoquinone was dissolved in 0.5% alkali and treated with a solution of potassium permanganate in water. The separation of manganese dioxide was complete only in one and one-quarter hours and when this was removed a pale red filtrate was obtained. On acidification there was obtained only a small amount of the normal oxidation product, 2-benzyl-3-hydroxy-1,4-naphthoquinone. On making the filtrate alkaline the solution gradually acquired a deeper crimson color, and more of the above compound separated on acidification. It was observed that the darkening of the solution occurred at the same rate whether the alkaline solution was allowed to remain undisturbed or was shaken vigorously with air.

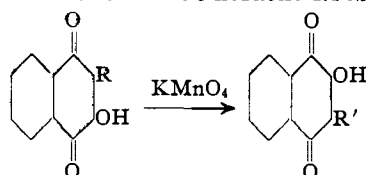
2-Methyl-3-hydroxy-1,4-naphthoquinone seemed well adapted to a study of the intermediate stages of the reaction because the changes occur somewhat more slowly with

(10) Fieser, *THIS JOURNAL*, **49**, 857 (1927).

(11) Fieser, *ibid.*, **50**, 465 (1928); **51**, 940, 1896 (1929).

(12) The final result is the same if the manganese dioxide is removed at once and the filtrate is allowed to stand for several hours before acidifying.

TABLE I  
 PERMANGANATE OXIDATION OF 2-ALKYL-3-HYDROXY-1,4-NAPHTHOQUINONES



Subst. oxidized, R =	Solution of substance			Solution of KMnO <sub>4</sub>				Oxidation product, R =	Yield		
	Subst., g.	Volume of NaOH soln., cc.	concn. %	KMnO <sub>4</sub> , g.	2[O], %	Vol., cc.	NaOH, %		Wt., g.	%	
1	—(CH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	0.5	125	2	0.4	11	40	0	—(CH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	0.37	78
2	—(CH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	2	400	5	2	32	200	0	—CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	1.49	78
3	—CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	1	200	5	1	25	100	0	—C <sub>6</sub> H <sub>5</sub>	0.66	70
4	—(CH <sub>2</sub> ) <sub>6</sub> CH <sub>3</sub>	6	600	1	5.1	10	600	4	—(CH <sub>2</sub> ) <sub>6</sub> CH <sub>3</sub>	4.86	85
5	—(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	3	300	0.5	2.7	10	300	15	—(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	2.72	96
6	—(CH <sub>2</sub> ) <sub>4</sub> CH <sub>3</sub>	3	300	.5	2.85	10	300	10	—(CH <sub>2</sub> ) <sub>4</sub> CH <sub>3</sub>	2.57	91
7	—(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	6.27	630	.5	6.05	5	630	10	—(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	5.22	89
8	—(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub>	3.43	350	.5	3.51	5	350	10	—CH <sub>2</sub> CH <sub>3</sub>	2.80	88
9	—CH <sub>2</sub> CH <sub>3</sub>	1.72	175	.5	1.88	5	175	10	—CH <sub>3</sub>	1.28	80
10	—CH <sub>3</sub>	0.1	10	.5	0.12	5	10	10	—H	(0.04)	(43)

Solvent	Crystalline form	M. p., °C.		Analyses				
		Found	Recorded	% C		% H		
1	Alcohol	Orange-yellow prisms	171.5–172.5	171.5–172.5 <sup>4</sup>	77.67	77.46	5.07	5.02
2	Alcohol	Golden-yellow plates	176.2–177.2	175–176 <sup>5</sup>	77.25	77.48	4.58	4.42
3	Alcohol	Orange-yellow plates	142.6–143.6	143.5–144.5 <sup>6,13</sup>	76.77	77.02	4.03	4.12
4	Alc., pet. ether	Yellow needles	98–98.5	.....	74.38	74.70	7.03	6.93
5	Alc., pet. ether	Orange-yellow needles	103.2–103.7	104–104.3 <sup>4</sup>	73.73	73.92	6.61	6.57
6	Alc., pet. ether	Orange-yellow needles	99.2–99.7	100.3–100.7 <sup>4</sup>	73.01	73.20	6.13	6.23
7	Pet. ether	Orange-yellow plates	100–101	100.5–101.5 <sup>4</sup>	72.19	72.36	5.60	5.71
8	Pet. ether	Yellow plates	138.2–138.7	.....	71.26	71.37	4.99	4.84
9	Pet. ether, alcohol, ether	Yellow needles	172–173	173–174 <sup>8,14</sup>	70.19	70.14	4.29	4.20
10	Alcohol	Yellow needles, scales	187–188, dec.	About 192, dec. <sup>15</sup>	...	...	...	...

this compound than in other cases. Under the conditions outlined in Table I the solution could be filtered from the manganese dioxide without acquiring more than a light brownish-red color. The acidified solution was yellow and it was kept in the dark for several weeks without undergoing any apparent change. A small amount of hydroxynaphthoquinone separated, but no intermediate product could be obtained. From time to time portions of the solution were made alkaline, which caused the gradual appearance of a dark red-brown color. Hydroxynaphthoquinone was then obtained on acidification.

**Test for Formic Acid.**—In the attempt to establish the manner in which a single carbon atom is eliminated in the oxidation, the mother liquor remaining after acidifying the alkaline solution with sulfuric acid and collecting the reaction product was investigated for the presence of formic acid. The solution was distilled and the nearly colorless, faintly acidic distillate was heated with 5% mercuric chloride solution. There was no precipitate, although in control experiments it was found that an amount of formic acid equivalent to the quinone employed can be detected easily by this method.

**Further Observation.**—A number of attempts were made to obtain an oxidation product similar to those described

(13) Volhard, *Ann.*, **296**, 18 (1897), gives 146–147°.

(14) J. Madinaveitia, *Anales soc. españ. fis. quim.*, **31**, 750 (1933); *Rev. acad. cienc. Madrid*, **31**, 617 (1934).

(15) Fieser, *This Journal*, **48**, 2930 (1926).

above from 2- $\beta$ -hydroxyisobutyl-3-hydroxy-1,4-naphthoquinone,<sup>8</sup> but the experiments were not successful. The alkalinity and the temperature were varied over a wide range, but a large part of the material was invariably converted into resinous products and 35–50% of the starting substance was recovered unchanged. There were some indications of the formation of 2-hydroxy-1,4-naphthoquinone, but the substance was not completely identified.

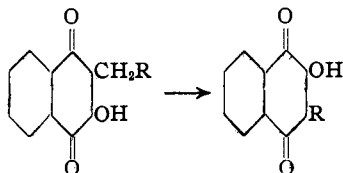
**Color Test for Hydroxynaphthoquinones.**—Volhard<sup>13</sup> has recorded that 2-phenyl-3-hydroxy-1,4-naphthoquinone gives with concentrated sulfuric acid and benzene containing thiophene a dark blue color. I have found that this reaction is a general one. Hydroxynaphthoquinone itself and those of its derivatives having saturated carbon chains in the quinone ring, with or without phenyl groups, respond to it.

The test can be made conveniently by dissolving a small quantity of the substance to be examined in two drops of concentrated sulfuric acid on a watch glass and adding to this 2 drops of benzene containing one drop of thiophene in 5 cc. As the sulfuric acid containing the hydroxynaphthoquinone or its derivative is thoroughly mixed with the benzene, a brown color usually first develops which passes slowly on standing through an olive green to a deep blue, the color being first observed at the edges of the solution as moisture is absorbed. Finally a blue precipitate is

formed. All of the substances listed in Table I gave the test, and this was true also of hydrolapachol and of 2-isobutyl-3-hydroxy-1,4-naphthoquinone.<sup>3</sup>

### Summary

It is shown how alkaline potassium permanganate oxidation of hydroxynaphthoquinone derivatives can result in a general reaction involving the following change:



Thus it is possible to eliminate  $\text{CH}_2$  adjoining

the quinone ring without otherwise disturbing the structure of the chain. In the course of the oxidation the quinone ring is split and then reformed. One carbon atom of the original ring is eliminated, another from the side chain taking its place, with the result that the chain is shortened by one carbon atom and the positions of the hydroxyl and the side chain are reversed in the new ring. The steps involved are fully discussed and many examples of the reaction are given. It is also shown how the oxidation can be of assistance in determining the structure of the side chain and, if unsaturated, the position of the double bond.

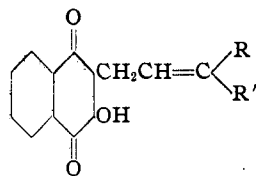
82 REMSEN STREET  
BROOKLYN, NEW YORK

RECEIVED MARCH 25, 1936

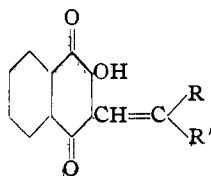
## On the Oxidation of 2-Hydroxy-1,4-naphthoquinone Derivatives with Alkaline Potassium Permanganate. Part II. Compounds with Unsaturated Side Chains<sup>1,2</sup>

BY SAMUEL C. HOOKER AND AL STEYERMARK

It has been shown that the novel oxidation reaction described recently by one<sup>3</sup> of us is applicable to a large number of hydroxynaphthoquinones with saturated side chains in the quinone ring, but only one example of a substance containing a double bond in the side chain was included in the previous studies, namely, lapachol.<sup>3a</sup> Lapachol (I, R and R' =  $\text{CH}_3$ ) is converted by alkaline permanganate in the cold into the next lower homolog of the type II, in which  $\text{CH}_2$  has been eliminated and the double bond shifted from the  $\beta,\gamma$ - to the  $\alpha,\beta$ -position. In order to extend this observation the following additional com-



I (Yellow)



II (Orange or red)

pounds have been examined: the 2-allyl, 2- $\gamma$ -methylallyl, and 2-cinnamyl derivatives of 3-hydroxy-1,4-naphthoquinone. The materials were in part kindly supplied by Dr. L. F. Fieser, who has described the preparation of all three of these quinones.<sup>4</sup>

(1) See Editor's note (1), *THIS JOURNAL*, **58**, 1163 (1936).

(2) Dr. Hooker left no manuscript for the first part of this paper but wrote the description of the three oxidations recorded in the experimental part.—L. F. FIESER.

(3) HOOKER, *THIS JOURNAL*, (a) **58**, 1168 (1936); (b) **58**, 1174 (1936).

(4) Fieser, (a) *ibid.*, **48**, 3201 (1926); (b) **49**, 857 (1927).

The three compounds of the type I are yellow, like lapachol, and on oxidation with permanganate they behave in an entirely similar manner yielding orange or red quinones of the type II. The product resulting from the oxidation of 2- $\gamma$ -methylallyl-3-hydroxy-1,4-naphthoquinone (I, R =  $\text{CH}_3$ , R' = H) proved to be identical with the substance prepared<sup>5</sup> by the condensation of propionaldehyde with hydroxynaphthoquinone, namely, 2- $\alpha$ -propenyl-3-hydroxy-1,4-naphthoquinone. The oxidation product of the cinnamyl compound similarly was identified by direct comparison with the compound II (R =  $\text{C}_6\text{H}_5$ , R' = H) prepared<sup>5</sup> by the aldehyde synthesis.

The oxidation of the allyl compound presented some difficulties but conditions eventually were defined permitting the isolation of the sensitive reaction product, 2-vinyl-3-hydroxy-1,4-naphthoquinone (III). This compound, which is described for the first time, was fully identified by its conversion on catalytic hydrogenation into 2-ethyl-3-hydroxy-1,4-naphthoquinone (IV), a substance previously prepared<sup>5b</sup> in this Laboratory by the oxidation of the propyl compound (V).

These results fully confirm and extend the observations made in the case of lapachol. In all four of the examples investigated it has been found that the oxidation of a yellow alkyl hydroxynaphthoquinone having a double bond in the  $\beta,\gamma$ -position in the side chain leads to the re-

(5) Hooker, *ibid.*, **58**, 1163 (1936).