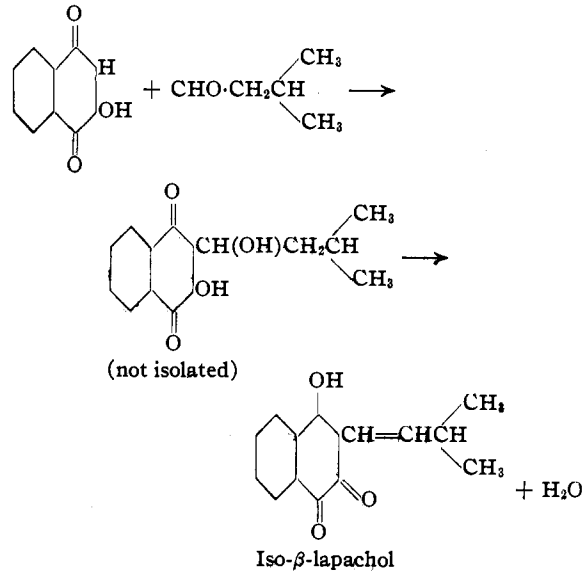
Condensation of Aldehydes with β-Hydroxy-α-naphthoquinone. Synthesis of Hydrolapachol[1,2]

BY SAMUEL C. HOOKER

In the course of my researches on the constitution of lapachol and in hope of synthesizing this substance I studied in 1896 the interaction of isovaleraldehyde and 2-hydroxy-1,4-naphthoquinone,[3] and was thus led to a compound isomeric with lapachol which I was able to convert into several substances which I had previously obtained from lapachol itself, and which contained the full complement of carbon atoms. With these facts in mind the condensation was interpreted as follows:



Iso-β-lapachol

It was originally thought that this condensation compound owing to its *red* color must be considered a derivative of β-naphthoquinone and it was referred to as iso-β-lapachol in consequence. Fieser,[4] who has examined many of the compounds obtained in my laboratory, has shown however that the reduction potential of iso-β-lapachol agrees very closely with that of derivatives of 2-hydroxy-1,4-naphthoquinone having

(1) This is the first of a group of eleven papers reporting the results of investigations carried out by the late Dr. Samuel Cox Hooker (1864–1935) in continuation of his studies of lapachol, lomatiol, and related compounds as described for the most part in papers published in 1889–1896 in the *Journal of the Chemical Society*. The early investigations were resumed shortly after Dr. Hooker's retirement from the board of directors of the American Sugar Refining Company in 1915 and the work was continued to the time of his death on October 12, 1935 (see obituary sketch by Dr. C. A. Browne, *J. Chem. Soc.*, 550 (1936)). The papers have been assembled and prepared for purification by Dr. L. F. Fieser, of Harvard University, in whose care Dr. Hooker left the samples from all of his investigations. Dr. Fieser states that the collection includes a large supply of lapachol and a moderate amount of lomatiol, and that it was Dr. Hooker's intention that these be made available to other interested investigators.—THE EDITOR.

(2) Dr. Hooker had no intention of withholding the results accumulating in the course of twenty years of research, but he was reluctant to publish work on any one of the closely related problems until quite satisfied that all phases of the different investigations had been adequately explored. With one or two minor exceptions, this point had been reached at the time of his death and he had already prepared the manuscript for the theoretical part of several of the papers. Frequent periods of ill health and eventually death prevented him from completing the writing, but fortunately his observations had been recorded with such fluent expression and his records kept with such meticulous care that the experiments can be reported with complete accuracy, if not always in Dr. Hooker's own clear style.

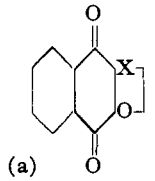
The theoretical part of the present paper, with the exception of the last paragraph, is taken from an original draft written by Dr. Hooker in 1934 and the second section of the experimental part, excepting the last paragraph, is likewise compiled almost entirely from original summaries. Dr. Hooker was assisted in the experiments by Dr. G. H. Connitt (1926–1927), Dr. C. A. Lear (1932–1933), and Dr. A. Steyermark (1934–1935). Four of the analyses were carried out by Dr. Connitt and the remainder were done by Dr. D. Price of Columbia University. Dr. Steyermark has been very helpful in collecting the notes.

Certain statements in these papers cannot be properly appreciated without some explanation of the special and perhaps unique methods of identification and characterization which Dr. Hooker developed and on which he placed great reliance. Most of these involved the microscopic examination of crystals obtained in different ways, using merely a simple, low-powered instrument. In his "fusion test" a few granules of material are spread on a cover glass and barely fused over a small flame, giving characteristic crystalline patterns. An acidic substance is dissolved in 1% sodium hydroxide or other alkali and a drop of the solution allowed to evaporate on a slide and deposit crystals of the salt, or acidified under microscopic observation. A drop of a solution of the substance in concentrated sulfuric acid on being exposed on a slide absorbs moisture and deposits characteristic crystals, at first at the edges and then in the body of the solution. In Dr. Hooker's skilled hands these tests provided a means of making a positive identification which he felt was at least as reliable as a mixed melting point determination. Such microscopic examination proved to be of invaluable service in working with substances which when heated decompose rather than melt. The tests were also employed to advantage in following the progress of a reaction and in working out methods of purification and separation. In purifying small amounts of material, Dr. Hooker made much use of the "dry crystallization method." A dilute solution of the substance is allowed to go to dryness in an Erlenmeyer flask set in an inclined position with the liquid covering less than half of the bottom. Often the impurities are deposited in an outer ring while uncontaminated crystals of the substance appear at the lowest part of the vessel and can be detached and caught on the clean part of the flask after this has been rotated to the proper position. Very sensitive substances frequently can be crystallized satisfactorily by this method, the solution being prepared at room temperature. The homogeneity of a colored, acidic substance was tested to advantage by dusting a small amount of the powdered material onto the surface of 1% sodium hydroxide, when the presence of more than one compound often could be detected by a differential coloration of the solution. Dr. Hooker took full advantage of the beautiful color phenomena peculiar to the group of compounds under investigation, but many of his methods of experimentation can be applied quite generally. Of considerable importance in paving the way to discoveries was his habit of looking for any changes which might occur in solutions of his compounds or even in the solid state, often over long periods of time, and his practice of conducting reactions under the mildest conditions sufficient to effect a change.—L. F. FIESER.

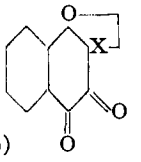
(3) Hooker, *J. Chem. Soc.*, **69**, 1356 (1896).

(4) Fieser, THIS JOURNAL, **50**, 439 (1928).

similarly located side chains, and further that it agrees almost exactly with the values of lapachol and hydrolapachol, both of which are *yellow*. The reduction potential of iso-β-lapachol also agrees far better with the values determined for compounds of the general formula (a) derived from lapachol than it does with those obtained for substances of the general formula (b), having the ortho quinone group.



(a) Yellow

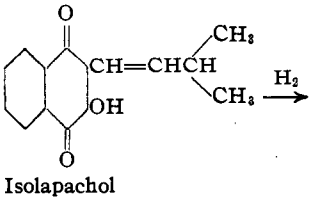


(b) Red

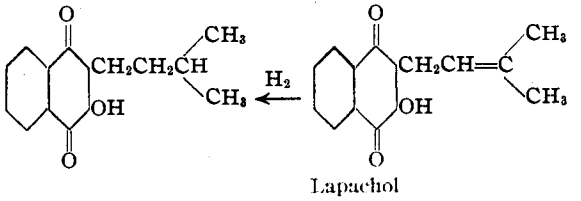
It would seem necessary therefore to accept for iso-β-lapachol the paraquinone structure as suggested by Fieser and the compound will in future be referred to as isolapachol. The *red* color of isolapachol, however, is not without significance and I shall return to its consideration later in another paper.

The study of the above condensation has been extended to a number of other aldehydes as the resulting compounds were required for an investigation on the oxidation of derivatives of 2-hydroxy-1,4-naphthoquinone. In most cases fairly uniform results have been obtained and the reaction has thus proved to be a general one.

Hydrocinnamaldehyde, phenylacetaldehyde, oenanthol, *n*-valeraldehyde, *n*-butyraldehyde, and propionaldehyde have all yielded compounds corresponding to isolapachol, which like it are much deeper in color than the previously known derivatives of 2-hydroxy-1,4-naphthoquinone. They vary from a deep orange or orange-red to a deep red in color, and all give intensely violet solutions with 1% alkali from which the sodium salts



Isolapachol



Lapachol

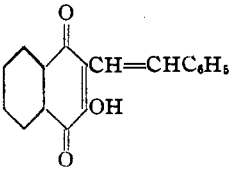
can be readily obtained in crystalline form. Hydrogen addition is easily effected by Roger Adams' method with platinum oxide–platinum black, the resulting substances affording ample proof of the structure assigned to the condensation products, as the latter are thus converted into compounds identical with the hydrogenation products of similar substances of known structure differing only from the condensation products in having the double bond in the chain located other than in the α,β-position. Thus isolapachol and lapachol yield the same compound, namely, hydrolapachol. Incidentally it may be noted that this step completes the synthesis of hydrolapachol.

The other 2-hydroxy-1,4-naphthoquinone derivatives examined which have yielded identical compounds on hydrogenation are shown side by side in the following columns, the chains only being given.

$-CH=CHCH_2CH_3$	$-CH_2CH=CHCH_3$
$-CH=CHCH_3$	$-CH_2CH=CH_2$
$-CH=CHCH_2C_6H_5$	$-CH_2CH=CHC_6H_5$

The first column contains the chains of the aldehyde condensation compounds; the second those of compounds obtained by Fieser[5] in part by the Claisen rearrangement and in part by direct carbon alkylation. The identity of the hydrogenation products of the two sets of compounds leaves no doubt, therefore, as to the correctness of the interpretation of the aldehyde condensation. I am greatly indebted to Dr. Fieser for the substances represented in the second column which were hydrogenated in my laboratory.

In the earlier work[3] attention was called to the striking difference in color between the orange-red isolapachol and its yellow acetyl derivative. It was suggested at the time that acetylation may be attended with a change from a β- to an α-quinone group, but it is now recognized that both compounds very probably are α-quinones and that the difference in color is attributable to the effect of masking the free hydroxyl group. In order to extend the observations two additional acetyl derivatives were prepared. The first of these, 2-α-butenyl-3-acetoxy-1,4-naphthoquinone,



(5) Fieser, THIS JOURNAL, **48**, 3201 (1926); **49**, 857 (1927).

is similarly yellow, in comparison with the red hydroxy compound from which it is derived. 2-β-Phenylvinyl - 3 - hydroxy - 1, 4 - naphthoquinone is deeper in color (deep red) than the condensation products having completely aliphatic side chains (orange-red) or the chain $-CH{=}CHCH_2C_6H_5$ (orange), an effect doubtless attributable to the conjugation of the phenyl group with the chromophoric system. Acetylation in this case also was found to lighten the color, and the interesting observation was made that the acetyl derivative is capable of existing in two distinct modifications. The two forms are orange-yellow and bright red and they separate from the same solvents under similar conditions. The latter substance changes to the former on heating, and only one melting point is observed.

Experimental Part

1. Condensation of Aldehydes with 2-Hydroxy-1,4-naphthoquinone

Following a number of trials, 2-α-butenyl-3-hydroxy-1,4-naphthoquinone was most satisfactorily obtained by the following procedure, which served with minor changes for the other condensations investigated. Two grams of 2-hydroxy-1,4-naphthoquinone was dissolved in 35 cc. of hot glacial acetic acid, the temperature was brought to 80° and concentrated hydrochloric acid (2 cc.) was added, followed at once by *n*-butyraldehyde (5 cc.). The mixture was digested at 75–80° for one and one-half hours and poured into 200–300 cc. of water. After allowing several hours for the dark, resinous, partly crystalline material to collect, the aqueous solution was decanted through a filter, the oily residue was dissolved in 100 cc. of ether (or in benzene or ether–benzene) and the solution was extracted with 200 cc. of aqueous 1% sodium hydroxide solution. On acidifying the intensely violet alkaline extract a deep orange oil precipitated and gradually became crystalline. After washing and drying, the crude material (1.5 g.) was extracted with petroleum ether (b. p. 35–55°) in the Soxhlet apparatus. This left a brown, earthy residue and gave 1.1 g. of purified material as orange-red plates. The sample for analysis was recrystallized from alcohol.

In the condensation of hydroxynaphthoquinone with other aldehydes some variations in the proportions of the reagents and in the time of heating were found advisable, as indicated in Table I. The reaction can be followed readily by removing from the mixture during digestion a fraction of a drop, evaporating this to dryness, dissolving the residue in a drop of alcohol, and adding a drop of 1% alkali. As the condensation progresses the test solution becomes increasingly violet, and when the color ceases to increase in intensity the reaction may be assumed to be reasonably complete. The digestion is then stopped. The time varies with the different aldehydes from about fifteen minutes to one and one-half hours, and can be shortened and the yield slightly increased by using larger quantities of the aldehyde. As a general rule about five molecules of the aldehyde to one of the hydroxynaphthoquinone give satisfactory results.

Attempts to prepare condensation products under similar conditions from acetaldehyde and from isobutyraldehyde were unsuccessful. In the case of the latter aldehyde the reaction mixture was heated for a total of five hours, but

TABLE I

PREPARATION AND PROPERTIES OF THE CONDENSATION PRODUCTS

Aldehyde	For 2 g. hydroxynaphthoquine: Aldehyde, cc.	Concd. HCl, cc.	Time of heating, min.	Yield in g.: Crude	Pure	2-α-Alkenyl-3-hydroxy-1,4-naphthoquinones: Alkenyl group	M. p., °C.	Crystalline form	Calcd., % C	Calcd., % H	Found, % C	Found, % H
Propionaldehyde	5	2	75	1.22[a]	0.56	α-Propenyl	135.2–135.7	Orange-red plates[b]	72.87	4.71	72.79	4.85
n-Butyraldehyde	5	2	90	1.5	1.1	α-Butenyl	107.5	Orange-red plates[b]	73.68	5.26	73.66 73.61	5.36 5.43
n-Valeraldehyde	6.4	6	37	1.2		α-Pentenyl	98–98.5	Orange-red needles	74.35	5.83	74.53	6.03
Heptaldehyde	12	10	25	1.6	1.1	α-Heptenyl	86.5	Orange-red needles, voluminously grouped; also as plates	75.30	6.69	75.28 75.55	6.68 6.66
Phenylacetaldehyde (50% alcoholic solution)	13.6	6	20	1.94	1.3	β-Phenylvinyl	166.5–167.5	Red scales, or small, heavy needles, or voluminous branches	78.23	4.38	77.99	4.56
Hydrocinnamaldehyde	7	10	90	1.6		γ-Phenyl-α-propenyl	140.5–141.5, dec.	Orange-red needles[c]	78.59	4.86	78.62	4.86

[a] By concentrating the benzene solution after extraction with alkali, brown, sword-shaped crystals of a by-product (0.2 g.) were obtained. Recrystallized from alcohol, the substance formed light yellow, arrowhead-shaped crystals, m. p. 160–160.5°. (Found: C, 84.87; H, 5.24; mol. wt., 241.4.)

[b] Best crystallized from petroleum ether; the material decomposes badly when crystallized in large lots from alcohol.

[c] The substance undergoes far-reaching changes when the crude material is crystallized from alcohol or benzene. Acetic acid gave better results but the recovery was less than 50%.

color tests made throughout this period failed to give any indication of the formation of a compound of the desired type. With acetaldehyde it appeared that a condensation product if formed is rapidly destroyed in the acid mixture.

The condensation products having aliphatic side chains are very soluble in benzene or acetone and somewhat less soluble in alcohol. A phenyl group decreases the solubility. Characteristic of all of the compounds is the intense violet color of their sodium salts, and distinctive patterns often can be observed by allowing a drop of the alkaline solution to evaporate under the microscope. Some decomposition usually occurs at the melting point.

The crystallization of the crude condensation products presents some difficulties for the quinones are subject to decomposition in solution, particularly in the presence of impurities. The crude materials may suffer extensive destruction when crystallized directly from alcohol or benzene, and it is best first to extract the products with petroleum ether. The purified substances then can be crystallized successfully from alcohol or benzene if care is taken to avoid undue heating or prolonged exposure of the solutions to the air. Even the most highly purified samples in time undergo far-reaching changes in contact with these solvents, and in a preliminary study of these changes carried out in conjunction with Dr. Steyermark it was found possible in some cases to isolate crystalline transformation products. Thus a solution of 1 g. of 2-γ-phenyl-α-propenyl-3-hydroxy-1,4-naphthoquinone in 45 cc. of benzene after standing with free access to the air for about four days deposited 0.04 g. of yellow needles which after recrystallization from benzene (sparingly soluble) melted at 227–228°, dec. The analyses are suggestive of a formula having one atom of oxygen more than the starting material (calcd. for $C_{19}H_{14}O_4$: C, 74.51; H, 4.57. Found: C, 73.95, 74.10; H, 4.61, 4.51) and it is perhaps safe to conclude that in this case an oxidation is involved. The substance is neutral, but it dissolves in boiling alkali and the yellow material is precipitated unchanged on acidifying the red, alkaline solution.

Yellow, neutral decomposition products were obtained from some of the unsaturated quinones in alcoholic solution but the substances have not been characterized. The propenyl compound, refluxed in alcoholic solution for about ten hours in the course of three days, gave in 10% yield a substance forming yellow prisms from benzene, m. p. 197–198°, dec., insoluble in cold alkali (found: C, 73.16, 73.20; H, 4.69, 4.81; mol. wt., 364). A solution of the butenyl compound in alcohol on standing for four months at room temperature deposited in 11% yield a yellow substance which formed yellow plates from dilute acetic acid, m. p. 207–208°, dec. (found: C, 70.63; H, 5.05). Like the other substances it is insoluble in cold alkali and dissolves on boiling to give a crimson solution.

2-α-Butenyl-3-acetoxy-1,4-naphthoquinone.—A mixture of 1 g. of 2-α-butenyl-3-hydroxy-1,4-naphthoquinone, 2 g. of fused sodium acetate and 20 cc. of acetic anhydride was boiled for three minutes, when the initially red solution had become brownish-yellow in color. The mixture was poured into water and the green oil which separated crystallized on standing overnight. The yield was quantitative. On crystallization from alcohol the substance formed bright yellow needles, m. p. 83.5–84.0°. The compound is insoluble in dilute alkali in the cold but it dissolves readily on boiling and the original hydroxyquinone is obtained on acidifying the solution.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.08; H, 5.22. Found: C, 71.28; H, 5.55.

2-β-Phenylvinyl-3-acetoxy-1,4-naphthoquinone.—This compound was prepared in good yield by the above procedure and crystallized from alcohol or from acetic acid. The substance crystallizes from these solvents either as orange-yellow needles or as bright red needles, the orange-yellow form being the more common. Both forms melt sharply at 138.7–139.2°, and it appears that the red form changes into the other modification before this temperature is reached, for on gentle heating the red needles become coated with small yellowish needles, making them appear opaque. Neither form contains solvent of crystallization, for a mixture of the two lost no weight on being heated at 130° for one-half hour. Both forms yield the original hydroxy quinone on alkaline hydrolysis and they impart a purple coloration to concentrated sulfuric acid. Both varieties become resinous on rubbing.

Anal. Calcd. for $C_{20}H_{14}O_4$: C, 75.45; H, 4.44. Found: C, 75.60; H, 4.56.

2. Hydrogenations

The condensation products are of the type $C_{10}H_4\begin{cases}O_2\\CH=\\OH\end{cases}CHCH_2X$ are deep orange in color and they dissolve in dilute alkalies to intensely violet solutions varying but little in tone. In these respects they differ materially from the compounds of the general type $C_{10}H_4\begin{cases}O_2\\CH_2CH_2CH_2X\\OH\end{cases}$ into which they are readily converted by hydrogenation. These are yellow (occasionally golden brown when in fair sized crystals) and give solutions with alkalies of a claret red shade. These differences between the two classes of compounds enable the hydrogenation of very small quantities to be satisfactorily followed. The catalyst was prepared in accordance with the directions of Roger Adams and the hydrogenations were carried out in the cold, mostly in alcoholic solution at a pressure of 38–40 lb. (2.53–2.66 atm.). The time necessary varies from a few minutes to several hours, depending on the quantity and condition of the catalyst. To ascertain when the hydrogenation is complete, it is simply necessary to remove a trace of the solution from the pressure flask, allow it to evaporate to dryness, and redissolve the residue in a drop of 1% sodium hydroxide solution. If the oxidation of the hydroquinone group resulting from the action of the hydrogen has not already taken place by atmospheric oxygen during evaporation, it will be almost instantly effected in contact with the alkali. The hydrogenation may be considered complete as soon as the alkaline solution obtained is red without any trace of violet. A drop of dilute hydrochloric acid added to the alkaline solution also should yield a yellow precipitate instead of the orange one given by the substance before hydrogenation.

Hydrolapachol was first prepared by Monti[6] by the action of hydrogen in the presence of palladium black on the acetyl derivative of lapachol, followed by hydrolysis

(6) Monti, *Gazz. chim. ital.*, **45**, II, 52 (1915).

TABLE II

HYDROGENATION PRODUCTS

Substances hydrogenated, side chains	2-Alkyl-3-hydroxy-1,4-naphthoquinones			Calcd., %		Found, %	
	Alkyl group	M. p., °C.	Crystalline form	C	H	C	H
$-CH=CHCH_3$ } $-CH_2CH=CH_2$	*n*-Propyl	100.5–101.5	Bright yellow, prismatic needles	72.19	5.60	72.11	5.80
$-CH=CHCH_2CH_3$ } $-CH_2CH=CHCH_3$	*n*-Butyl	101–101.5	Radiating clusters of yellow needles	73.04	6.08	72.85	6.16
$-CH=CH(CH_2)_2CH_3$	*n*-Amyl	104–104.3	Long, yellow needles	73.73	6.61	73.69	6.72
$-CH=CHCH(CH_3)_2$ } $-CH_2CH=C(CH_3)_2$	*i*-Amyl	93.5–94.5	Fine, silky needles	73.73	6.61	73.90	6.72
$-CH=CH(CH_2)_4CH_3$	*n*-Heptyl	82.7–83.3	Bright yellow plates	74.96	7.41	74.96	7.56
$-CH=CHC_6H_5$	β-Phenylethyl	171.5–172.5	Orange-yellow prismatic plates	77.67	5.07	77.56	5.26
$-CH=CHCH_2C_6H_5$ } $-CH_2CH=CHC_6H_5$	Hydrocinnamyl	131.7–132.2	Golden-yellow plates	78.05	5.52	78.17	5.48

and exposure of the solution to the oxidizing action of the air. Fieser and Brodie[7] obtained hydrolapachol from lapachol itself by employing the method of hydrogenation of Roger Adams. A more detailed study of hydrolapachol has been undertaken here in order that the identity of the substance obtained by the hydrogenation of isolapachol might be established without doubt. Several lots of hydrolapachol have been prepared in my laboratory from lapachol with very satisfactory results by Adams' method, a yield of fully 97% being obtained. The reaction was carried out at room temperature, using 6 g. of lapachol in 100 cc. of alcohol and 0.2 g. of catalyst. The progress of the absorption may be followed and its end determined by removing a drop of the solution from time to time and allowing it to evaporate completely on a watch glass. As evaporation proceeds the hydroquinone is again oxidized and the residue on solution in concentrated sulfuric acid and subsequent dilution gives a *yellow* suspension when the hydrogenation is complete, in place of the *orange* β-lapachone which would be obtained from lapachol under like circumstances.

In preparing moderately large lots of hydrolapachol the oxidation of the hydroquinone may be advantageously hastened by drawing air through the alcoholic solution. After oxidation the solution was evaporated to about 50 cc. and cautiously diluted with water, the dilution being increased from time to time as crystallization proceeded. The fine, silky needles obtained were washed with 50% alcohol. Recrystallized, the substance melted constantly at 93.5–94.5°, a temperature considerably higher than that reported by Monti (87–89°) and by Fieser and Brodie (88–89°). Isolapachol, hydrogenated in the same manner, gave a substance identified by melting point, mixed melting point and all other properties, as hydrolapachol. In hydrogenating the synthetic compounds of the type $C_{10}H_4\begin{cases}O_2\\CH_2CH=CHX\\OH\end{cases}$ the progress of the reaction was followed by the color test with sulfuric acid, as in the case of lapachol.

The yields in the hydrogenation experiments were uniformly good and the quinones with reduced side chains were easily obtained in a pure condition, usually by crystallization from alcohol. 2-*n*-Propyl-3-hydroxy-1,4-naphthoquinone crystallized well from petroleum ether. The properties and analyses of the compounds are recorded in Table II. In those cases in which it is indicated that the same hydrogenation product was obtained from two different quinones, the identity was established by melting point and mixed melting point determinations and by a careful comparison of the crystalline forms and color reactions of the two substances.

Summary

1. The condensation of aldehydes with 2-hydroxy-1,4-naphthoquinone, which in the case of isovaleraldehyde resulted in the formation of isolapachol, is shown to be generally applicable to the preparation of corresponding alkenyl derivatives of hydroxynaphthoquinone, the alkenyl group being situated in the quinone ring adjoining the hydroxyl, and the double bond occupying the α,β-position in the chain.

2. It is shown that by the addition of hydrogen to the synthetic isolapachol the same product, namely, hydrolapachol, is formed as is obtained from the natural product, lapachol, under similar circumstances.

82 REMSEN STREET
BROOKLYN, NEW YORK

RECEIVED MARCH 11, 1936

(7) Fieser and Brodie, THIS JOURNAL, **50**, 449 (1928).