both hyposantonin and isohyposantonin by reduction should be designated isohyposantonous acid because it is dextrorotatory, and reductive opening of the lactone ring causes reversal in the direction of rotation.

I am indebted to Prof. L. F. Fieser for his encouragement in the persuance of this investigation and to Mrs. Mary Fieser for help in the preparation of this manuscript.

Summary

The mechanism of the acid-catalyzed rearrangement of santonin to desmotroposantonin and that of the interconversion of the four isomers of desmotroposantonins by acid and alkali has been postulated. The relative configurations of all the known desmotroposantonins have been formulated. *l*-Desmotropo-β-santonin of Clemo has been found to be identical with *l*-β-desmotroposantonin. The spacial configurations of santonin, hyposantonin and isohyposantonin have also been discussed.

CAMBRIDGE 38, MASS. RECEIVED AUGUST 15, 1947

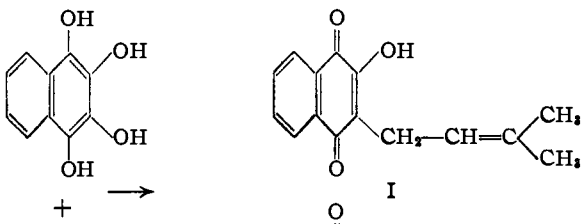
[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORY, BRYN MAWR COLLEGE, AND THE CHEMICAL LABORATORY, HARVARD UNIVERSITY]

Syntheses in the Lapachol Series

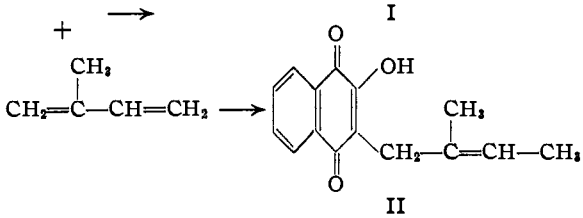
BY MARSHALL GATES AND DOROTHY L. MOESTA[1]

In an extension of the condensation reaction between allylic alcohols and hydroxyhydroquinones reported by Fieser and Gates,[2] we have investigated the condensation of leucoisonaphthazarin with isoprene and with several allylic alcohols related to isoprene. As in earlier examples[2] yields are low, but the inaccessibility of the products by other methods may warrant consideration of this method for the preparation of small amounts.

Isoprene condenses with leucoisonaphthazarin in the presence of oxalic acid to yield, after oxidation, a mixture of lapachol (I)[3] and an isomer of lapachol, presumably 2-hydroxy-3-(2′-methyl-2′-butenyl)-1,4-naphthoquinone (II), in roughly equal parts.

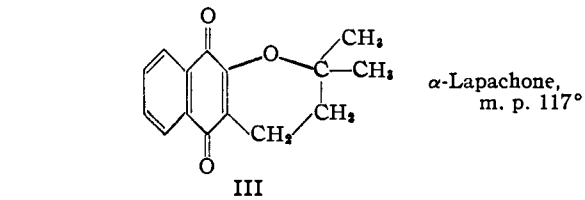


I



II

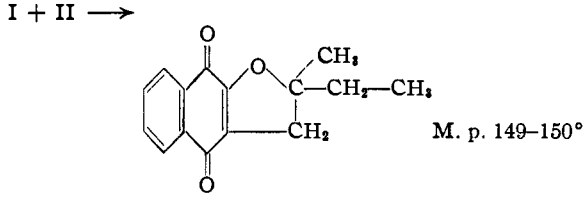
Separation of the two was achieved by fractional crystallization, although the more soluble isomer II was obtained pure only in small amounts by this method. Additional material containing the side-chain carbon skeleton of II could be obtained from the filtrate by cyclization to a mixture of the α-lapachone type isomers III and IV in which the solubility relationships are reversed.



α-Lapachone, m. p. 117°

III

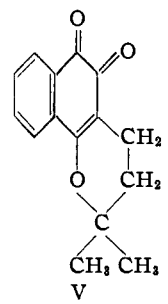
I + II ⟶



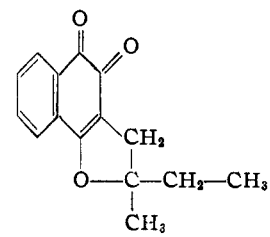
M. p. 149–150°

IX

The hydroxynaphthoquinones I and II were further characterized by cyclization with concentrated sulfuric acid to β-lapachone (V) and its isomer, α-methyl-α-ethyldihydrofurano-1,2-naphthoquinone (VI),[4] respectively.



V



VI

2-Hydroxy-3-(2′-methyl-2′-butenyl)-1,4-naphthoquinone (II) also results from the condensation

(1) Mrs. George Hain.

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

(3) Earlier syntheses of lapachol have been reported by Fieser, *ibid.*, 49, 857 (1927), and by Hooker, *ibid.*, 58, 1181 (1936).

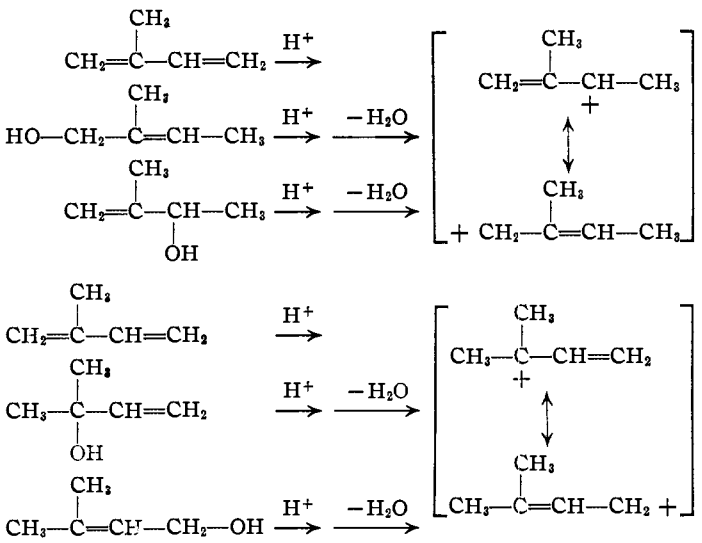
(4) Structure VI is one, although not the preferred one, of three structures originally considered possible for dunnione by Price and Robinson (*J. Chem. Soc.*, 1525 (1939)). If the structure assigned above is correct, VI is eliminated as a possible structure for dunnione since its physical properties do not agree with those of dunnione. Later work by Price and Robinson (*J. Chem. Soc.*, 1493 (1940)) continues to support their original preference (α,α,β-trimethyldihydrofurano-1,2-naphthoquinone) for the structure of this substance.

of 2-methylbutene-2-ol-1 with leucoisonaphthazarin in the presence of oxalic acid. In this case it is the sole hydroxynaphthoquinone isolated and its structure has been assigned on this basis.

Dimethylvinylcarbinol condenses with leucoisonaphthazarin in the presence of oxalic acid to yield lapachol as the sole hydroxynaphthoquinone.

The secondary alcohol 2-methylbutene-1-ol-3 does not yield any hydroxynaphthoquinone when allowed to react with leucoisonaphthazarin under the conditions used in the above condensations.

Any comment on the mechanism of this condensation at present must necessarily, in view of the paucity of data bearing on the question, be largely speculation. It may be noted, however, that the simple postulation of an attack on leucoisonaphthazarin by a carbonium ion produced by the action of acid on either isoprene or the allylic type alcohols used followed by the necessary eliminations[5] is not entirely adequate. For example, an identical resonating carbonium ion should result from isoprene, 2-methylbutene-2-ol-1 and 2-methylbutene-1-ol-3, but only the first two of these give the same product (II), whereas the condensation fails with the third. Isoprene can, in addition, yield the same resonating carbonium ion as dimethylvinylcarbinol and 3-methylbutene-2-ol-1 (not investigated in this work). The first two of these yield lapachol.



We wish also to report here the preparation for use in another problem of lapachol methyl ether by the action of the theoretical quantity of diazomethane on lapachol.

Experimental Part[6]

Condensation of Leucoisonaphthazarin with Isoprene. Lapachol (I) and 2-Hydroxy-3-(2'-methyl-2'-butenyl)-1,4-naphthoquinone (II).—A mixture of 3.86 g. of leucoisonaphthazarin (prepared by hydrosulfite reduction of an ether suspension of isonaphthazarin), 12 cc. of isoprene, 2.5 g. of anhydrous oxalic acid and 50 cc. of dioxane (refluxed and distilled over sodium) was heated at 90 to 100° for sixty hours under nitrogen in a capped bottle. After filtration from some crystalline isonaphthazarin (0.73 g.) the solvent was completely removed by a current of dry air and the residue was taken into ether and extracted four times with dilute sodium carbonate solution. The red-black carbonate extract on acidification with glacial acetic acid and extraction with ether yielded an orange-yellow ethereal solution which was further processed by an additional extraction into carbonate and acidification followed by two chromatographic adsorptions from benzene–hexane onto anhydrous magnesium sulfate. During the second of these a bright yellow band (45 mm. on an 18-mm. diameter column) passed readily into the filtrate and on concentration yielded 446 mg. of bright yellow plates, m. p. 111–126°. Several distinct more strongly adsorbed bands remained on the column and from the two adsorptions a further 0.13 g. of unchanged isonaphthazarin was recovered.

The solid material from the filtrate was subjected to a systematic fractional crystallization from ether–petroleum ether and after numerous crystallizations 156 mg. of lapachol (I) of m. p. 139–140° and 15 mg. of an additional substance (II), m. p. 123–124.5°, were obtained. The lapachol did not depress the melting point of an authentic sample, m. p. 139–140.5°, from the collection of the late Dr. Samuel Cox Hooker, and was further characterized by conversion to β-lapachone, m. p. 154–155°, which likewise did not depress the melting point of an authentic sample from Dr. Hooker's collection. The samples from this collection were kindly placed at our disposal by Professor Louis F. Fieser of Harvard University.

The substance (II) of m. p. 123.5–124.5° crystallizes from ether–petroleum ether in long bright yellow needles and gives a scarlet solution with dilute potassium hydroxide, the color of which can be completely extracted by amyl alcohol.[7] It is isomeric with lapachol.

Anal.[8] Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.04; H, 5.57.

As the following example demonstrates it may be converted into an isomer (VI) of β-lapachone by the action of concentrated sulfuric acid: 8.6 mg. was dissolved in about 0.3 cc. of concentrated sulfuric acid, and after standing for five minutes the deep orange-red solution was diluted with water and the precipitated red solid was collected, washed with water and crystallized twice from dilute alcohol to give 3.5 mg. of beautiful scarlet-orange needles, m. p. 118.5–119°.

Anal.[8] Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.29; H, 5.78.

Selected filtrates from the fractional crystallization described above were concentrated to dryness, taken into 2 cc. of glacial acetic acid, treated with 0.5 cc. of concentrated hydrochloric acid and heated on the steam-bath for one hour. Under these conditions lapachol is converted to α-lapachone.[9] The reaction mixture was diluted with water and the resultant dark oil was taken into ether and washed with sodium bicarbonate and water. After drying the ether was replaced by benzene–hexane and the material was chromatographed on anhydrous magnesium sulfate. A poorly adsorbed broad canary yellow band passed into the filtrate rapidly and on concentration to dryness and crystallization from ether–petroleum ether yielded 130 mg. of canary yellow plates, m. p. 131–140°, which on two further crystallizations from this solvent pair and a final crystallization from alcohol afforded 72 mg.

(5) Bondhus (Dissertation, Bryn Mawr College, 1947) has discussed the mechanism of this reaction as well as the silver salt alkylation used by Fieser[3] for the synthesis of lapachol.

(6) All melting points are corrected.

(7) Price and Robinson, *J. Chem. Soc.*, 1522 (1939).

(8) Microanalysis by Miss Eleanor Werbel.

(9) Hooker, *J. Chem. Soc.*, **61**, 611 (1892).

of yellow leaves of IV, m. p. 149.4–150.2°. It does not dissolve immediately in dilute aqueous potassium hydroxide, but the suspension on standing slowly acquires a red color.

Anal.[8] Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.29; H, 5.79.

This material (15 mg.) on standing in concentrated sulfuric acid solution for fifteen minutes yields, on dilution with water and crystallization from dilute alcohol, the isomer VI of β-lapachone described above (9 mg.), m. p. 118.5–119°, mixed melting point not depressed.

Condensation of Leucoisonaphthazarin with Dimethylvinylcarbinol. Lapachol (I).—Dimethylvinylcarbinol[10] (4 cc.) was condensed with 2.77 g. of leucoisonaphthazarin under approximately the conditions outlined above. The reaction mixture, filtered from 0.70 g. of isonaphthazarin, was made alkaline, aerated, extracted with ether and the acidic material taken into ether after acidification with glacial acetic acid. Further processing included extraction by dilute potassium carbonate and chromatographic adsorption on magnesium sulfate from benzene–hexane of the material recovered from the deep red carbonate solution by acidification. Elution of a homogeneous bright yellow band by absolute ether and concentration yielded a yellow residue of impure lapachol (I) (186 mg.) which readily solidified, m. p. 132–136°. One crystallization from petroleum ether raised its melting point to 139–140.5°. The material did not depress the melting point of an authentic sample of lapachol.

Condensation of Leucoisonaphthazarin with 2-Methylbutene-2-ol-1. 2-Hydroxy-3-(2′-methyl-2′-butenyl)-1,4-naphthoquinone (II).—2-Methylbutene-2-ol-1[11] (4 g.) was condensed with leucoisonaphthazarin (from 4 g. of isonaphthazarin) under approximately the conditions outlined above. A processing scheme similar to those described above yielded bright yellow platelets of II, 175 mg., m. p. 120–121°. Recrystallization from ether–petroleum ether gave 160 mg., m. p. 120.5–121.5°.

α-Methyl-α-ethyldihydrofurano-1,4-naphthoquinone (IV) was prepared by stirring the above substance (28 mg.) into a mixture of 8 cc. of glacial acetic acid and 1.5 cc. of concentrated hydrochloric acid and heating on the steam-bath for one hour. Dilution of the reaction mixture with 30 cc. of water at the end of this time resulted in the separation of bright yellow needles which, after recrystallization from alcohol, melted at 147.5–148°; yield 12 mg. The isomeric **α-methyl-α-ethyldihydrofurano-1,2-naphthoquinone** (VI) was prepared by stirring the above isomer of lapachol (29 mg.) into 2 cc. of concentrated sulfuric acid and diluting the orange-brown solution with 35 cc. of water. Recrystallization from alcohol of the precipitated red solid afforded 13 mg. of dark red needles, m. p. 113–114°.

Although a direct comparison was not made, the methods of preparation and the correspondence in melting points of the hydroxyquinones and of the derivatives of the α- and β-lapachone types make the identity of the above isomer of lapachol and that isolated from the isoprene reaction highly probable.

Attempted Condensation of Leucoisonaphthazarin and 2 Methylbutene-1-ol-3.—2-Methylbutene-1-ol-3[12] was treated with leucoisonaphthazarin (from 4 g. of isonaphthazarin) as described for earlier examples. On working up the reaction mixture by the same general scheme used above only isonaphthazarin was recovered. A similar reaction carried out at 65–80° over a period of nine days was also unsuccessful.

Lapachol Methyl Ether.—To 121 mg. of lapachol in a few cc. of ether at 0° was added 1.50 cc. of cold freshly prepared and standardized 0.334 *N* diazomethane solution. The resulting deep orange solution was allowed to stand for several hours during which time the color lightened to yellow. The solution was extracted several times with dilute carbonate solution (acidification of the crimson carbonate extracts gave 11 mg. of unchanged lapachol, m. p. 138–140.5°), washed with water and brine and then filtered and concentrated to dryness. The residual orange oil (116 mg.) solidified on manipulation and was crystallized several times from methanol, in which it is quite soluble, to give 50 mg., m. p. 51–51.8°, of beautiful bright yellow needles. A sample was crystallized once again for analysis and dried at 10^{-4} mm. for several hours, m. p. 52–52.4°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.51; H, 6.14.

The material is readily hydrolyzed to lapachol on warming with dilute potassium hydroxide in water and methanol.

Summary

Leucoisonaphthazarin has been shown to condense with isoprene, dimethylvinylcarbinol and 2-methylbutene-2-ol-1 in the presence of anhydrous oxalic acid to give low yields of 2-hydroxy-3-alkenyl-1,4-naphthoquinones. Dimethylvinylcarbinol gives rise to lapachol, 2-methylbutene-2-ol-1 gives 2-hydroxy-3-(2′-methyl-2′-butenyl)-1,4 naphthoquinone, and isoprene yields a mixture of these products.

BRYN MAWR, PENNSYLVANIA, AND
CAMBRIDGE, MASSACHUSETTS

RECEIVED SEPTEMBER 18, 1947

(10) We are indebted to Mr. Edward F. Greene of Harvard University for this sample, which was prepared by catalytic reduction over Raney nickel of dimethylethynylcarbinol, prepared by the method of Newman, Fones and Booth, THIS JOURNAL, **67**, 1053 (1945).

(11) Prepared from trimethylethylene by the method of Guillemonat, *Ann. chim.*, [11] **11**, 154 (1939).

(12) Kondakow, *J. Russ. Phys.-Chem. Soc.*, **17**, 296 (1885). Our sample was prepared by the action of methylmagnesium bromide on methacrolein.