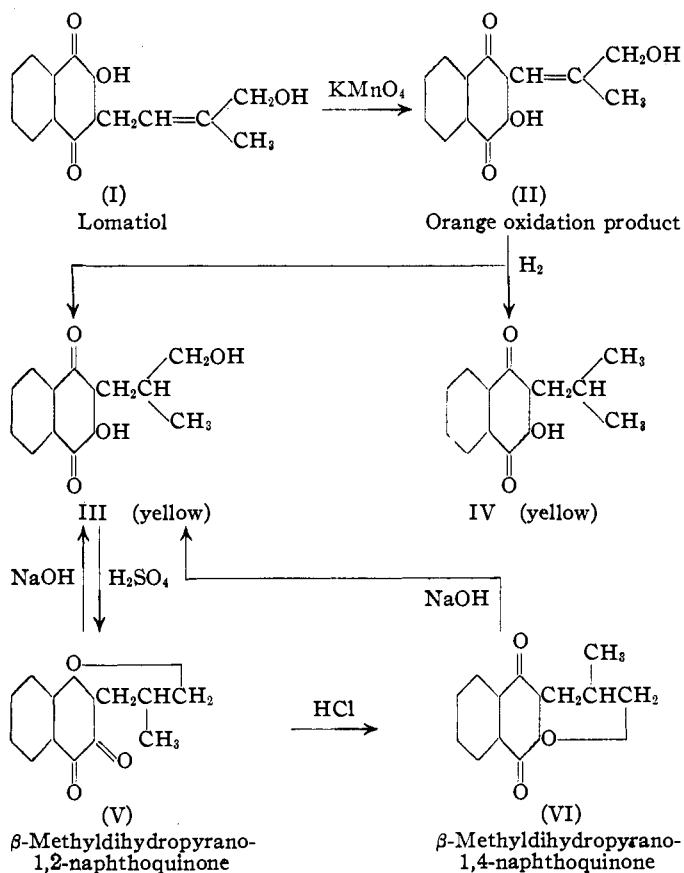


Lomatiol. Part III. Oxidation with Alkaline Potassium Permanganate<sup>1,2</sup>

BY SAMUEL C. HOOKER AND AL STEYERMARK

In a previous paper<sup>3</sup> evidence was presented indicating that lomatiol has the constitution represented by formula I, and it was reported that on oxidation with alkaline potassium permanganate the yellow substance yields an orange compound of the formula II, a change of the type observed<sup>4</sup>



in the case of lapachol and related hydroxynaphthoquinone derivatives. The present paper includes a full account of the reaction and a description of a second substance which is formed in small amounts in the course of the oxidation.

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

(2) The orange oxidation product from lomatiol and the interesting red closed ring compound obtained from it were isolated by Dr. Hooker as early as 1917, but as the nature of the oxidation was not at the time understood the matter was dropped for the time being. After the course of the reaction of lapachol with alkaline permanganate had been established, work on the present problem was later resumed in conjunction with Dr. Steyermark. Dr. Hooker wrote no manuscript describing the investigation and the paper has been constructed from his notes and from the notes and reports of his assistant.—L. F. FIESER.

(3) Hooker, THIS JOURNAL, 58, 1181 (1936).

(4) Hooker, *ibid.*, 58, (a) 1168; (b) Hooker and Steyermark, *ibid.*, 58, 1174; (c) 1179 (1936).

The structure of the orange compound (II) is established by the following observations. On hydrogenation two substances are formed concurrently, one by the saturation of the double bond in the side chain (III), the other by the simultaneous replacement of hydroxyl by hydrogen and the addition of hydrogen to the double bond (IV). As such a reaction is characteristic of an allylic system, the original hydroxyl group must occupy a position adjacent to the double bond. The compound in which the hydroxyl has been removed from the side chain was found to be identical with a quinone previously described<sup>4a</sup> and known to have the structure of IV, and consequently the allylic system must be arranged either in the manner indicated in II or with the hydroxyl group in the  $\alpha$ -position and the double bond at the end of the chain. A choice between the two possibilities is easily made, for it can be inferred from other observations<sup>5</sup> that if the latter structure were correct the alcoholic hydrogenation product (III) would readily lose water to form a substance with an unsaturated side chain. Instead it is converted by sulfuric acid into an orange closed-ring compound (V) very similar in properties to  $\beta$ -lapachone. That this is a  $\beta$ -quinone is shown by its ability to form an azine and by its conversion by means of hydrochloric acid into a yellow  $\alpha$ -quinone, VI. Consequently the hydroxyl group must

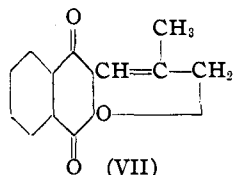
be at the end of the chain in the saturated alcohol III and in the oxidation product (II) itself.

The observations thus lend further support to the structure assigned to lomatiol and the oxidation is shown to proceed, as in the examples already studied, by the removal of  $\text{CH}_2$  from the position adjacent to the quinone group. The change is all the more remarkable because both the primary alcoholic group and the double bond remain unattacked. Comparing the orange oxidation product II with the compounds which it yields on hydrogenation (III and IV) and with lomatiol, all of which are yellow, it is seen that

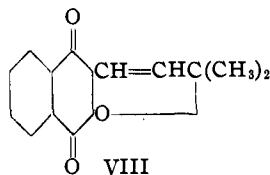
(5) Hooker, THIS JOURNAL, 58, 1163 (1936).

the presence of a double bond in II in the  $\alpha,\beta$ -position of the chain could be safely inferred from the orange color.

The orange compound II easily loses a molecule of water under various conditions, for example when it is gently heated, or when the aqueous solution is boiled. The anhydride, which forms dark red needles, has been recognized as a para quinone of the structure VII by its conversion on hydrogenation into the yellow  $\alpha$ -quinone VI.



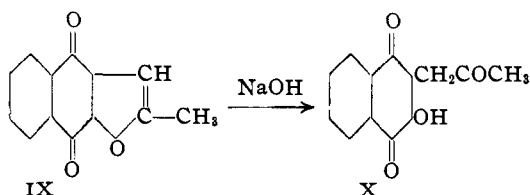
(VII)  
 $\beta$ -Methylpyrano-1,4-naphthoquinone



VIII  
Dehydrolapachone

The compound has the type of unsaturated, six-membered ring characteristic of Paternò's dehydrolapachone,<sup>6</sup> VIII, and it closely resembles this substance in its red color, which no doubt is due to the conjugation of the double bond with the quinone ring, in its behavior when treated with sulfuric acid, and its ready formation from the open chain compound. The substance has been found to undergo a number of additional changes, which will be described in a later paper.

As in the oxidation of other quinones having unsaturated side chains,<sup>4a,c</sup> the action of alkaline potassium permanganate is not limited to a single reaction and the quantity of the orange compound II produced amounts to no more than about one-third of the lomatiol used. As another product of oxidation there was isolated a small quantity of a yellow substance which was fully identified, by direct comparison with a sample prepared by a method which will be described in a later paper, as  $\beta$ -methylfurano-1,4-naphthoquinone, IX. On treatment with alkali the substance is converted



IX

X

into the salt of the ketonic compound X. Two of the original carbon atoms of lomatiol are lost in the formation of this oxidation product, one probably being that next to the quinone ring and the other the carbon atom carrying the hydroxyl

group at the end of the chain. The course of the reaction is not known.

### Experimental Part<sup>7</sup>

**Orange Oxidation Product, II (2- $\beta$ -Methyl- $\gamma$ -hydroxy- $\alpha$ -propenyl-3-hydroxy-1,4-naphthoquinone).**—Four grams of lomatiol was dissolved in 400 cc. of 1% sodium hydroxide solution and this was cooled in ice water and treated quickly with a similarly cooled solution of 4 g. of potassium permanganate in 400 cc. of water. The solution turned green, then brown, and the manganese dioxide had largely separated within a minute or two. The solution was filtered at once from the precipitate and very carefully neutralized with dilute hydrochloric acid, avoiding an excess as this promotes the conversion of the material into the red anhydride (VII). The resulting orange solution was transferred to four flat dishes and evaporated at room temperature with the aid of electric fans to a volume of 45–140 cc. (four and one-half hours to five and one-half hours). By this time a considerable amount of crystalline, orange material had separated and this was collected and washed with a small volume of cold water. A small quantity of the red anhydride can be obtained by boiling the mother liquor.

The crude product (1.2–1.4 g.) was contaminated with a small amount of the red anhydride, but it was easily separated from this material by extraction with cold 1% sodium carbonate solution (33 cc. per g.), which does not attack the red compound on short contact. The orange material reprecipitated from the soda solution was crystalline and nearly pure (recovery, 86%). The substance separates from benzene or from benzene–ligroin as orange, crystalline masses, while from petroleum ether it forms woolly orange needles. It has no true melting point for it is rapidly converted into the red anhydride on being heated. Loss of water also occurs on boiling the aqueous solution for a few minutes or treating the compound with sulfuric or hydrochloric acid at room temperature. The change occurs on prolonged boiling of the solution in alcohol, in which the orange compound is very soluble, and even in the solid state the hydroxy compound undergoes slow, spontaneous cyclization.

*Anal.* Calcd. for  $C_{14}H_{12}O_4$ : C, 68.82; H, 4.96. Found: C, 68.79; H, 5.37.

**The Red Anhydride, VII ( $\beta$ -Methylpyrano-1,4-naphthoquinone).**—For the preparation of this substance in quantity it is convenient to effect the dehydration of the oxidation product II directly in the reaction mixture, rather than to first isolate it. In a typical experiment 10 g. of lomatiol was oxidized exactly as described above and the filtered alkaline solution was neutralized with dilute (1:3) hydrochloric acid and treated with an additional 50 cc. of the dilute acid. The orange solution was boiled gently for twenty minutes, avoiding any appreciable decrease in the volume, as the product is then contaminated with other substances. During this time the solution became red and crystals of the red anhydride were deposited from the hot solution. After cooling to room temperature, the product was collected and washed with water; yield 3 g. The crude material usually contains a small amount (2–3%)

(6) Hooker, THIS JOURNAL, 58, 1190 (1936).

(7) Analyses by Dr. D. Price, Columbia University.

of the second oxidation product,  $\beta$ -methylfurano-1,4-naphthoquinone, IX, which was recognized in separate experiments by its greater resistance to alkaline hydrolysis. The substance is eliminated in the course of the crystallization.

The anhydride VII is sparingly soluble in alcohol and crystallizes from this solvent as fiery red, prismatic needles melting at 196.5–197.5°. It dissolves readily in benzene or glacial acetic acid and is very sparingly soluble in water, from which it is deposited as very fine, bright red needles.

*Anal.* Calcd. for  $C_{14}H_{10}O_2$ : C, 74.30; H, 4.45. Found: C, 73.93; H, 4.45.

Very characteristic of the red anhydride, as well as of Paternò's dehydrolapachone, is the following color reaction. The compound dissolves in concentrated sulfuric acid to give a clear, deep green solution and if this is exposed on a watch glass it gradually absorbs moisture from the atmosphere, acquires a plum pink color, and finally deposits the unchanged substance in the form of red needles, sometimes curved, leaving the solution colorless. The same changes are noted with Paternò's compound.

Heated for six hours with *o*-phenylenediamine in glacial acetic acid solution, the red anhydride was in part resinified and in part recovered unchanged. There was no evidence of azine formation.<sup>8</sup>

**$\beta$ -Methyldihydropyrano-1,4-naphthoquinone (VI).**—A suspension of 4 g. of the red anhydride (VII) in 200 cc. of alcohol was agitated with hydrogen at 40 lb. (2.66 atm.) pressure in the presence of Adams catalyst. The red compound soon went into solution in the form of the hydroquinone and this gradually added hydrogen to the double bond. The course of the reaction was followed by removing a drop of the solution, allowing it to evaporate and oxidize on a watch glass, and adding a drop of concentrated sulfuric acid. The starting material gives a green color with the acid while the dihydro derivative gives a red color. The hydrogenation was found to be complete in forty-five minutes. After filtering and allowing time for oxidation, a part of the reaction product crystallized from the solution and further crops were obtained after concentration of the mother liquor; yield, 3.8 g. The product was purified by crystallization from alcohol, using animal charcoal, and it was obtained as bright yellow, elongated plates, m. p. 170.5–171°.

*Anal.* Calcd. for  $C_{14}H_{12}O_2$ : C, 73.65; H, 5.30. Found: C, 73.74; H, 5.74.

The red solution of the quinone in concentrated sulfuric acid on exposure to the air deposits long yellow needles of the unchanged compound on absorption of moisture. The action of boiling alkali on the substance and its formation from the isomeric ortho quinone are described below.

**2- $\gamma$ -Hydroxyisobutyl-3-hydroxy-1,4-naphthoquinone (III).**—This compound is most conveniently prepared by the saponification of the dihydropyrano-*p*-quinone VI, described immediately above. This material (2.9 g.) was finely ground and boiled with 1% sodium hydroxide solution (400 cc.) for about ten minutes, when it had completely dissolved. The resulting crimson colored solution was carefully treated with dilute hydrochloric

acid and left faintly alkaline, as in the presence of excess acid the product is readily dehydrated to the dihydropyrano-*o*-quinone V. The crude product which precipitated (2.8 g.) contained in addition to the desired acidic compound a small amount of a neutral, yellow substance not identical with the starting material. The two were easily separated by extraction with cold 1% alkali, the hydroxy quinone III being recovered from the filtered solution by careful neutralization; yield, 2.6 g. The substance crystallizes from benzene or from benzene-ligroin in the form of yellow needles, m. p. 147.5–148.5°. It is very soluble in alcohol, but crystallizes well from dilute alcohol as needles.

*Anal.* Calcd. for  $C_{14}H_{14}O_4$ : C, 68.26; H, 5.73. Found: C, 68.25; H, 5.99.

The compound was obtained by the action of alkali on the isomeric *o*-quinone V in exactly the same manner.

**$\beta$ -Methyldihydropyrano-1,2-naphthoquinone (V).**—A solution of 1.6 g. of the hydroxyquinone III in 20 cc. of concentrated sulfuric acid was prepared at room temperature and after standing for forty-five minutes the red solution was poured into 100 cc. of water. The reaction product separated in the form of orange needles and in a very pure condition; yield 1.5 g. The product, purified by crystallization from alcohol, was obtained either as orange prismatic needles or as elongated orange plates, m. p. 148–148.5°.

*Anal.* Calcd. for  $C_{14}H_{12}O_2$ : C, 73.65; H, 5.30. Found: C, 73.32; H, 5.37.

The compound is also formed when the hydroxyquinone III is allowed to stand for one to two days in contact with dilute hydrochloric acid. It is insoluble in cold dilute alkali, but on boiling it soon dissolves with opening of the oxide ring. The conversion of the substance into the isomeric para quinone VI was accomplished by heating a solution of 0.1 g. of the material in 3 cc. of concentrated hydrochloric acid at 55–65° for one and a half hours. The red solution on cooling deposited yellow needles (0.09 g.) of the para quinone in a very pure condition.

The azine of the ortho quinone V was prepared by heating a solution of the substance and *o*-phenylenediamine in glacial acetic acid at the boiling point for a few minutes. The yellow product separated in part from the boiling solution. Recrystallized from alcohol (fluorescent solution), it formed yellow needles, m. p. 160–161°. The solution in concentrated sulfuric acid is deep green and deposits an orange sulfate on dilution.

*Anal.* Calcd. for  $C_{20}H_{16}ON_2$ : C, 79.97; H, 5.37. Found: C, 80.11; H, 5.25.

**Hydrogenation of the Orange Oxidation Product II.**—The two compounds III and IV, which are formed simultaneously in the hydrogenation of the unsaturated alcohol II, are not both easily separated as such from the reaction mixture, but on treatment with acids the saturated alcohol III is converted into its ortho quinone anhydride and IV can then be removed from it by extraction with alkali. The following procedure gave satisfactory results. A solution of 0.2 g. of the oxidation product II in 4 cc. of alcohol was submitted to hydrogenation (Adams catalyst) for forty-five minutes and on filtering and concentrating the solution to a small volume a small crop (0.06 g.) of 2-iso-

(8) Similarly, the quinone does not dissolve in cold sodium bisulfite solution.—L. F. F.

butyl-3-hydroxy-1,4-naphthoquinone (IV) was deposited. After allowing the mother liquor to evaporate to dryness the residue was dissolved in 0.25% alkali and the solution was filtered from a small amount of resin and acidified with dilute (1:3) hydrochloric acid, adding 5 cc. excess. The crystalline yellow precipitate, consisting of a mixture of the two products of hydrogenation, was allowed to stand in contact with the acid liquor for two days, during which time the alcohol III was converted into its ortho quinone anhydride. The collected material was then shaken with cold 0.25% alkali for one to two minutes and the solution was quickly filtered from unchanged orange needles of V (0.03 g.) and acidified, giving 0.04 g. of the yellow isobutyl compound IV. After recrystallization the orange substance melted at 148–148.5° and the yellow one at 132.5–133.5°. Identifications with known samples were made by mixed melting point determinations and by microscopic examination of the character of the precipitates resulting on the acidification of the solutions in alkali.

**The Second Oxidation Product, IX ( $\beta$ -Methylfuran-1,4-naphthoquinone).**—This compound is produced only in small quantities in the oxidation of lomatiol, but by the following procedure it is possible to free the substance from other products of the reaction and to obtain it in a very pure condition. The new compound was isolated from the acid mother liquor remaining from the oxidation of 10 g. of lomatiol, after removing the orange product in the form of its red anhydride as described above for the preparation of the latter substance. The acid filtrate was boiled down to a volume of about one liter and allowed to cool to room temperature, when about 0.6 g. of crude material was deposited. This contained, in addition to the new compound, some material easily soluble in alkali and some of the red anhydride, VII. It was first ground with 40 cc. of cold 0.25% alkali, and after standing for three hours the undissolved material was collected and boiled for about three minutes with 20 cc. of 1% alkali. This treatment left the new compound largely unattacked, but a small amount of the red anhydride also escaped the action of the alkali, and the orange residue (0.2 g.) was still impure. In order to remove the red anhydride, the crude product was submitted to hydrogenation in alcoholic solution, it having been established that the new compound is converted only into its hydroquinone under these conditions.

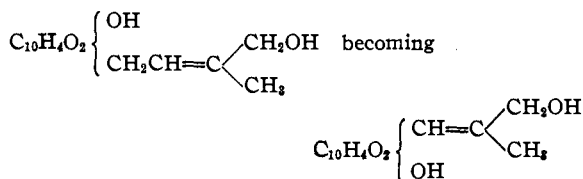
This procedure removed the red color due to anhydride (VII), for the latter was converted into its yellow dihydro derivative VI, which is more soluble in alcohol and which can be removed by crystallization. After agitation with hydrogen the filtered alcoholic solution was exposed to the air and on standing it slowly deposited yellow needles of the purified product (IX). On further crystallization the substance was obtained as yellow needles or prisms, m. p. 246–247°.

*Anal.* Calcd. for  $C_{13}H_8O_3$ : C, 73.58; H, 3.57. Found: C, 73.75; H, 3.73.

The substance did not depress the melting point of a sample prepared by a method which will be described in a forthcoming paper. Both samples were converted into the same acidic substance X (m. p. 176.5–177.5°) by boiling sodium hydroxide solution.

### Summary

The oxidation of lomatiol with alkaline potassium permanganate proceeds exactly as in the case of other examples studied in this Laboratory:



There is formed in addition a very small amount of a substance having one less carbon atom, but although the structure of the compound has been established the manner in which it is formed is still obscure. The principal product of the oxidation yields two substances simultaneously on hydrogenation, and it gives rise to an interesting red ring compound which has been recognized as an  $\alpha$ -quinone of a type analogous to Paternò's dehydrolapachone.

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