acid. The resulting dark red precipitate consisting of microscopic needles was collected, washed with water and air dried, yielding approximately 0.045 g. The substance when crystallized from alcohol melted at 166–167°. It was compared directly with 2-β-phenylvinyl-3-hydroxy-1,4-naphthoquinone, prepared by the aldehyde condensation,[5] with which it is undoubtedly identical, the various points of similarity being further confirmed by a mixed melting point determination.

Conversion of 2-γ-Methylallyl-3-hydroxy-1,4-naphthoquinone into 2-α-Propenyl-3-hydroxy-1,4-naphthoquinone.—A solution of 0.1 g. of potassium permanganate in 10 cc. of water was cooled in an ice-bath and quickly added to a similarly cooled solution of 0.1 g. of the crotyl compound in 10 cc. of 1% alkali. Manganese dioxide separated in a few minutes leaving an almost colorless solution which rapidly became purple. After two hours the filtered solution was partially precipitated by cautiously adding dilute hydrochloric acid until the mother liquor, still alkaline, had become red. The orange, crystalline precipitate was collected, washed and air dried. The yield was 0.03 g. For purification it was dissolved in 6 cc. of a 0.5% solution of sodium hydroxide and then nearly but not completely reprecipitated with dilute acid. Washed and air dried it melted at 134–135° and gave a dark crystalline sodium salt which dissolved in water to an intensely violet solution. Comparison of its properties and a mixed melting point established its identity with the compound prepared from propionaldehyde by condensation with hydroxynaphthoquinone.[5] Oxidation in more strongly alkaline solution gave less satisfactory results.

Summary

Extending an observation regarding the oxidation of lapachol with potassium permanganate, three similarly constituted derivatives of 3-hydroxy-1,4-naphthoquinone having in the 2-position side chains of the type —CH_2CH=CHR have been converted into the corresponding compounds of the side chain —CH=CHR. The hitherto unknown vinyl derivative of hydroxynaphthoquinone has in this way been isolated.

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RECEIVED MARCH 25, 1936

Lomatiol. Part II. Its Occurrence, Constitution, Relation to and Conversion into Lapachol. Also a Synthesis of Lapachol.[1,2]

BY SAMUEL C. HOOKER

In a paper published in 1895 the late Dr. Edward H. Rennie[3] showed that the yellow coloring matter with which the seeds of *Lomatia ilicifolia* and *Lomatia longifolia* are more or less surrounded is closely related to lapachol; and he succeeded in converting the lomatia coloring matter into the hydroxy-β-lapachone which I had previously prepared indirectly from lapachol.[4] The results of Dr. Rennie's work together with the study of numerous compounds which I had obtained from lapachol led me to assign to the lomatia coloring matter the constitution of an hydroxyisolapachol, instead of that of hydroxylapachol proposed by Dr. Rennie, and as at least one other hydroxyisolapachol had been isolated, the name lomatiol was suggested for the lomatia coloring matter.[5]

At the time of this later publication Dr. Rennie had already courteously announced the determination of leaving the further study of the coloring matter to me, and it was my intention to pursue the work as soon as a sufficient supply of raw material had been secured in hope of eliminating all doubts regarding the structure of lomatiol. Conditions arose subsequently which made it impossible to carry out my intentions and it was not until after an interval of many years that I was able to resume the investigation.

Occurrence of Lomatiol.—In addition to the seeds of the two species above referred to, *L. ilicifolia* and *L. longifolia*, I have also examined the seeds of *L. silaifolia* from the Sydney district, New South Wales, and of *L. tinctoria* and *L. polymorpha* from Tasmania.[6] The seeds of all

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

(2) The theoretical part of this paper is from an original manuscript written by Dr. Hooker and modified only to the extent of numbering the formulas and notes and making minor editorial changes. The experimental part has been constructed by consolidating, with some abridgment, descriptions of the experiments written by Dr. Hooker. The summary was supplied by the undersigned. In the experiments Dr. Hooker was assisted by Dr. G. H. Connitt.—L. F. FIESER.

(3) Rennie, *J. Chem. Soc.*, **67**, 784 (1895).

(4) Hooker, *ibid.*, **61**, 611 (1892).

(5) Hooker, *ibid.*, **69**, 1381 (1896).

(6) The seeds of *L. silaifolia* were kindly sent to me by the late Mr. J. H. Maiden, Director of the Botanical Gardens, Sydney. For one sample of *L. tinctoria* I have to thank Dr. J. K. Small, of the New York Botanical Gardens, New York City; and for another, and also for the seeds of *L. polymorpha*, I am indebted to Mr. L. Rodway, then the Government Botanist, Hobart, Tasmania. Of the seeds forwarded by Mr. Rodway, those of *L. polymorpha* were collected near Macquarie Harbour, on the west coast of Tasmania; and those of *L. tinctoria*, principally near Eaglehawk Neck, about 50 miles from Hobart. For the several specimens from Chile I am indebted to Prof. Charles Sprague Sargent of the Arnold Arboretum of Harvard University; to Lt.-Col. Sir D. Prain, F. R. S., Director of the Royal Botanical Gardens, Kew; and to Dr. J. K. Small of the New York Botanical Gardens.

the varieties mentioned were surrounded with a yellow coloring matter which was positively identified as lomatiol in every case. The seeds of three varieties of *Lomatia* growing in Chile were also examined, namely, *L. dentata*, *L. ferruginea* and *L. obliqua*, but they failed to give any indication of the presence of lomatiol, two different specimens of *L. dentata* being tested, three of *L. ferruginea* and two of *L. obliqua*. Thus all the species from Australia were found to be associated with lomatiol; whereas the coloring matter was absent in the seeds of the several species examined growing in Chile.

The greater part of the substance accumulated for investigation was extracted from seeds of *L. longifolia*, obtained near Clarence in the upper parts of the Blue Mountains, about 85 miles from Sydney. For this material I am very much indebted to the late Mr. J. H. Maiden, who, through several seasons, and in the face of a number of difficulties, most courteously arranged for its collection.

The *Lomatia longifolia* fruits when quite ripe, the follicles being open and the seeds exposed, were found when air dried to yield rather more than 3.5% of lomatiol; and the seeds when detached from the follicles slightly over 12%. Fruits subsequently received which were not quite ripe and which had not opened yielded rather less than 1.5%, the amount actually present being slightly greater as the process of extraction in the case of the unripe material was not without waste.

Extraction of Lomatiol.—Lomatiol was extracted by Rennie by boiling the seeds with water slightly acidified with acetic acid, and subsequently purifying the material by recrystallization several times from hot water also acidified. The disadvantage of this method in handling considerable quantities of seeds lies in the large volume of boiling water which must be used inasmuch as each gram of lomatiol extracted requires nearly 300 cc. for its solution; and further in the decomposition which lomatiol slowly undergoes on prolonged heating with water.

The following method of extraction will be found to give very satisfactory results: 250 g. of the seeds removed from the follicles are immersed in 3000 cc. of 0.75% sodium carbonate solution at the prevailing laboratory temperature. After digestion for about two hours, during which time the mixture is stirred frequently, the whole is transferred to a percolator and the alkaline solution drawn down to the level of the seeds and then completely displaced by cold water. Lomatiol, accompanied by a brown amorphous substance, is precipitated from the crimson alkaline extract by the gradual addition of dilute hydrochloric acid, it being desirable to add the acid at short intervals and to avoid at first a material excess, in order that a granular precipitate may be obtained which can be readily decanted, filtered off and washed with water. The mother liquor, rendered very slightly alkaline by the addition of sodium carbonate, may be concentrated in small portions at a time by evaporation on a water-bath avoiding in this way unnecessary exposure to heat. Upon the addition of hydrochloric acid to the concentrated solution a further quantity of lomatiol may be obtained in a less pure condition; the amount however is small and unless material is scarce perhaps hardly justifies the time and effort to obtain it.

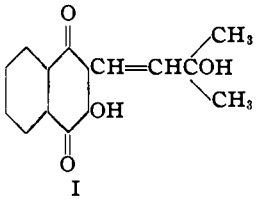
Lomatiol dissolves freely in boiling benzene and being but slightly soluble in this solvent in the cold can be very satisfactorily purified by means of it, as the accompanying brown substance above referred to, which may be present in considerable quantity in the crude material, is practically insoluble in benzene and therefore readily separated. The dried crude lomatiol should be finely pulverized and refluxed for a few minutes with about 20 cc. of benzene per gram. The addition of a small quantity of blood charcoal previous to filtration gives a brilliancy to the lomatiol which cannot be readily obtained without it. If the above directions are followed the one crystallization suffices to yield a very pure material.

It was found necessary to modify the process of extraction in the case of unripe fruits as the opening of the follicles and the removal of the seeds proved to be a difficult matter. The air dried fruits after being ground in a pebble mill were immersed for a short time in a cold 1% solution of sodium carbonate. The solution when filtered was exposed to the air and allowed to ferment. After two weeks it was decanted off and filtered from the deposit which had formed; the deposit was discarded and the solution containing lomatiol oxidized by drawing through air, as the crimson color had been partly discharged below the surface. Lomatiol was then precipitated by the addition of hydrochloric acid at intervals, collected after several days and purified by crystallization from benzene. Whenever possible, lomatiol should be obtained from thoroughly ripe seeds, partly because of much better yields, and

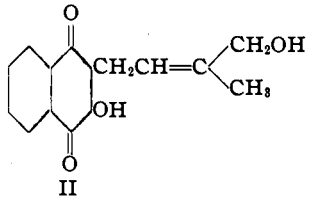
further because the extraction from the unripe material was found to be tedious and otherwise not fully satisfactory.

Chemical Investigations.—Since the appearance of my paper[5] in 1896 the chemistry of lomatiol and its derivatives has remained without further development. No additional facts whatever have been published regarding this coloring matter and no light has been thrown on its structure. The formula which I then suggested and indeed regarded as reasonably well fortified by experimental evidence was largely based upon the action of concentrated sulfuric acid in giving rise to hydroxy-β-lapachone. This change however, was thought to be far simpler than is actually the case for it involves a shift in the position of the double bond and also of the hydroxyl in the chain. Consequently deductions made in ignorance of this were erroneous.

I shall show in this communication that the formula I for lomatiol as accepted in the literature must be changed to II. In the light of our present knowledge the position of the double bond in I would alone condemn the structure of the chain in this formula, as lomatiol is yellow and I would undoubtedly be deep orange to red.[7] Moreover



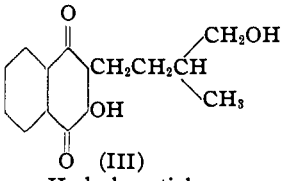
I



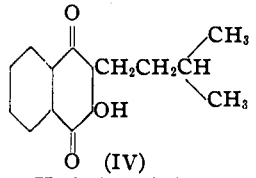
II

a compound of this formula has been obtained in my laboratory in alkaline solution.[8] On liberation by acids it forms an internal anhydride and its possible existence in a free condition is doubtful. These are in themselves sufficient reasons for abandoning the formula I.

The hydrogenation of lomatiol gives rise to two substances (III and IV). Of these hydrolapachol (IV) is also obtained by the hydrogenation of lapachol. This demonstrates not only that lomatiol is a 3-hydroxy-1,4-naphthoquinone derivative but also that it has the same skeleton structure as that of lapachol, namely, —C—C—C(C)C.



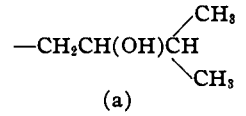
(III)
Hydrolomatiol



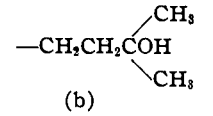
(IV)
Hydrolapachol

The ready absorption of hydrogen moreover proves the presence of a double bond in the lomatiol *chain* as the resulting hydrolapachol retains all the characteristics of a hydroxynaphthoquinone derivative.

The formation of the second compound, hydrolomatiol (III), is of importance because it locates the position of the hydroxyl group in lomatiol. Of the three other possible isomeric substances in which hydroxyl is situated in the side chain two have been isolated in my laboratory and their structure determined with reasonable certainty. The location of hydroxyl in these compounds is as follows:

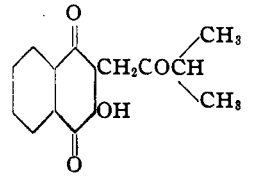


(a)

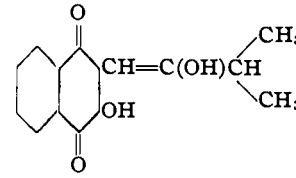


(b)

The compound containing the chain (a) will be described in this paper. It is formed by the hydrogenation of hydroxyisolapachol, V, and also of isolomatiol VI, formerly regarded as a stereoisomer of lomatiol.

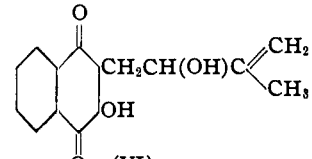


(Va)



(Vb)

Tautomeric forms of hydroxyisolapachol



(VI)
Isolomatiol

This conversion of isolomatiol and hydroxyisolapachol into the same hydrogenated compound determines the position of hydroxyl in isolomatiol, as the structure of hydroxyisolapachol is definitely known.[9] It is thus clear that the hydroxyl groups in lomatiol and isolomatiol are attached to different carbon atoms and that these substances cannot therefore be stereoisomers, as I previously suggested.

The chain (b) is contained in hydroxyhydrolapachol, a substance which results from the action

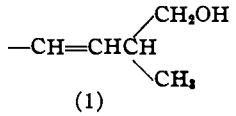
(7) Hooker, THIS JOURNAL, **58**, 1163 (1936).

(8) The results will be communicated in a later paper.

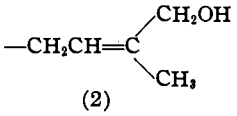
(9) Hooker, *J. Chem. Soc.*, **69**, 1355 (1896).

of alkalies on both α- and β-lapachone. The structure of this compound is also well established.[9] The third isomer in which hydroxyl occupies the α-position in the chain, though not isolated, is satisfactorily accounted for as it undoubtedly occurs as an intermediate product in the formation of isolapachol by the condensation of isovaleraldehyde and hydroxynaphthoquinone.[7,9] There is therefore only the δ-position available for the hydroxyl group in hydrolomatiol and consequently in lomatiol itself.

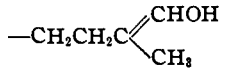
With the skeleton of the chain known, the hydroxyl located, and the existence of a double bond demonstrated, there remains only the position of the double bond to be determined in order that the constitution of lomatiol may be regarded as settled. There are four possible formulas which meet the requirements of an isoamyl skeleton and the hydroxyl in the δ-position. They are:



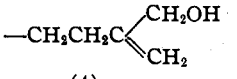
(1)



(2)



(3)



(4)

Of the above chains (1) is at once eliminated because lomatiol is yellow. Of the remainder (2) alone explains the behavior of lomatiol. The action of sulfuric acid is particularly illuminating, and is described by Rennie[3] in some detail. While recording the facts his theory fails to account satisfactorily for them. The discovery, however, that the hydroxyl group is attached to the β-carbon of the chain in isolomatiol and to the δ-carbon in lomatiol enables the reaction to be readily understood. Thus:

The intermediate compounds shown, while not isolated in the progress of the change, nevertheless can be obtained by the action of dilute alkalies on the closed ring substances and again reconverted into them by moderately concentrated sulfuric acid.

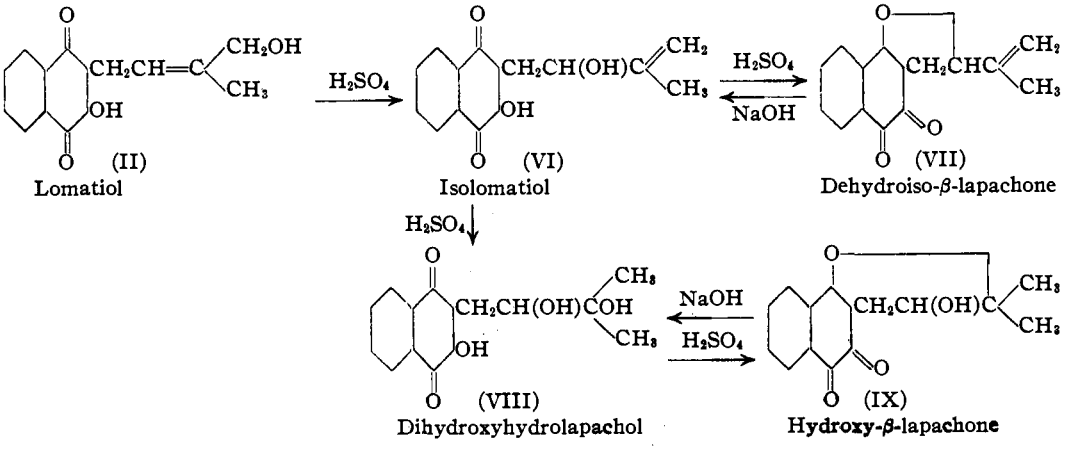
The action of concentrated sulfuric acid on lomatiol has thus brought about a change in the location of the hydroxyl group and, simultaneously, the double bond has necessarily shifted. Similar changes are already well known in compounds having like groupings (allylic rearrangement):[10] $>C=\overset{|}{C}CH_2OH \longrightarrow >C(OH)\overset{|}{C}=CH_2$. Thus these formulas for lomatiol and isolomatiol are in perfect harmony with all the experimental facts and enable satisfactory explanations to be advanced not only of the changes which these substances themselves undergo, but also of their relation to the very numerous compounds in this group which have been prepared in my laboratory.

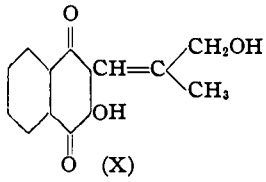
The oxidation of lomatiol with alkaline permanganate following the general method given in recent papers[11] yields, with the elimination of CH_2, a *deep orange* compound[12] having the characteristic properties of a hydroxynaphthoquinone derivative. It can be safely inferred therefore from the color of this oxidation product that it has a double bond in the α,β-position in the chain and consequently the formula X, confirming the structure of chain (2) as that of the lomatiol chain. Chains (3) and (4) under similar circumstances, that is, with the elimination of CH_2, would have

(10) Compare for instance, Burton and Ingold, *J. Chem. Soc.*, 904 (1928); Burton, *ibid.*, 759 (1931).

(11) Hooker, THIS JOURNAL, **58**, 1168, 1174, 1179 (1936).

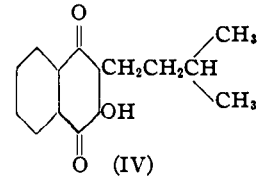
(12) The substance formed by the oxidation of lomatiol has been studied in my laboratory in conjunction with Dr. Al Steyermark. The results obtained will be recorded in another paper.





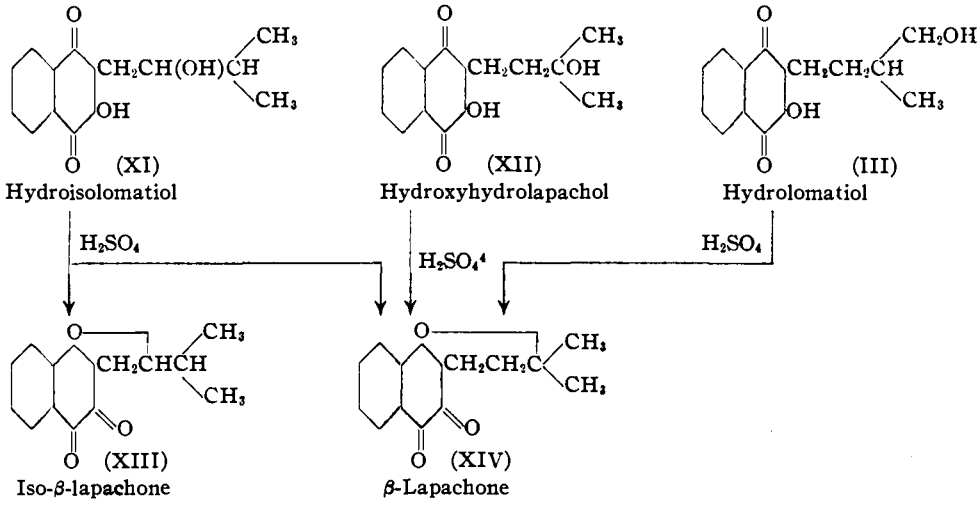
(X)

the *yellow* color of their respective compounds left unchanged owing to the double bonds in the oxi-



(IV)
Hydrolapachol

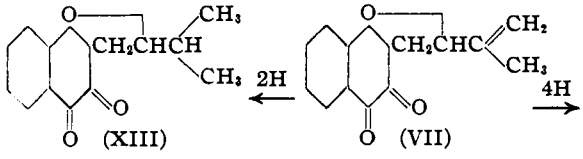
Having converted lomatiol following hydrogen-



(XI) Hydroisolomatiol
(XII) Hydroxyhydrolapachol
(III) Hydrolomatiol
H_2SO_4
H_2SO_4
H_2SO_4
(XIII) Iso-β-lapachone
(XIV) β-Lapachone

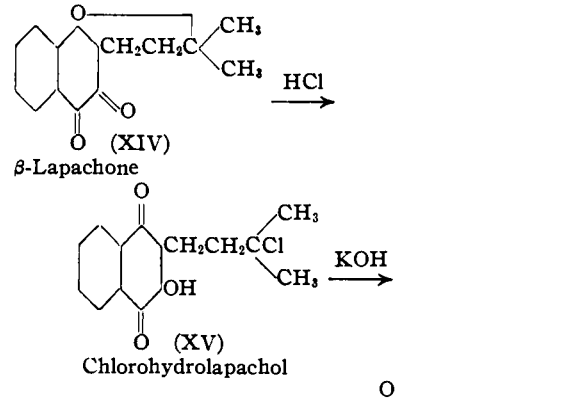
dation products being otherwise situated than in the α,β-position.

The action of concentrated sulfuric acid on the three known hydroxy-amyl derivatives of hydroxy naphthoquinone is interesting because all give as the principal product or one of the principal products the same substance, β-lapachone, thus involving a migration of the hydroxyl group in two cases and indicating a general tendency toward the formation of a six-membered ring. Simultaneously, iso-β-lapachone is also formed from hydroisolomatiol and like β-lapachone is red and undoubtedly a β-quinone derivative. Iso-β-lapachone (XIII) is closely related to the red compound first obtained by Rennie[8] by the action of sulfuric acid on lomatiol. Rennie's compound is now recognized as dehydroiso-β-lapachone (VII), for on hydrogenation it yields iso-β-lapachone along with hydrolapachol, the latter substance arising from the cleavage of the oxide ring adjacent to the unsaturated carbon atom:



(XIII) Iso-β-lapachone
2H
4H
(VII) Dehydroiso-β-lapachone

ation into β-lapachone it is a simple matter to continue through to lapachol,[4] thus:



(XIV) β-Lapachone
HCl
(XV) Chlorohydrolapachol
KOH
(XVI) Lapachol

Also the conversion of hydroxyisolapachol, which has been obtained by synthesis as well as from lapachol,[9] into hydroisolomatiol by hydrogenation and then into β-lapachone completes the steps necessary for a synthesis of lapachol. A much more direct synthesis has been recorded already by Fieser.[13]

(13) Fieser, THIS JOURNAL, 49, 857 (1927).

The formation of isolomatiol from lomatiol and of β-lapachone from hydrolomatiol, as well as from the two isomeric compounds in which the hydroxyl occupies the β- and γ-positions in the chain, indicates the difficulties and dangers which exist in drawing conclusions as to the structure of the compounds of this group from a single reaction. Moreover, my experiments demonstrate that the shifting of the double bond in lapachol and lomatiol and their derivatives must be also recognized as an ever present possibility, and, therefore, that great caution must be exercised in attributing formulas to these substances.

Still another fact must be constantly borne in mind, namely, that changes from the para to the ortho quinone grouping occur frequently and insidiously in the conversion of open to closed ring compounds and *vice versa* in opening the ring. Also similar changes from ortho to para and from para to ortho quinones may take place in the case of the closed ring compounds themselves.

In the course of my investigations, however, I have been fortunate in being able to prepare a large number of substances in the formation of which many interesting and unexpected changes have been developed and studied, and as the formulas adopted are able to explain satisfactorily the relation of these numerous compounds to each other as well as to account for all observations so far made, they may be accepted, I believe, as representing with reasonable certainty the correct structure of the compounds to which they have been assigned. The very number of these compounds and the necessity of fitting each one into the complex whole, has prevented errors which might otherwise have occurred, as with fewer substances the number of available formulas would have been greater and the chances of wrong interpretation thus increased.

Experimental Part

Identification of Lomatiol.—Lomatiol may be positively and comparatively easily identified even in very small quantity owing to its striking characteristics admirably adapted for microscopic tests. Crude lomatiol is best purified by crystallization from benzene as above described, and if only a small quantity is available for identification the benzene can be allowed to evaporate almost to dryness on a watch glass and the resulting crystals may then be washed freely with the cold solvent. The substance is thus obtained matted in fine needles often accompanied by a few microscopic groups of heavier crystals of the same compound. It melts quite sharply at 127° and may be further identified by crystallization from water in which it is but sparingly soluble and in which it fuses at the boiling temperature. If the hot aqueous solution be allowed to cool gradually it becomes somewhat turbid and yellow needles separate which are visible to the naked eye. If the solution be quickly cooled, the emulsion which first results gives rise to minute spherical clusters of very fine needles together with irregular groups of crystals with thorn-like projections. These two forms appear to be invariably present and can be recognized with the help of the microscope. Thus examined the crystals are strikingly beautiful and characteristic.

Lomatiol may be further identified by the crimson color of its solution in alkalies and particularly by means of its barium salts[3] which are extremely typical, the one *orange* and the other dark *claret red*. The test may be made by moistening a very small quantity of lomatiol in contact with an excess of barium carbonate with a few drops of cold water, and filtering off the excess barium carbonate after an hour or so. If a very small quantity of the crimson filtrate be allowed to evaporate spontaneously on a glass slide, needles of the orange salt form readily, and a careful microscopic examination will reveal in addition minute masses of the dark claret colored salt, sometimes recognizable as consisting of thread-like forms suggesting cobwebs. If the solution be very dilute microscopic clusters of needles of lomatiol may also separate. The orange salt when vigorously rubbed on a hard surface yields a dark claret red, resin-like substance, the color change being quite striking.[14]

For further identification a trace of lomatiol may be moistened with an extremely small quantity of concentrated sulfuric acid. A bromine-colored solution is obtained, and if to this a drop or two of water be immediately added an orange-red emulsion forms from which microscopic ribbon-like orange-red crystals slowly separate, many grouped in characteristic root-like forms. After standing exposed to the air in contact with the acid solution the crystals completely disappear in the course of two to three days, an orange resin remaining in their place.[14]

Conversion of Lomatiol (II) into Hydrolomatiol (III) and Hydrolapachol (IV).—Several experiments in which from 1 to 5 g. of lomatiol dissolved in alcohol (50–100 cc.) was hydrogenated in the presence of reduced platinum oxide catalyst (Adams) at ordinary pressure or at a pressure of 38 lb. (2.53 atm.) at the laboratory temperature failed to give entirely concordant results. At times mostly hydrolapachol was obtained, at others mostly hydrolomatiol, a difference presumably due to variations in the condition of the catalyst. The hydrogenation was continued in each case until a drop of the solution, evaporated to dryness, gave with concentrated sulfuric acid a somewhat bromine-colored solution yielding a *yellow* emulsion on dilution. This indicates the absence of lomatiol, as the latter dissolves more to a brown and gives an *orange* emulsion when similarly treated.

In one experiment two 1-g. lots of lomatiol were hydrogenated with the same catalyst derived from 0.2 g. of platinum oxide and the combined, filtered solutions were allowed to stand overnight for oxidation. After evaporation to about 25 cc. the solution was diluted with about an equal volume of hot water. After standing for several

(14) Cf. Rennie, ref. 3.

hours the long needles which had formed were filtered off after chilling, washed with 30% alcohol, and dried, giving 1.14 g. of material melting at 92.5–93°. Recrystallized from dilute alcohol the substance melted at 93.5–94° and was identified as **hydrolapachol** by all the characteristics and properties previously described.[7] The melting point was not lowered by admixture with hydrolapachol from lapachol.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.77; H, 6.55. Found: C, 73.76; H, 6.64.

Hydrolomatiol was obtained in another experiment in which 5 g. of material was hydrogenated in the presence of the catalyst derived from slightly less than 0.3 g. of platinum oxide, about one-third having been used previously once and one-third twice. As attempts to obtain the substance well crystallized directly from the alcohol proved unsuccessful, the solution was allowed to go to dryness. After efforts to obtain from the residue satisfactory crystals from several solvents had failed, the larger part was dissolved in 500 cc. of 1% alkali and the substance was reprecipitated from the filtered solution by hydrochloric acid in three fractions (0.97, 1.92 and 1.08 g.), thus finally completely discharging the crimson color of the alkaline solution. In each case an emulsion was first formed and became crystalline on standing, an interval of an hour or more being allowed between the precipitations. The first fraction contained some hydrolapachol while the second and third were almost pure hydrolomatiol. The second fraction was dissolved in 14 cc. of hot benzene, filtered and allowed to stand overnight. The prismatic yellow needles of **hydrolomatiol** which separated weighed 1.75 g. and melted at 101–102°.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.23; H, 6.15. Found: C, 68.99, 69.23[15]; H, 6.07.

In other experiments fractional precipitation as above described proved generally a satisfactory method of separating the two compounds.

Hydrogenation of Hydroxyisolapachol (V).—The hydrogenation of hydroxyisolapachol has proved more uncertain than that of the other substances of this group. In two experiments the hydrogen was added readily, in others under apparently essentially similar conditions the starting material was recovered unchanged. Possibly a slight difference may have existed in the condition of the catalyst, platinum oxide-platinum black, and perhaps the fact that the stable form of hydroxyisolapachol is that having the chain $-CH_2COCH(CH_3)_2$ (since it is *yellow*) increases the difficulties of hydrogenation and renders the success of the operation dependent upon very exact conditions which have not been determined with sufficient precision. However this may be, the addition of hydrogen gives rise to hydroisolomatiol (XI), which was positively identified by direct comparison with the compound obtained from isolomatiol as described below.

In the successful experiments, using 0.1 g. of substance in 15 cc. of alcohol and 0.1 g. of catalyst, hydrogenation was complete in ten minutes. A drop of the solution, allowed to evaporate (and oxidize) on a watch glass, when tested with concentrated sulfuric acid no longer gave the dark brown almost immediately produced by hydroxyisolapachol, but an orange-red solution which held its color. The residue from another drop gave with 1% alkali a more crimson solution than hydroxyisolapachol, and on acidification the *deep* yellow cloud which formed gave way rapidly to characteristic needles, a behavior entirely different from hydroxyisolapachol, which under similar circumstances gives a *light* yellow jelly-like mass which soon becomes permeated with extremely minute bacillus-like, short crystals. These tests, which must of course be made with the help of a microscope, may be of assistance in following the progress of the hydrogenation.

After standing exposed for about forty-eight hours to ensure complete oxidation of the hydroquinone, the alcoholic solution was evaporated to about 5 cc. and an equal quantity of water was added. The yellow crystalline scales which had formed in the course of a few days weighed 0.055 g. Recrystallized first from alcohol and then from benzene the substance was obtained in fine, orange-yellow needles, m. p. 120–120.5°, identical in all properties with hydroisolomatiol described below. The melting point of the mixed substances from both sources remained the same as for the individual compounds.

Hydrogenation of Isolomatiol (VI): Hydroisolomatiol or β-Hydroxyhydrolapachol (XI).—No difficulty was found in readily obtaining hydroisolomatiol by this method. Several lots were prepared with slight variations, but the irregularities noticed in the hydrogenation of hydroxyisolapachol were not experienced. The catalyst differed slightly in amount in the several lots and possibly also in its condition, as varying amounts had been used previously. The results, however, were essentially the same. Isolomatiol (2 g.) was dissolved in alcohol (50 cc.), platinum oxide (0.4 g.) added and the whole agitated under pressure of 37–38 lb. (2.46–2.53 atm.) at laboratory temperatures. The progress of the hydrogenation can be followed by testing an evaporated drop of the solution, concentrated sulfuric acid giving, when the hydrogen absorption is complete, an orange-red solution which does not change to the brown characteristic of isolomatiol. The addition of water to the acid solution gives a yellow cloud which shortly crystallizes, whereas in the case of isolomatiol an orange-red precipitate is obtained. Ten minutes of contact with hydrogen under the above conditions was found to be sufficient.

Hydroisolomatiol was isolated from the solution essentially as described in the preceding section, 6.1 g. of material hydrogenated in four lots giving 5 g. of product. Recrystallized from alcohol the substance melted constantly at 120.5–121.5°.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.23; H, 6.15. Found: C, 69.26; H, 6.17.

Conversion of Lomatiol (II) into Dehydroiso-β-lapachone (VII).—It was found that the red compound obtained by Rennie[3] by the action of concentrated sulfuric acid on lomatiol can be prepared more satisfactorily by using acid of more moderate concentration, for further change is thus prevented. After various trials the following method was adopted.

A flask containing 10 g. of pulverized lomatiol is immersed in ice water and thoroughly cooled; 100 cc. of ice-cold acid prepared by mixing five volumes of concentrated sulfuric acid with three volumes of water is then added

(15) In this analysis the hydrogen was lost.

and well stirred for a few minutes until the lomatiol has dissolved completely, the flask being kept throughout in ice water. The bromine-colored solution is then immediately poured into water (750 cc.). The new substance separates as an orange-red emulsion which soon crystallizes, forming a voluminous precipitate. After standing until crystallization is complete (usually thirty minutes), the material is filtered off with the aid of suction, washed, broken up under water to facilitate the complete removal of acid, and again washed on the filter. The air-dried material (8.74 g.) is crystallized from 50 cc. of alcohol. As the solution cools dehydroiso-β-lapachone sometimes forms silky, radiating, red needles and sometimes heavier prismatic crystals. If the needles are allowed to stand in contact with the mother liquor they disappear in the course of a few days and the prismatic crystals take their place. Rennie analyzed the needles and reported the melting point 110–111°. The prisms were used for the analysis reported below and the melting point found was 116–116.5°. Dehydroiso-β-lapachone appears to be somewhat sensitive to light and unnecessary exposure should be avoided in its preparation. It dissolves in concentrated sulfuric acid to an orange-red solution.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 75.00; H, 5.00. Found: C, 74.96; H, 5.00.

The azine of dehydroiso-β-lapachone (VII) was easily formed by heating the red compound with *o*-phenylenediamine in glacial acetic acid solution for a minute or two. Crystallized from alcohol the substance formed yellow needles, m. p. 157.5–158°. It dissolves in concentrated sulfuric acid with a deep green color and gives a salmon-colored sulfate.

Anal. Calcd. for $C_{21}H_{16}ON_2$: C, 80.74; H, 5.17. Found: C, 80.45; H, 5.09.

Conversion of Dehydroiso-β-lapachone (VII) into Isolomatiol (VI).—Isolomatiol was first obtained by Rennie[8] by boiling dehydroiso-β-lapachone with strong potassium hydroxide solution, but the crude material precipitated on acidification had to be crystallized four or five times before it was obtained pure. Better results are possible by immersing 1 g. of the finely ground red compound in 75 cc. of 1% sodium hydroxide solution at the laboratory temperature. In the course of some hours solution is essentially complete, and after filtering to remove any possible trace of the unaltered substance dilute hydrochloric acid is added in slight excess to the intensely crimson solution. Isolomatiol is thus precipitated as a yellow oil which slowly crystallizes in groups of branch-like flattened needles with scales attached. Rosets of scales are also sometimes obtained. After washing with water and drying, the crude substance (1 g.) is dissolved in 10 cc. of alcohol, the solution filtered, warmed and gradually diluted with 10 cc. of water. Isolomatiol usually separates in clusters of scales melting at 109–110°. It appears to be sensitive to light.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.77; H, 5.42. Found: C, 69.71; H, 5.39.

Action of Sulfuric Acid on Isolomatiol (VI). (a) Dilute Acid.—Finely ground isolomatiol (0.25 g.) was quickly dissolved in 7.5 cc. of dilute sulfuric acid (5 vol. concentrated acid to 3 vol. water) by stirring for about two minutes and the solution was immediately poured into 75 cc. of cold water. The resulting red emulsion slowly became crystalline and the product (0.12 g.) after crystallization from alcohol was obtained as red needles, m. p. 116–116.5°, and fully identified as dehydroiso-β-lapachone.

(b) Concentrated Acid.—Isolomatiol (0.25 g.) was dissolved in concentrated sulfuric acid (5 cc.) and after four minutes the dark red-brown solution was poured into 65 cc. of cold water. The turbid solution after standing overnight was filtered from a small amount of resinous material and after standing four to five days the filtrate deposited orange-red prisms of hydroxy-β-lapachone (0.04 g.). After recrystallization from alcohol the product melted at 203–205°. The resinous material on further treatment with concentrated acid yielded a trace of yellow needles of what, most probably, was isopropylfurano-1,4-naphthoquinone,[9] but it was not fully identified.

Hydrogenation of Dehydroiso-β-lapachone (VII) and its Conversion into Iso-β-lapachone (XIII).—A solution of 1 g. of dehydroiso-β-lapachone in 100 cc. of alcohol containing 10 drops of acetic acid was agitated with 0.2 g. of platinum oxide catalyst at 38 lb. pressure of hydrogen for twenty minutes at 18°. Dehydroiso-β-lapachone dissolves in concentrated sulfuric acid to an orange-red solution which rapidly darkens on slight warming, and this property enables the end of the hydrogenation to be satisfactorily determined, as the new compound under similar circumstances gives an apricot color which is not darkened by slight heat. In preliminary experiments a drop or two of the solution was removed from time to time, evaporated and tested, and thus the time required was determined. When completely hydrogenated the colorless solution was filtered and exposed to the air until oxidation was complete, as indicated by no further increase in color. The solution was evaporated to 20 cc. and diluted with 10 cc. of water. Slight turbidity ensued and the following morning a red crystalline crust had formed on the bottom of the flask, and after another day the crystals of iso-β-lapachone were filtered off and washed with 50% alcohol; yield, 0.44 g. The mother liquor and washings were further diluted with 2.5 cc. of water and after standing overnight yellow crystals of hydrolapachol were found to have separated; yield 0.13 g. On further dilution a small additional amount of iso-β-lapachone was obtained in a somewhat resinous condition. This was digested with 1% alkali to remove resin and hydrolapachol and crystallized from alcohol.

Iso-β-lapachone crystallizes in dark orange-red plates or scales and melts at 124.5–125.5°. It has also been obtained in voluminous masses of tufts of needles materially lighter in color. The sample for analysis was recrystallized from dilute alcohol without unnecessary exposure to light.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.38; H, 5.78. Found: C, 74.32; H, 5.81.

I have not been successful in attempts to transform isopropylfurano-1,2-naphthoquinone[9] directly into iso-β-lapachone by hydrogenation. Using alcohol as the solvent the starting material was recovered unchanged; in ethyl acetate only a red oil was obtained.

Conversion of Iso-β-lapachone (XIII) into Hydroisolomatiol (XI).—This change was quantitatively effected by

boiling powdered iso-β-lapachone (0.1 g.) for a minute or two with 1% sodium hydroxide solution (20 cc.). The deep crimson solution was filtered to remove possible traces of the unchanged substance, cooled and acidified with dilute hydrochloric acid, avoiding an undue excess. The oily, yellow suspension soon gave place to fine yellow needles which were filtered off on the following day. Crystallized from benzene the substance separated as needles and prisms melting at 121–122°.

Action of Concentrated Sulfuric Acid on Hydroisolomatiol (XI).—A solution of 0.5 g. of hydroisolomatiol in 10 cc. of concentrated sulfuric acid was allowed to stand for one hour in a corked vessel and poured into water (500 cc.). The emulsion first formed soon gave place to fine orange-red needles which were filtered off on the following morning and recrystallized a number of times from 50% alcohol (3 cc. at first and finally 2 cc.). Although the substance appeared to be pure under the microscope, the rise of the melting point with each crystallization from an initial 135–142° to eventually 153–154° clearly suggested the presence of more than one compound.

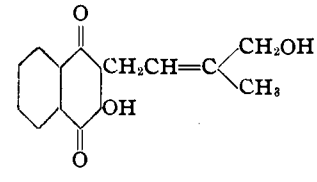
The crystals finally obtained pure were identified as β-lapachone by a mixed melting point and by conversion into γ-hydroxyhydrolapachol and its characteristic barium salt. The second substance, which proved to be iso-β-lapachone, was not itself isolated but its presence was proved by reconversion into hydroisolomatiol. In order to demonstrate the presence of iso-β-lapachone in the mixture another lot was prepared from 0.1 g. of hydroisolomatiol as before and collected one and one-half hours after pouring the acid solution into water. Microscopic examination of the material both while still wet and after being air dried definitely established the absence of yellow crystals of unchanged hydroisolomatiol. The material (0.07 g.) was immersed in cold 1% alkali which in the course of two hours had dissolved the greater part of the iso-β-lapachone, leaving 0.02 g. of β-lapachone unattacked. To the filtered crimson solution an excess (2.5 cc.) of dilute (1:3) hydrochloric acid was added. This gave a yellow suspension which soon crystallized in spherical groups of light needles characteristic of hydroisolomatiol. The crystals were allowed to stand in contact with the acid liquor so that any hydroxyhydrolapachol derived from the action of alkali on β-lapachone might be reconverted into β-lapachone. After a day or so microscopic examination revealed a very small quantity of orange-red crystals (assumed to be β-lapachone) which did not appear to increase on further standing (fifteen days). The mixture of crystals was then filtered off and immersed in a very dilute solution of sodium hydroxide to dissolve and thus separate the hydroisolomatiol from the orange crystals. Hydrochloric acid reprecipitated the yellow substance from the filtered solution and this was twice crystallized from benzene and identified by direct comparison with hydroisolomatiol by melting point (120–121°) and other characteristics.

Conversion of Hydrolomatiol (III) into β-Lapachone (XIV).—A small quantity of hydrolomatiol (0.1 g.) was dissolved in concentrated sulfuric acid (3 cc.) in a test-tube which was then corked to prevent the absorption of water and allowed to stand at the laboratory temperature. Action was slow. A drop of the solution was diluted from time to time and the color of the resulting emulsion taken as indicating the progress of the change. After one hour this was still yellow; subsequent tests tended more and more toward orange, and on the following morning the acid solution was poured into water (75 cc.). The resulting deep orange-red emulsion soon crystallized into root-like forms, which were thoroughly washed, dried (yield, 0.07 g.) and crystallized four times from alcohol, as, although the brilliant orange-red needles obtained appeared to be pure from the first, each crystallization resulted in a higher melting point. Identification was made as β-lapachone by direct comparison with this substance, by melting point (153–154°), mixed melting point and by conversion into hydroxyhydrolapachol and the characteristic barium salt of the latter. Owing to the repeated crystallizations necessary to obtain β-lapachone melting correctly, the presence of a second substance as the result of the action of concentrated sulfuric acid would seem to be indicated.

Summary

Various species of *Lomatia* from Australia have been found to be associated with lomatiol, whereas the coloring matter was absent in the seeds of several species examined growing in Chile. Methods of extracting lomatiol from both ripe and unripe fruits are described.

Lomatiol was found by Rennie to have the same skeletal structure as lapachol, from which it differs only in the character of the side chain. In the present investigation it is shown that the alcoholic hydroxyl group of hydrolomatiol is located in the δ-position in the chain ($-CH_2CH_2CH(CH_3)CH_2OH$) because substances having the other three possible structures have been obtained or characterized by synthesis or from lapachol. The double bond present in the lomatiol side chain is recognized as occupying the α,β-position with respect to the primary alcoholic group ($-CH_2CH=C(CH_3)CH_2OH$) by the observation that an allylic shift occurs in the conversion of lomatiol into isolomatiol, a substance having the chain $-CH_2CH(OH)C(CH_3)=CH_2$. It is thus proved that lomatiol has the constitution of 2-[δ-hydroxy - β - isopentenyl] - 3 - hydroxy - 1,4 - naphthoquinone:



The formula is in perfect harmony with all the experimental facts and enables satisfactory explanations to be advanced of many changes which

the compounds of the lomatiol series undergo and of their relationship to substances of the lapachol series. The transformations described in this paper include the conversion of lomatiol into lapachol through a series of intermediate substances, and since one of these can be prepared also from synthetic isolapachol, the work reported constitutes a synthesis of lapachol.

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BROOKLYN, N. Y.

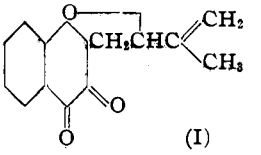
RECEIVED APRIL 3, 1936

The Constitution of Lapachol and its Derivatives. Part V. The Structure of Paternò's "Isolapachone"[1,2]

BY SAMUEL C. HOOKER

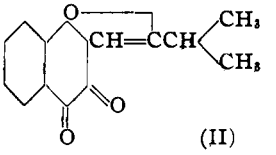
"Isolapachone" was first referred to by Paternò[3] in 1882 in his "Ricerche sull'acido lapacico" (lapachol). It was obtained by the removal of two acetyl groups, followed by spontaneous oxidation, from a compound formed by the action of acetic anhydride and sodium acetate upon lapachol. Seven years later the compound was studied by Paternò and Minunni[4] and the conclusion reached that the substance is similar to and isomeric with lapachone (β), the compound resulting from the action of concentrated sulfuric acid on lapachol. This view was shown by me to be untenable,[5] for in investigations published in 1892 it was found that the so-called "isolapachone" and also the diacetyl compound from which it had been obtained had each two atoms of hydrogen less than required by the formulas assigned by Paternò and Minunni. At that time I suggested a structural formula for the diacetyl compound which twenty-three years later received additional support from the experiments of L. Monti.[6] The matter was discussed by Monti apparently in ignorance of the revised and now generally accepted formula[7] for lapachol which necessitated a corresponding modification in "isolapachone" and all the compounds derived from lapachol studied previous to 1896.

In the course of the study of the action of concentrated sulfuric acid upon lomatiol, the discovery by Rennie[8] of a compound isomeric with and in some respects similar to Paternò's "isolapachone" gave rise to uncertainties and errors of interpretation both as to its own structure and that of "isolapachone."[9] This was mainly due to misconceptions regarding the structure of lomatiol. In a recent paper[10] evidence has been presented which fully establishes the structure of lomatiol, and in the course of this work it was shown that Rennie's compound has the formula I and can be regarded as a dehydroiso-β-lapachone. An isomeric dehydro derivative of iso-β-lapachone was obtained in an earlier investigation[7] both from lapachol and by synthesis and



(I)

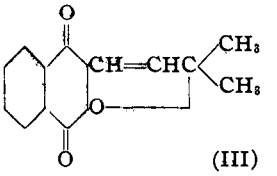
Rennie's Compound



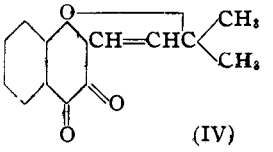
(II)

Isopropylfurano-1,2-naphthoquinone

it was assigned the structure II. The corresponding para quinone was also fully characterized. In this paper it will be shown that the preponderance of the facts now known favors formula III, or possibly IV, for "isolapachone." The equivalent of formula IV, based upon what was then



(III)



(IV)

believed to be the structure of lapachol, was previously suggested by me[5] but afterward aban-

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

(2) Dr. Hooker wrote a preliminary version of the introductory part of this paper in April, 1931, but he did not find time subsequently to incorporate in the manuscript certain modified views and new interpretations growing out of his more recent work on this and related problems. I was informed of his views throughout this period, however, through correspondence and conversations, and from the letters and from the notes of his assistant Dr. A. Steyermark, I have been able to revise the paper in accordance with Dr. Hooker's wishes and in large part in his own words. The experiments recorded were carried out with the collaboration of Mr. H. W. Shepard and Mr. J. G. Walsh, Jr., in 1891–1896, and of Dr. G. H. Connitt and Dr. A. Steyermark in the more recent period.—L. F. FIESER.

(3) Paternò, *Gazz. chim. ital.*, **12**, 337 (1882).

(4) Paternò and Minunni, *ibid.*, **19**, 607 (1889).

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

(6) Monti, *Gazz. chim. ital.*, **45**, II, 58 (1915).

(7) Hooker, *J. Chem. Soc.*, **69**, 1355 (1896).

(8) Rennie, *ibid.*, **67**, 786, 792 (1895).

(9) Hooker, *ibid.*, **69**, 1362, 1370, 1377, 1382 (1896).

(10) Hooker, THIS JOURNAL, **58**, 1181 (1936).