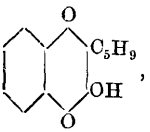
LXXXVII.—*The Constitution of Lapachol and its Derivatives.* Part III. *The Structure of the Amylene Chain.*

By Samuel C. Hooker.

The formula  , expresses all that is definitely known regarding the constitution of lapachol. It is true that Paternò assigned to the $-C_5H_9$ group the structure $-CH{:}CH{\cdot}CH{<}^{CH_3}_{CH_3}$, and that I have adopted this in my former papers, but I have been careful to point out that this formula was employed provisionally only (Trans., 1892, 612; 1893, 430).

In assigning the above constitution to the $-C_5H_9$ group, Paternò was mainly influenced by the two following reasons.

I. He had identified isobutylene among the reduction products resulting from the distillation of lapachol over zinc dust.

II. He believed that he had obtained β-iso-amylnaphthalene by submitting lapachol to the action of hydriodic acid and phosphorus.

The substance obtained was not, however, β-iso-amylnaphthalene, as was subsequently proved by the synthesis of this compound by Roux (*Bulletin*, 1884, [2], **41**, 380). β-Iso-amylnaphthalene differs essentially from Paternò's hydrocarbon.

Thus, since the publication of Roux's paper, the only two experiments bearing on the structure of the amylene chain lead to contrary conclusions. On the one hand, the formation of isobutylene points to the probability that the $-C_5H_9$ group contains isopropyl; and, on the other, the dissimilarity between Paternò's hydrocarbon, $C_{10}H_7 \cdot C_5H_{11}$, and the β-iso-amylnaphthalene prepared by Roux, renders the presence of isopropyl improbable.

The results of the experiments now to be communicated to the Society clearly prove that the amylene chain of lapachol must be written $-CH_2 \cdot CH{:}C{<}\begin{matrix}CH_3\\CH_3\end{matrix}$, and not $-CH{:}CH \cdot CH{<}\begin{matrix}CH_3\\CH_3\end{matrix}$, as has been previously assumed.

It has been shown by Hooker and Carnell (Trans., 1894, **65**, 84), that isovaleraldehyde and β-hydroxy-α-naphthaquinone, when heated in alcoholic solution, interact according to the following equation,

$$\text{I.}\quad 2C_{10}H_6O_3 + C_4H_9 \cdot CHO = C_4H_9 \cdot CH(C_{10}H_5O_3)_2 + H_2O;$$

but if the same substances, dissolved in acetic acid, are heated in the presence of a sufficiently large quantity of hydrochloric acid, the following entirely different reaction occurs (compare Proc., 1893, **9**, 259).

$$\text{II.}\quad C_{10}H_4\begin{Bmatrix}O_2\\H\\OH\end{Bmatrix} + C_4H_9 \cdot CHO = C_{10}H_4\begin{Bmatrix}O_2\\CH(OH) \cdot C_4H_9\\OH\end{Bmatrix} =$$

$$C_{10}H_4\begin{Bmatrix}O_2\\CH{:}CH \cdot CH{<}\begin{matrix}CH_3\\CH_3\end{matrix}\\OH\end{Bmatrix} + H_2O.$$

In the first case, the isovaleraldehyde unites with 2 mols. of the hydroxynaphthaquinone, an action which appears to be a general one, and which was first studied by Zincke and Thelen with benzaldehyde; in the second, the same quantity of the aldehyde unites with 1 mol. of the hydroxynaphthaquinone only,* and the resulting compound, $C_{15}H_{14}O_3$, is isomeric with lapachol.

That the action has occurred as above indicated, is clearly demonstrated by the following facts.

* Further details of this reaction, so far as other aldehydes are concerned, will be communicated later.

1. The compound exhibits all the properties of a hydroxyquinone. Having well developed acid properties, it dissolves readily in alkalis, and forms intensely coloured, crystalline salts.

2. It yields an acetyl derivative, which is no longer capable of forming salts.

3. When oxidised with nitric acid, it yields phthalic acid.

4. It combines readily with bromine, forming an unstable additive compound, in which the bromine, as is apparent from the reactions of the compound, is unquestionably situated in the side chain.

These properties demonstrate

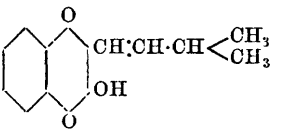
1. That the quinone group has taken no part in the reaction.

2. That the hydroxyl group also remains undisturbed.

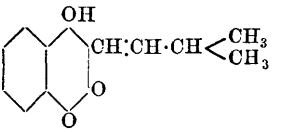
3. That the side chain must be situated in the benzene ring containing the quinone and hydroxyl groups, and consequently that it occupies the β-position, which is the only one available.

4. That there is a double bond present in the side chain.

If, therefore, the origin of isolapachol from β-hydroxy-α-naphthaquinone were alone considered, it would be necessary to assign to it the first of the following formulæ,



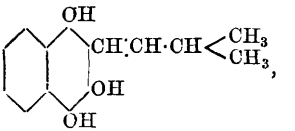
(1).



(2).

but as isolapachol differs from the derivatives of β-hydroxy-α-naphthaquinone, in being of a brilliant brick-red colour instead of yellow, we must accept the second formula as the more probable one. (Compare pp. 1363, 1364.)

The first of the above formulæ is that which, up to the present time, has been used as probably representing the constitution of lapachol, and thus the question arises, does the isomerism existing between lapachol and isolapachol merely depend on a difference in the quinone group? This can be readily answered in the negative, for if these compounds were related as shown in the formulæ (1) and (2), it is evident that on reduction they both must yield the same hydrolapachol,



but as this is not the case, the amylene chain in lapachol cannot be

identical with that in isolapachol; hence the above formula (1) can no longer be accepted as representing the structure of lapachol.*

I shall show in the following pages that lapachol and isolapachol can be converted without loss of carbon atoms into the same compounds. The changes involved are simple, and could hardly give rise to any alteration in the skeleton structure of the side chain, which must, therefore, in both cases be written $-C\cdot C\cdot C<^{C-}_{C-}$, the carbon atom to the extreme left being attached to the naphthalene nucleus. This follows as a necessary consequence from the synthesis of isolapachol from isovaleraldehyde.

Now, from a skeleton of this structure, it is only possible to derive three amylene chains, namely,

$$-CH{:}CH\cdot C<^{CH_3}_{CH_3}, \qquad -CH_2\cdot CH{:}C<^{CH_3}_{CH_3}, \qquad -CH_2\cdot CH_2\cdot C\lessdot^{CH_2}_{CH_3},$$

(1) (2) (3)

and of these the first, being that present in isolapachol, cannot represent the structure of the chain in lapachol itself, whilst the third will not explain the reactions of lapachol, more particularly those connected with the passage of its derivatives into those of isolapachol.* There remains consequently the second formula only, and this alone enables all the numerous reactions already studied to be satisfactorily interpreted.

The reduction of lapachol, if carried sufficiently far, might, therefore, be expected to lead to β-iso-amylnaphthalene, the hydrocarbon which Paternò believed to be formed by the action of hydriodic acid and phosphorus. As already stated, however, β-iso-amylnaphthalene has been synthesised by Roux, and it differs essentially from Paternò's hydrocarbon.

Paternò's conclusions regarding the composition of his reduction product cannot, therefore, be accepted, for if the compound obtained were really $C_{10}H_7\cdot C_5H_{11}$, *i.e.*, an amylnaphthalene, it is evident that the amylene chain in lapachol could not have for its structure the formula, $-CH_2\cdot CH{:}C<^{CH_3}_{CH_3}$, which the results of my experiments necessitate. I have therefore repeated in more detail Paternò's work, and have found that the reduction product described by him is not a hydrocarbon, but a mixture of two isomeric compounds of the formula, $C_{15}H_{16}O$.

In order to understand the formation of these compounds, it is only necessary to remember that, by the action of mineral acids,

* The possibility of stereoisomerism has not been overlooked; the assumption of its existence is however unnecessary. The relation of lapachol and isolapachol to each other, as will be presently seen, is made perfectly clear by their reactions.

lapachol is readily converted into either α- or β-lapachone, or a mixture of these substances; and as the lapachones contain a closed side chain, in which the hydroxylic oxygen forms the connecting link between the amylene group and the naphthalene nucleus, it is evident that some difficulty might be anticipated in the removal of the whole of the oxygen; hence it is not surprising that the reduction products obtained should have the formula, $C_{10}H_6<\begin{matrix}C_5H_{10}\\ |\\ O\end{matrix}$.

No analysis is given by Paternò of his supposed hydrocarbon, but its composition was deduced by him from the following analyses of a picrate prepared from it.

	Paternò found.	Calculated for $C_{10}H_7{\cdot}C_5H_{11} + C_6H_2(NO_2)_3{\cdot}OH$.
C.....	57·41, 57·29, 57·27	59·01
H	4·61, 4·76, 5·15	4·91
N	Not determined.	9·83

Paternò explained the deviation of his analytical results from those required by the formula $C_{15}H_{18},C_6H_2(NO_2)_3{\cdot}OH$, by the supposition that the picrate analysed contained small quantities of free picric acid. This explanation is however, no longer tenable.

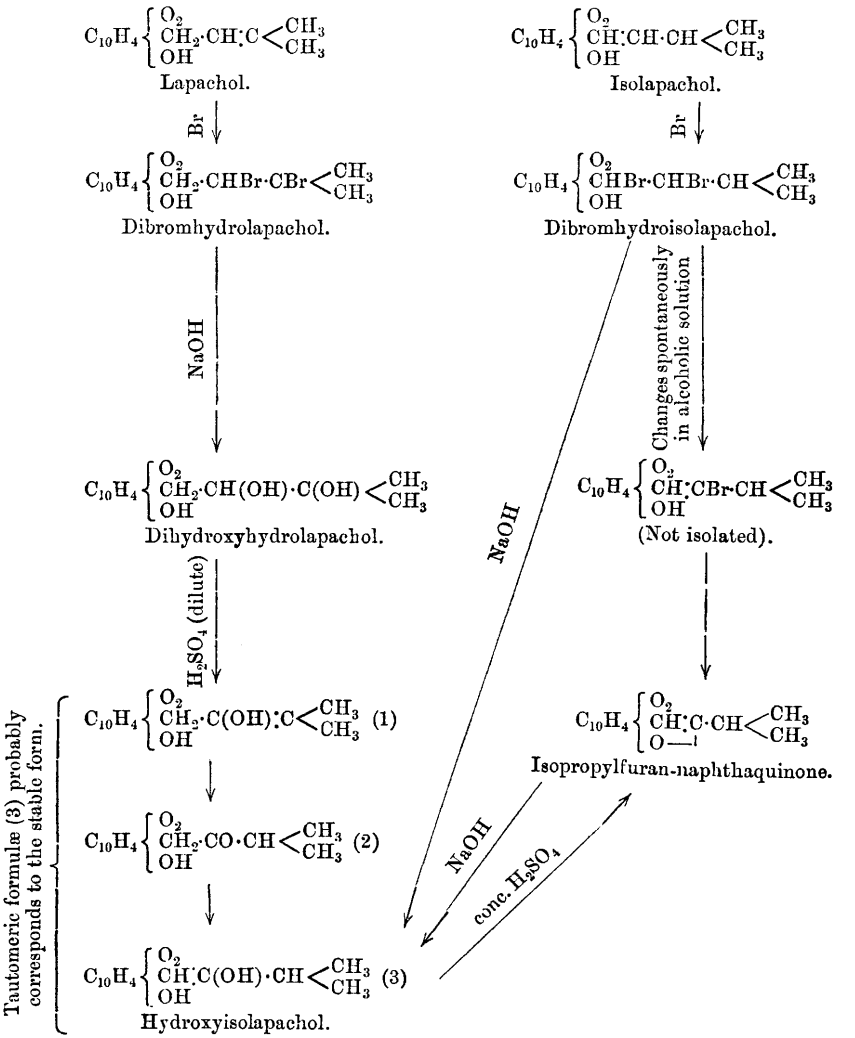
The analytical figures given below are the averages of all those obtained; that is, they include the results of Paternò's analyses, as well as those of my own; and the comparison shows that they agree with the requirements of the theory suggested above.

	Calculated for $C_{15}H_{16}O,C_6H_2(NO_2)_3{\cdot}OH$.	Mean of the analytical results.*
C	57·14	57·14
H	4·30	4·57
N	9·52	9·61

I have further confirmed the formula $C_{15}H_{16}O$, by the analysis of the reduction product itself (compare p. 1367), and have found that of the two substances of which it is a mixture, the one—that predominating—can be obtained by the reduction of β-lapachone, whilst the other, which appears to be present in a small quantity only, can be readily prepared by the reduction of α-lapachone. There is, therefore, no doubt possible regarding the composition of Paternò's reduction product, and the discovery that it contains oxygen has removed the difficulties which, as a hydrocarbon, its existence suggested.

The conversion of the derivatives of lapachol into those of isolapachol, to which reference has been already made, can be best shown graphically as follows.

* For details compare p. 1366.

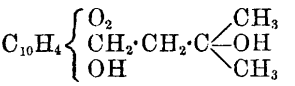


The above illustrates in outline the reactions involved in the conversion of lapachol and isolapachol into hydroxyisolapachol. For the sake of clearness, I have avoided reference to the changes which in some instances simultaneously occur in the quinone group. These will be discussed in detail in the following pages.

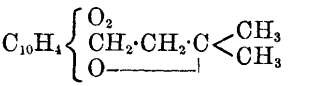
Several simpler methods of passing from the derivatives of lapachol into those of isolapachol, and *vice versa*, readily suggest themselves; but experimentally, with the exception of the above, all have failed to accomplish the desired end.

The revision of the formula of lapachol renders necessary some modification in the formulæ of the remaining substances of this group; these changes may now be briefly discussed.

The conversion of lapachol into the isomeric lapachones has been shown to depend on the absorption of a molecule of water, which is again subsequently eliminated, but in a different direction (Trans., 1892, **61**, 613); and there is every reason to believe that in the formation of the intermediate additive compound the general rule has been followed, and the hydroxyl or negative group has attached itself to the carbon atom poorest in hydrogen. Consequently the following formulæ must be ascribed to hydroxyhydrolapachol and lapachone respectively.

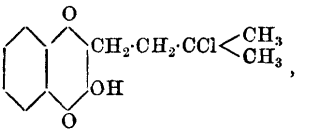


Hydroxyhydrolapachol.

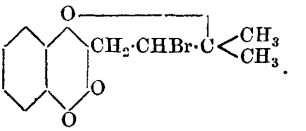


Lapachone.

Similarly, chlorhydrolapachol becomes

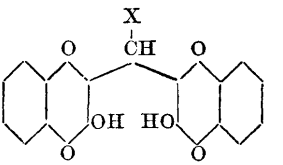


and bromo-β-lapachone



Thus, the side ring of the lapachones consists of six members, instead of five, as has been heretofore assumed.

That a similarity exists between the lapachones, on the one hand, and the anhydrides of the synthetical compounds of the general formula



on the other, has been established by Hooker and Carnell (Trans., 1894, **65**, 76). In the case of the latter compounds, the anhydride formation can only give rise to a ring consisting of six members, hence the lapachones are more closely related to this group than was at first supposed.

The only remaining compound of the lapachol group to which it seems necessary to make special reference in the introductory portion of this paper is Paternò's so-called *isolapachone*. In a former communication to the Society (Trans., 1892, **61**, 624), it was shown that this compound contains 2 atoms of hydrogen less than lapachone: it has, in consequence, the formula $C_{15}H_{12}O_3$, being isomeric with dehydrolapachone (see next paper) and the isopropylfuran-naphthaquinones (pp. 1370, 1376).

The structural formula provisionally suggested at that time, revised in accordance with the requirements of the new formula for lapachol, is, however, no longer tenable. I shall hope to discuss in the near future the results which have led to this conclusion. In the meantime the compound may be conveniently referred to as pseudo-dehydrolapachone.

Experimental Part.

Synthesis of Iso-β-lapachol (compare Proc., 1893, **9**, 259).—This compound, to which reference has already been made on p. 1356, was prepared as follows:—10 grams of hydroxynaphthaquinone were heated on a steam bath with 175 c.c. of acetic acid. As soon as the substance had completely dissolved, 35 c.c. of isovaleraldehyde, immediately followed by 50 c.c. of concentrated hydrochloric acid, sp. gr. 1·20, were added; the flask was at once returned to the steam bath, and the heating continued for exactly 20 minutes. The solution was then poured into a relatively large volume of water. The dark oil which rose to the surface commenced to crystallise almost immediately. After standing over night, the crystalline crust was lifted off, allowed to drain, and finally repeatedly pressed between porous paper, so as to remove the oil as thoroughly as possible. The substance was then crystallised from a small quantity of alcohol.*

Two preparations were made, the one from Kahlbaum's "valeraldehyde," the other from isovaleraldehyde synthesised from isobutylic iodide. The purified products were found to be identical, equally satisfactory results being apparently obtained with Kahlbaum's valeraldehyde, although optically active, as with the aldehyde synthetically prepared. The yield is very fair, from 7 to 9 grams of the purified substance being obtained from 10 grams of hydroxynaphthaquinone.

* The alcoholic mother liquor, after concentration to a small bulk, so as to first yield a second crop of crystals, was poured into about 400 c.c. of an aqueous 1 per cent. solution of sodium hydroxide. The iso-β-lapachol which remained in the mother liquor was thus extracted by the alkaline solution, from which, after filtration from the resin, it was precipitated by hydrochloric acid as an orange oily substance, which gradually became crystalline.

Iso-β-lapachol was prepared for analysis by recrystallisation from alcohol. It separated in brilliant, brick-red needles, which melted at 120°, showing signs of fusion at a slightly lower temperature. The following figures were obtained on analysis.

I. 0·2035 gave 0·5528 CO_2 and 0·1071 H_2O. C = 74·08; H = 5·84.
II. 0·1991 „ 0·5400 „ „ 0·1057 H_2O. C = 73·97; H = 5·89.
$C_{15}H_{14}O_3$ requires C = 74·38; H = 5·78 per cent.

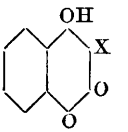
Dilute aqueous solutions of sodium and potassium hydroxide dissolve iso-β-lapachol readily, becoming intensely purple. From these solutions the corresponding salts can be easily obtained in a crystalline condition by the addition of a concentrated solution of the respective hydroxide; when dry, the salts are dark violet, almost black.

Iso-β-lapachol is very soluble in the ordinary organic solvents. In alcohol, more especially when in dilute solution, it slowly undergoes change, the odour of acetaldehyde becomes noticeable, and a yellow, granular, although crystalline, substance, sparingly soluble in alcohol, separates. This dissolves to some extent in 1 per cent. sodium hydroxide, but is apparently mostly converted into a salt by the alkali without passing into solution. Iso-β-lapachol is dissolved by concentrated sulphuric acid to a solution, which, after passing through various shades, soon becomes crimson, the odour of sulphurous acid being distinctly perceptible. The precipitate obtained on the addition of water became resinous on drying, and consisted of more than one substance.

Several attempts were made to form an additive compound with hydrogen chloride and hydrogen bromide respectively, as it was thought possible that if such a compound were obtained it might serve as a stepping-stone to the preparation of lapachol itself: these experiments have proved entirely unsuccessful.

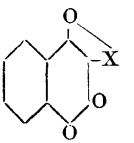
The constitution of iso-β-lapachol has been already discussed in the theoretical portion of this paper. Reference may, however, be made somewhat more in detail to the fact that I have assigned to it the structure of a β-naphthaquinone derivative. This has been done because it is extremely probable that the difference in colour between α- and β-naphthaquinone derivatives of the types occurring in the lapachol group is a sharp and distinct one.

In previous papers I have regarded the structure

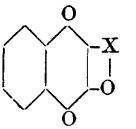


as an unstable one, but the existence of iso-β-lapachol, as well as of similar compounds which have since been prepared in my laboratory, renders it probable that although frequently unstable this structure is not necessarily so.

In the case of the internal anhydrides of the general formulæ



Red.



Yellow.

the relation of colour to structure can be readily established. Thus we have the red anhydrides which, without exception, form azines, and the yellow ones which do not; and whilst it is not possible with any degree of certainty to apply the azine test to the hydroxynaphthaquinone derivatives themselves, owing to the mobility of the hydroxylic hydrogen, it may nevertheless be presumed, with a fair amount of probability, that a similar relation to colour in their case also holds good. Hence the red and yellow hydroxynaphthaquinones must, for the present at least, be regarded as ortho- and para-quinone derivatives respectively.

Acetyl Derivative.—An acetyl derivative was readily obtained by boiling for two or three minutes 2 grams of iso-β-lapachol with 4 grams of anhydrous sodium acetate and 13 c.c. of acetic anhydride; the solution was then poured into a large volume of water; the oil which separated soon became crystalline. The acetate was purified by crystallisation from alcohol, in which it dissolves very readily, and from which it separates as yellow needles. The portion for analysis was again recrystallised, and then melted sharply at 74°. The analytical results were as follows.

0·2128 gave 0·5568 CO_2 and 0·1071 H_2O. C = 71·36; H = 5·59.

$C_{15}H_{13}(COCH_3)O_3$ requires C = 71·83; H = 5·63 per cent.

The acetate, being yellow, is most likely an α-naphthaquinone derivative. Thus it is probably derived from isolapachol, the β-hydroxy-α-naphthaquinone derivative isomeric with iso-β-lapachol. Concentrated sulphuric acid gives with the acetate a violet coloration, which rapidly changes into crimson. The acetyl group is readily removed by caustic alkalis; the compound was boiled for a short time with a 1 per cent. solution of sodium hydroxide until it had completely dissolved; hydrochloric acid precipitated iso-β-lapachol from the alkaline solution, and this, when once crystallised from alcohol, fused at about 119·5°.

For the analyses of iso-β-lapachol, and also those of the acetate, I

am much indebted to Mr. C. C. Burger, who also rendered valuable assistance in the preparation of these compounds.

Reduction of Lapachol.—This was conducted essentially as described by Paternò (*Gazzetta*, 1882, **12**, 329). One part of lapachol, one part of amorphous phosphorus, and four parts by weight of hydriodic acid, sp. gr. 1·7, were heated together until the action which is at first quite brisk, appeared to be entirely ended. The lower or oily layer was separated, washed slightly with water, and then distilled in a current of steam. The oil which collected in the receiver passed over with very great difficulty, and the distillation was continued for some days. As a further means of purification, the oil was converted into the picrate described by Paternò. This was crystallised from alcohol and then decomposed by a dilute solution of ammonia, the liberated oil being extracted by agitation with ether. The ethereal solution was repeatedly washed with water, dried over calcium chloride and distilled; after the ether had been driven off, the temperature rose rapidly and no further distillate was obtained until the thermometer registered over 300°. The first portions of the oil were discarded: that collected for analysis passed over at about 310°.

The following figures were obtained.

I. 0·2256 gave 0·7075 CO_2 and 0·1542 H_2O.
II. 0·2438 „ 0·7596 „ „ 0·1671 H_2O.

	Found.		Calculated for	
	I.	II.	$C_{15}H_{16}O$.	$C_{10}H_7{\cdot}C_5H_{11}$.
C	85·52	84·97	84·90	90·90
H	7·59	7·61	7·54	9·09

It is apparent from these analyses that the oil is not an amylnaphthalene. The analytical results point rather to the formula $C_{15}H_{16}O$, and this was further confirmed by the experiments given below. The action of hydriodic acid in giving rise to a reduction product, $C_{15}H_{16}O$, is a two-fold one. The lapachol first merely undergoes the change which is brought about by all the stronger mineral acids, and which invariably results in the formation of α- or β-lapachone, or of a mixture of these substances. The quinone group is then completely reduced, and the product, $C_{15}H_{16}O$, is formed.

Theoretically, therefore, the formation of two isomeric substances is possible, the one derived from α-lapachone the other from β-lapachone; and indeed it was subsequently found that the oil analysed was a mixture of these two isomerides. They will in future be referred to as α- and β-*lapachan* respectively.

The reduction product as prepared above was amber coloured

when freshly obtained, but, subsequently, it darkened considerably, even though protected from the light. It does not appear to distil entirely without decomposition at the ordinary atmospheric pressure, and the slight colour of the freshly prepared substance was probably due to this cause. About nine months after preparation, a few perfectly colourless prismatic crystals had formed, whilst by far the larger quantity of oil still remained in a liquid condition. Efforts were then made to obtain enough of the substance in a crystalline condition for analysis, and in view of the theoretical explanation of the reduction process suggested above, α- and β-lapachone were in turn submitted to the action of hydriodic acid and phosphorus. It was thus found that the reduction of α-lapachone gave rise to a substance which crystallised readily, and which was identical with that deposited in crystals from the oil. β-lapachone, on the other hand, gave an oil which could not be obtained in a crystalline condition, and which was recognised by its picrate as being identical with the permanently fluid constituent of the oil obtained by the reduction of lapachol.

A portion of the picrate obtained from the lapachol reduction product was several times recrystallised from alcohol and then analysed.

0·2564 gave 0·5367 CO_2 and 0·1036 H_2O. C = 57·08; H = 4·48.
0·1847 ,, 0·3846 CO_2 ,, 0·0746 H_2O. C = 56·79; H = 4·48.
0·2013 ,, 0·4211 CO_2 ,, 0·0756 H_2O. C = 57·05; H = 4·17.
0·2007 ,, lost ,, 0·0793 H_2O. H = 4·39.
0·2484 ,, 20·8 c.c. moist nitrogen at 19·6° and 761 mm. N = 9·60.
0·1512 ,, 12·3 c.c. ,, ,, 16·2° ,, 771 mm. N = 9·61.
$C_{15}H_{16}O,C_6H_2(NO_2)_3{\cdot}OH$ requires C = 57·14; H = 4·30; N = 9·52 p.c.

Subsequent to the discovery that there are in the lapachol reduction product two distinct substances, a portion of the picrate analysed was carefully examined; it was found to consist entirely of the β-lapachan derivative, the smaller quantity of the corresponding α-lapachan product having been entirely eliminated in the alcoholic mother liquors. In the substance which these deposited on evaporation, the presence of α-lapachan picrate could be readily demonstrated.

Reduction of α-Lapachone.—Twenty grams each of α-lapachone and amorphous phosphorus were gently heated with 110 c.c. of hydriodic acid of sp. gr. 1·5. The action was moderated by occasional withdrawal from the source of heat, and when it appeared to be ended, the temperature was raised to, and maintained at, the boiling point for a few minutes. The resulting oil, after thorough washing with hot water, was dissolved in alcohol and freed from phosphorus by filtration. The α-lapachan present was then converted

by the addition of picric acid (15 grams) into its picrate which separated readily, and was purified by recrystallisation several times from alcohol. Rather more than 10 grams of the picrate was thus obtained in a satisfactory condition, although its colour remained persistently darker than that of the pure substance. From the alcoholic solution of the picrate, α-lapachan was obtained by the addition of sodium hydroxide dissolved in a little water, in quantity theoretically sufficient to combine with the picric acid. It was prepared for analysis by recrystallisation from alcohol, a small quantity of a much less soluble compound being thus removed. The substance first analysed was slightly coloured, treatment with animal charcoal having failed to produce a perfectly white product.

I. 0·2375 gave 0·7336 CO_2 and 0·1573 H_2O. C = 84·24; H = 7·35.
II. 0·1824 „ 0·5657 CO_2 „ 0·1202 H_2O. C = 84·58; H = 7·32.
III. 0·1698 „ 0·5252 CO_2 „ 0·1130 H_2O. C = 84·35; H = 7·39.
$C_{15}H_{16}O$ requires C = 84·90; H = 7·54 per cent.

As the above figures were not entirely satisfactory, the preparation was further purified by distillation with steam, followed by recrystallisation from alcohol. It then melted sharply at 112·5 to 113·5°, was perfectly white, and gave analytical results as follows.

0·1822 gave 0·5655 CO_2 and 0·1255 H_2O. C = 84·64; H = 7·65.

α-Lapachan crystallises in long and remarkably brilliant needles readily soluble in hot alcohol. In concentrated sulphuric acid, it dissolves to a yellow solution: the addition of water produces in this a milkiness which slowly gives way to a formation of microscopic crystals. With picric acid, it combines very readily, the acid changing instantly to bright red on coming in contact with an alcoholic solution of α-lapachan. The picrate crystallises well from alcohol in red needles, being only moderately soluble in the cold: dilute solutions are, however, apt to deposit some crystals of α-lapachan simultaneously with the picrate.

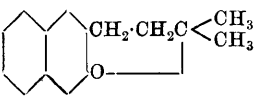
The picrate melts sharply at 140°, and gave the following analytical results.

0·2181 gave 0·4580 CO_2 and 0·0821 H_2O. C = 57·27; H = 4·18.
$C_{15}H_{16}O,C_6H_2(NO_2)_3{\cdot}OH$ requires C = 57·14; H = 4·30 per cent.

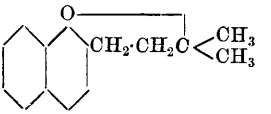
Reduction of β-Lapachone.—This was conducted essentially as previously described for the corresponding α-compound; the resulting oil, still enclosing amorphous phosphorus, was distilled with steam. The β-lapachan, which collected as an oil in the receiver, was filtered off from the water, dissolved in alcohol, and converted into its picrate. After recrystallisation, the latter fused at 143—144°, and was recognised as being identical with the picrate previously

obtained from lapachol, of which analyses are given on page 1366. In spite of the melting point being only 3—4° higher than that of the picrate of α-lapachan, and that in appearance the two are essentially identical, the picrate of β-lapachan can be readily recognised by the intensely blue-green colour which it yields when slightly warmed with concentrated sulphuric acid, a colour which β-lapachan itself develops under the same circumstances, but which in the case of α-lapachan and its picrate is entirely wanting, the last two substances giving only a yellow solution.

In consequence of their mode of formation, the following formulæ must be ascribed to α- and β-lapachan respectively.



α-Lapachan.



β-Lapachan.

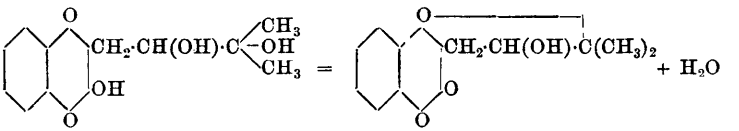
In the foregoing experiments I am indebted for valuable assistance to Mr. H. L. Wood, who undertook the somewhat tedious preparation of the lapachol reduction product, and also made several of the analyses of its picrate.

Action of Sulphuric acid on Dihydroxyhydrolapachol.

If dihydroxyhydrolapachol be dissolved in concentrated sulphuric acid, the solution, at first orange-red, almost instantly passes into a brown, and then more slowly into a dingy purple-red. Action takes place simultaneously in three directions, giving rise to the formation of hydroxy-β-lapachone, isopropylfuran-α-naphthaquinone, and isopropylfuran-β-naphthaquinone.

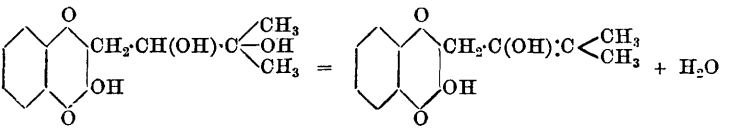
The changes involved are as follows.

I. Hydroxy-β-lapachone is formed,

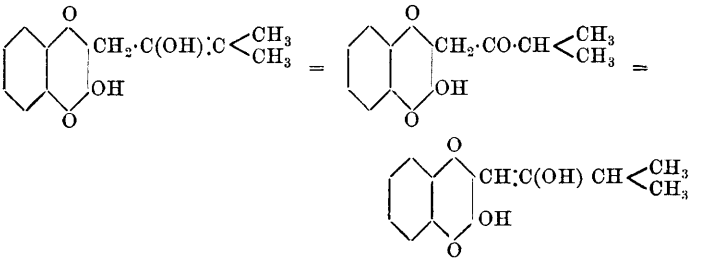


Dihydroxyhydrolapachol. Hydroxy-β-lapachone.

II. Dihydroxyhydrolapachol is converted into hydroxyisolapachol,

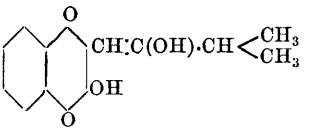


Not isolated.

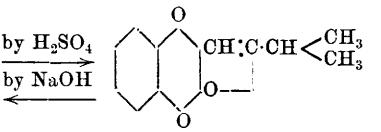
and 

Hydroxyisolapachol.

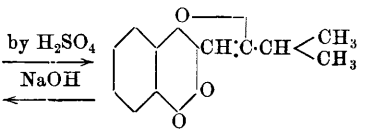
III. Hydroxyisolapachol then gives off water, and is simultaneously converted into its internal α- and β-anhydrides,



Hydroxyisolapachol.

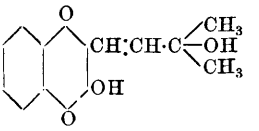


Isopropylfuran-α-naphthaquinone.

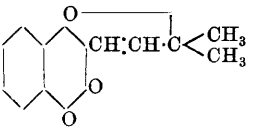


Isopropylfuran-β-naphthaquinone.

Whilst it is not possible to isolate hydroxyisolapachol under the above circumstances, because it so readily undergoes further change, its formation as an intermediate product can be demonstrated by employing sulphuric acid somewhat diluted, but even in this case small quantities only escape further action. That the change into the isopropylfuran-naphthaquinones takes place through the intermediate stage as above shown is further proved by the reconversion of both the anhydrides into the same hydroxyisolapachol by boiling aqueous solutions of the alkalis. The hydroxyisolapachol thus isolated, when submitted to the action of concentrated sulphuric acid is again converted into a mixture of both anhydrides. The above interpretation of the dehydration of dihydroxyhydrolapachol resulting in the formation of hydroxyisolapachol and the isopropylfuran-naphthaquinones, is the only one suggesting itself which is in perfect accord with the whole of the facts accumulated in the study of the compounds of this group. Its acceptance would seem to be rendered necessary by the possibility of converting iso-β-lapachol into hydroxyisolapachol and the isopropylfuran-naphthaquinones (pp. 1360, 1379), and also by the existence of the lomatiols and dehydrolapachone (see following paper), which have most probably the following formulæ respectively.



Lomatiol and isolomatiol.

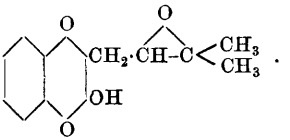


Dehydrolapachone.

Whilst the above changes are those occurring with concentrated sulphuric acid in the cold, there are yet others which are effected by the somewhat dilute acid at the boiling temperature. In this case however, the principal product of the action is isopropylfuran-α-naphthaquinone, small quantities of *hydroxy-α-lapachone* and *anhydrodihydroxyhydrolapachol* being simultaneously formed. The last two products are here met with for the first time.

The relation of hydroxy-α-lapachone to hydroxy-β-lapachone is the same as that existing between α- and β-lapachone, but the methods which are applicable for the conversion of α- into β-lapachone, and *vice versâ*, have failed to produce corresponding changes with the hydroxylapachones.

Anhydrodihydroxyhydrolapachol is formed by the removal of one molecule of water from dihydroxyhydrolapachol; it has consequently the formula $C_{15}H_{14}O_4$, being isomeric with the hydroxylapachones. Its structure is undoubtedly correctly represented as follows.



This may be inferred from the following facts.

I. Anhydrodihydroxyhydrolapachol dissolves in alkaline solutions readily, forms intensely coloured stable salts, and has the properties of a hydroxynaphthaquinone generally; consequently the hydroxyl group attached to the naphthalene nucleus has not been disturbed.

II. It can be dissolved in concentrated sulphuric acid, and precipitated therefrom unchanged. This proves the absence of the original hydroxyl groups attached to the second and third carbon atoms of the side chain, as in the presence of an hydroxyl group at either of these points, an internal anhydride would undoubtedly be formed by exposure to the action of the acid.

Isopropylfuran-α-naphthaquinone.

This compound was first prepared by heating dihydroxyhydrolapachol in acetic acid solution with a small quantity of sulphuric acid. This method of preparation has its disadvantages, and as it was subsequently improved on, it is only given in detail here, because,

in addition to isopropylfuran-α-naphthaquinone, two secondary products were isolated as the result of the action, which have not yet been obtained as satisfactorily in any other way.

Twelve grams of dihydroxyhydrolapachol were dissolved in 100 c.c. of acetic acid, to which 5 c.c. of concentrated sulphuric acid, sp. gr. 1·84, had been previously added. The solution was boiled with a reflux condenser for 20 minutes, during which time it changed in colour from orange to greenish-brown; it was then immediately poured into a large volume of cold water. A dark oily substance was precipitated, which soon commenced to crystallise, and on the following day was readily filtered off. In addition to dark coloured resinous products, the crude substance consisted of a mixture of isopropylfuran-α-naphthaquinone and another compound, fusing point 179·5°, which was subsequently proved to be acetoxy-α-lapachone. These compounds were separated by repeated crystallisation from alcohol, animal charcoal being at first freely used. It was found after the resin had been removed by one or two crystallisations that isopropylfuran-α-naphthaquinone, which crystallises very readily from sufficiently concentrated solutions, first separated. It was thus obtained in heavy needles, from which the supernatant liquid, still retaining the larger quantity of the acetoxy-α-lapachone, was readily poured off. The solution on further standing, deposited both substances, acetoxy-α-lapachone predominating, however, in the mixture. A preliminary separation having been thus effected, no difficulty was encountered in subsequently completely purifying the compounds. The yield of isopropylfuran-α-naphthaquinone amounted to about 33 per cent., and that of acetoxy-α-lapachone to about 6 per cent. of the dihydroxyhydrolapachol employed.

Isopropylfuran-α-naphthaquinone fuses at 110°, and, when absolutely pure, crystallises in canary-yellow needles, but as it is difficult to remove the last traces of colouring matter, the compound as usually obtained is apt to be light brown. From moderately impure solutions, the needles deposited are almost black, and frequently so much shortened that they appear as heavy grains. If a moderately concentrated alcoholic solution be rapidly cooled by immersion in cold water, care being taken not to agitate or otherwise disturb it, the solution apparently solidifies as the compound separates, in pale yellow, flattened needles, grouped together in globular masses. If now a few fragments of the crystals of the compound as ordinarily obtained be dropped upon the surface of the crystalline mass, they gradually increase in size and number at the expense of the more bulky variety, replacing it entirely in the course of a few hours. This change is very striking and characteristic.

Analysis gave the following figures.

0·1617 gave 0·4423 CO_2 and 0·0751 H_2O. C = 74·59; H = 5·16.
$C_{15}H_{12}O_3$ requires C = 75·00; H = 5·00 per cent.

Isopropylfuran-α-naphthaquinone can be distinguished from all the remaining compounds so far obtained from lapachol by the colour of its solution in concentrated sulphuric acid, which is intensely crimson. On dilution, the substance is reprecipitated from the acid unchanged.

Isopropylfuran-α-naphthaquinone is best prepared as follows. 600 c.c. of dilute sulphuric acid (one volume of acid, sp. gr. 1·84, and two volumes of water) are heated to boiling, and then transferred to a flask containing 8 grams of dihydroxyhydrolapachol. A few fragments of a porous tile, &c., are added to prevent the solution from becoming superheated and obviate bumping. A reflux condenser is then adjusted, the heating immediately resumed, and the solution kept briskly boiling for 15 minutes. Hydroxy-β-lapachone appears to be formed as the substance first dissolves, a clear orange-red solution being obtained; as the action is continued, the liquid becomes turbid, an oil separates which gradually darkens, and becomes ultimately greenish-brown. After the boiling has been continued for the required time, the solution is allowed to stand until the dark oily substance has completely crystallised; this is then collected,* washed, and digested for about 24 hours with a 1 per cent. solution of sodium hydroxide, in order to remove small quantities of anhydrodihydroxyhydrolapachol (compare p. 1378). The crude substance is then purified by crystallisation from alcohol, the addition of animal charcoal being desirable. The weight of the purified substance approximates to about half of that of the dihydroxyhydrolapachol employed in its preparation.

Acetoxy-α-lapachone and Hydroxy-α-lapachone.

The compound obtained in the preparation of isopropylfuran-α-naphthaquinone (p. 1371), crystallising from alcohol in pale yellow woolly needles, and fusing at 179·5°, was analysed, with the following results.

0·2044 gave 0·5072 CO_2 and 0·0993 H_2O. C = 67·67; H = 5·39.
0·2058 „ 0·5108 „ „ 0·0995 „ C = 67·69; H = 5·36.
$C_{17}H_{16}O_5$ requires C = 68·00; H = 5·33 per cent.

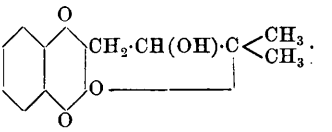
The formation of a compound of the formula $C_{17}H_{16}O_5$ from dihydroxyhydrolapachol is in part due to the action of the acetic acid used as a solvent. Thus,

* The sulphuric acid filtrate, in addition to isopropylfuran-α-naphthaquinone and anhydrodihydroxyhydrolapachol, also contains small quantities of hydroxy-α-lapachone.

I. $C_{15}H_{16}O_5 = C_{15}H_{14}O_4 + H_2O$.

II. $C_{15}H_{14}O_4 + CH_3{\cdot}COOH = C_{15}H_{13}(O{\cdot}CO{\cdot}CH_3)O_3 + H_2O$.

The dihydroxyhydrolapachol is thus first converted into an internal anhydride, which then yields an acetyl derivative; the acetate is yellow, and is derived from the hitherto unknown hydroxy-α-lapachone



The correctness of these conclusions was proved as follows.

I. By the removal of the acetyl group and the isolation of hydroxy-α-lapachone.

II. By the reconversion of hydroxy-α-lapachone into dihydroxyhydrolapachol by the action of a boiling aqueous solution of sodium hydroxide.

III. By the reconversion of the hydroxy-α-lapachone into the acetate fusing at 179·5° by the action of acetic anhydride.

Acetoxy-α-lapachone dissolves in concentrated sulphuric acid, giving an orange-red solution from which, when freshly prepared, the addition of water reprecipitates the compound apparently unaltered. The acid solution, on long standing, however, slowly undergoes a change, and eventually, after a week or two, becomes crimson in colour, doubtless owing to the formation of isopropylfuran-α-naphthaquinone.

The conversion of acetoxy-α-lapachone into hydroxy-α-lapachone cannot be accomplished by dilute caustic soda (1 per cent.), as it was found that in addition to effecting the removal of the acetyl group, the alkali simultaneously opened the side ring, converting the compound into dihydroxyhydrolapachol. From the behaviour of the lapachones previously studied this was to have been expected. Whilst apparently pure, the dihydroxyhydrolapachol obtained did not fuse sharply even after several recrystallisations from alcohol; and the hydroxy-β-lapachone into which it was converted for further identification, whilst also apparently pure, fused through a comparatively wide range. It is therefore probable that the dihydroxyhydrolapachol contained a small quantity of its acetyl derivative.

The acetyl group may be removed from acetoxy-α-lapachone by the action of dilute sulphuric acid. The strength of the acid is of importance, as if too weak, the hydrolysis does not occur, and if too strong, the hydroxy-α-lapachone first formed immediately undergoes further change, and cannot be isolated. After a number of experiments, it was found that good results may be obtained as follows.

For 1 gram of acetoxy-α-lapachone, 150 c.c. of dilute sulphuric acid (1 volume of acid, sp. gr. 1·84, and 3 volumes of water) are used. The substance is ground, and then thoroughly moistened with a small portion of the acid, this being most readily done, by adding a drop or two at a time, to the substance still in the mortar. It is then rinsed with a few c.c. of the acid, kept in reserve for the purpose, into the main portion previously heated to boiling in a vessel provided with a reflux condenser. The heating is continued for precisely six minutes from the time the solution recommences to boil, and if the substance has been carefully ground, it will dissolve almost completely in this time. The solution is now cooled as rapidly as possible, and immediately filtered, being poured back, if necessary, until quite bright. Hydroxy-α-lapachone soon commences to separate in small, bright, yellow crystals, but crystallisation occurs slowly, and is complete after some hours only. 2·02 grams of hydroxy-α-lapachone were obtained from 2·84 of the acetate.

For purification for analysis, the compound was crystallised from alcohol, from which it separates slowly in a rich, yellow crust consisting of numerous small rosettes, fusing at about 187°.

0·1948 gram gave 0·4955 CO_2 and 0·0946 H_2O. C = 69·37; H = 5·39.
$C_{15}H_{14}O_4$ requires C = 69·76; H = 5·42 per cent.

Hydroxy-α-lapachone was reconverted into its acetyl derivative as follows: 0·18 gram was mixed with 0·36 gram of dried sodium acetate, and boiled for a few minutes in a test tube with 5 c.c. of acetic anhydride. The liquid was then poured into water, and the oil which first separated soon solidified to a pale yellow, crystalline substance, which, after crystallisation from alcohol, was recognised by its melting point, 179°, by its crystalline form and other properties, to be the compound sought for.

By the action of dilute alkalis, hydroxy-α-lapachone, like hydroxy-β-lapachone (Trans., 1892, 649) is converted into dihydroxyhydrolapachol. 0·18 gram was boiled for a few minutes with about 13 c.c. of 1 per cent. sodium hydroxide; the substance dissolved readily to a claret coloured solution. Acetic acid was then added in slight excess. No precipitation occurred immediately, but yellow crystals separated slowly on standing, which were found to be identical in all particulars with those of dihydroxyhydrolapachol.

Hydroxy-α-lapachone dissolves in concentrated sulphuric acid in the cold to an orange-red solution. The addition of water discharges most of the colour, leaving the solution yellow, but does not cause the immediate formation of any precipitate; unchanged hydroxy-α-lapachone separates, however, slowly on standing.

Moderate heating with somewhat dilute sulphuric acid converts

hydroxy-α-lapachone into isopropylfuran-α-naphthaquinone, and for this reason it is necessary to carefully follow the directions given above in the preparation of hydroxy-α-lapachone from its acetate, otherwise the substance liberated will undergo this further change. 0·19 gram of hydroxy-α-lapachone was boiled with 10 c.c. of dilute sulphuric acid (acid sp. gr. 1·84, 1 volume, water 2 volumes) for about seven minutes. The substance dissolved to a clear, yellow solution, which soon became turbid. When cold, the partly crystallised, brown deposit was filtered off and purified by crystallisation from alcohol. It was then recognised by its fusing point, 109·5°, by the crimson colour with which it is dissolved in concentrated sulphuric acid, and by crystallising in the two characteristic forms, as isopropylfuran-α-naphthaquinone.

Hydroxyisolapachol.

When isopropylfuran-α-naphthaquinone is boiled with dilute caustic soda, the furfuran ring is opened, and hydroxyisolapachol is formed. The change does not take place as smoothly as in the conversion of the various lapachones into the corresponding hydroxyl compounds, and the action of the alkali is not so energetic.

The operation was conducted as follows: 6 grams of isopropylfuran-α-naphthaquinone were boiled under a reflux condenser with 600 c.c. of a 1 per cent. solution of sodium hydroxide for nearly three hours. The substance first fused, then gradually passed into solution, leaving a solid residue, consisting of a new compound, which did not appear to be further attacked by the alkali. As the highly coloured solution cooled, some unchanged isopropyl-furan-α-naphthaquinone separated, which had probably passed into solution in consequence of the reduction of its quinone group, and which in proportion as air gained access to it was oxidised and reprecipitated.* To complete the oxidation, air was drawn through the cold alkaline solution for two or three hours; the precipitate was then filtered off, and the filtrate acidified with dilute hydrochloric acid. The hydroxyisolapachol which then separated as a curdy precipitate weighed, when dry, about 3·4 grams.

Hydroxyisolapachol is very soluble in alcohol even when dilute. It separates from this solvent in yellow, silky needles, which, when pure, melt at 133·5—134°.

0·2311 gave 0·5893 CO_2 and 0·1119 H_2O. C = 69·54; H = 5·38.
$C_{15}H_{14}O_4$ requires C = 69·76; H = 5·42 per cent.

* The unchanged substance, mixed with the compound above referred to, was again submitted to the action of sodium hydroxide, and this resulted in the further gain of a small quantity, about 0·65 gram, of hydroxyisolapachol.

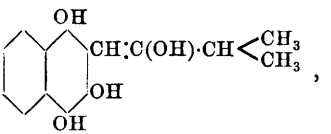
It dissolves readily in dilute alkaline solutions, the colour produced being intermediate in shade between the claret-red of lapachol and the orange-red of β-hydroxy-α-naphthaquinone. The cautious addition of hydrochloric acid to a moderately dilute alkaline solution causes the liquid to set to a pale yellow, jelly-like mass.

Hydroxyisolapachol is dissolved by concentrated sulphuric acid to an orange-red solution, which almost instantly changes to a brown, and ultimately becomes a dark, dull red. 0·25 gram was dissolved in about 5 c.c. of concentrated sulphuric acid, which was allowed to act for about five minutes. The acid was then poured into water. When the resulting orange-red precipitate had become crystalline, the microscope revealed a mixture of yellow and red needles. These were separated by crystallisation from dilute alcohol, and were then recognised by their melting points, crystalline form, and colour reactions with concentrated sulphuric acid as isopropylfuran-α- and isopropylfuran-β-naphthaquinone (see below) respectively.

Isopropylfuran-β-naphthaquinone.

If either dihydroxyhydrolapachol or hydroxyisolapachol be dissolved in concentrated sulphuric acid, isopropylfuran-β-naphthaquinone is formed. In both cases, however, it is only *one* (compare pp. 1368, 1369) of the products of the action, and hence its preparation from either of the above substances by this method is tedious, and the yield small.

If hydroxyisolapachol be reduced to the corresponding hydroquinone,



the anhydride formation still takes place readily. The action, however, under the conditions given below, is almost entirely confined to the hydroxyl group occupying the α-position in the naphthalene nucleus. The resulting compound can then be readily converted by oxidation into isopropylfuran-β-naphthaquinone.

The operation is conducted as follows.

2·5 grams of hydroxyisolapachol is dissolved by the aid of heat in 100 c.c. in acetic acid, and 80 c.c. of water. 2·5 grams of zinc dust, followed by 40 c.c. of dilute hydrochloric acid (3 volumes water and 1 voluume acid, sp. gr. 1·20), are then added, and the solution is boiled under a reflux condenser for five minutes. The excess of zinc is next filtered off, and 0·65 gram of chromic acid dissolved in 25 c.c.

of water added. Red needles of isopropylfuran-β-naphthaquinone commence to separate shortly afterwards.

For analysis, the substance was recrystallised from alcohol until it melted sharply at 94—95°.

0·2096 gave 0·5741 CO_2 and 0·0956 H_2O. C = 74·70; H = 5·07.

$C_{15}H_{12}O_3$ requires C = 75·0; H = 5·0 per cent.

If a small quantity of isopropylfuran-β-naphthaquinone be dissolved in a few drops of acetic acid, a deep, orange-red solution is obtained, which becomes intensely crimson on the addition of a few drops of concentrated sulphuric acid, and as the quantity of sulphuric acid is gradually increased becomes purple, and finally dark green. It is dissolved by concentrated sulphuric acid alone to a rich blue-green solution, from which water, if added soon afterwards, reprecipitates the substance essentially unaltered. The prolonged action of concentrated sulphuric acid gradually, however, produces a change, resulting in the formation, amongst other products, of some isopropylfuran-α-naphthaquinone.

Pseudodehydrolapachone (Paternò's isolapachone), which is isomeric with isopropylfuran-β-naphthaquinone, also develops almost exactly the same shade of green with concentrated sulphuric acid; it may, however, be readily distinguished by the fact that the green passes in a few minutes into a dark purple, whereas no such change occurs with isopropylfuran-β-naphthaquinone. The melting point of the two substances also differs widely, as pseudodehydrolapachone melts at 140—141°. They can, moreover, be readily distinguished by their behaviour with dilute caustic alkalis; in both cases acid substances are formed, but that obtained from isopropylfuran-β-naphthaquinone alone is stable, whilst that to which pseudodehydrolapachone gives rise (compare Trans., 1892, **61**, 623, 624), when liberated from its salts, immediately passes into its internal anhydride.

Dehydrolapachone (see following paper), the red anhydride obtained by Rennie (Trans., 1895, **67**, 792) from lomatiol, has also the formula $C_{15}H_{12}O_3$, being isomeric with the above compounds, but its melting point, 110—111°, as well as the orange-red colour, passing into a brown, developed with concentrated sulphuric acid, serves to distinguish it from them both.

Isopropylfuran-β-naphthaquinone (0·50 gram) was boiled with a 1 per cent. solution of sodium hydroxide (50 c.c.) for about 30 minutes. The crystals fused to a red oil, which gradually decreased in quantity and darkened, until finally little besides small quantities of a blue substance* remained undissolved. The alkaline solution was filtered off from this and acidified with acetic acid. The yellow,

* This was found by microscopic examination to be distinctly crystalline.

curdy, precipitate, consisting of microscopic tufts of needles, weighed 0·37 gram, and after crystallisation from dilute alcohol, was recognised by its melting point and other properties as hydroxyisolapachol.

Isopropylfuran-β-naphthaquinone dissolves in concentrated hydrochloric acid with difficulty, forming a purple solution. Under these circumstances, it is gradually changed, being ultimately converted into the corresponding α-naphthaquinone compound. When action is allowed to take place in the cold, it is possible to demonstrate the presence of an intermediate product soluble in alkalis, and, doubtless, corresponding to chlorhydrolapachol, which was previously shown (Trans., 1892, **61**, 621) to be formed by the action of hydrochloric acid on β-lapachone in its conversion into α-lapachone. The change can be readily effected in an hour or so by digesting the substance in a relatively large quantity of hydrochloric acid, sp. gr. 1·20, at a temperature of about 75°. The isopropylfuran-α-naphthaquinone obtained in this way possessed all the characteristics of that prepared as previously described from dihydroxyhydrolapachol.

Isopropylfuran-β-naphthaquinone, in virtue of its orthoquinone group, gives a characteristic azine with orthotolylenediamine, which crystallises in yellow, silky needles, and melts with decomposition at about 132°, darkening, and showing signs of fusion some degrees lower. The azine is coloured dark green by concentrated sulphuric acid, but the solution, when seen in sufficiently thin films, appears pink; the addition of a small quantity of water precipitates a dull-red salt, which is decomposed on further dilution. The azine undergoes a change when its alcoholic solution is allowed to stand for a few days at the ordinary temperature. The solution becomes darker, and exhibits increased fluorescence, depositing fluffy, orange-red crystals, which develop a carmine colour with concentrated sulphuric acid.

For much valuable experimental assistance in the preceding study of the dehydration of dihydroxyhydrolapachol, I am greatly indebted to Mr. J. G. Walsh, junior, whose painstaking and careful work has greatly contributed to the successful conclusion of this research.

Anhydrodihydroxyhydrolapachol (compare p. 1370).

This substance is formed in small quantity in the preparation of isopropylfuran-α-naphthaquinone from dihydroxyhydrolapachol. In order to isolate it, the latter, in its crude condition, is digested with a weak solution of sodium hydroxide (compare p. 1372). The alkaline extract is acidified with dilute hydrochloric acid, and the resulting precipitate purified by crystallisation several times from alcohol, animal charcoal being at first used. The crude substance, previous to recrystallisation, amounted to only about 4 per cent. of the dihydroxyhydrolapachol.

Anhydrodihydroxyhydrolapachol crystallises in small, yellow tufts of short needles, which fuse at 190·5—191°, and dissolve in alkaline solutions with a rich crimson-red colour; the substance is reprecipitated by acids in a distinctly crystalline condition.

Like all the other lapachol derivatives previously studied, it appears to be perfectly stable in alkaline solution; even after boiling for about five hours with a 1 per cent. solution of sodium hydroxide, the substance had undergone no change.

The following analytical results were obtained.

I. 0·1405 gave 0·3579 CO_2 and 0·0686 H_2O. C = 69·47; H = 5·42.
II. 0·1638 „ 0·4176 CO_2 and 0·0818 H_2O. C = 69·54; H = 5·54.
$C_{15}H_{14}O_4$ requires C = 69·76; H = 5·42 per cent.

Anhydrodihydroxyhydrolapachol dissolves in concentrated sulphuric acid to an orange-red solution, from which, water, if added soon afterwards, reprecipitates the substance essentially unaltered. If, however, the solution, previous to dilution, be allowed to stand for two or three days, the substance appears to be completely changed, and a brown precipitate is then obtained, which differs in its properties from anhydrodihydroxyhydrolapachol, but still remains almost entirely soluble to a red solution in dilute alkalis.

Conversion of Iso-β-lapachol into Isopropylfuran-β-naphthaquinone.

Seven grams of bromine, dissolved in 30 c.c. of chloroform, were gradually added to 10 grams of iso-β-lapachol, dissolved in 65 c.c. of chloroform. The bromine appeared to be completely absorbed, and the solution of iso-β-lapachol became lighter in colour as it was added. The chloroform was at once distilled off from a water bath; the residue, which was resinous, was taken up in 50 c.c. of alcohol. No perceptible quantity of hydrogen bromide passed over with the chloroform, hence an additive product had undoubtedly been formed. The alcoholic solution was allowed to stand eight days at the autumn temperature of the laboratory, during which time it darkened in colour, becoming intensely orange-red; the alcohol was then partially distilled off. During the operation, hydrogen bromide and other pungent fumes passed over. When reduced to a small bulk, water was added to the solution; the dark red resin precipitated was washed and then gently warmed with a small quantity of a 1 per cent. solution of sodium hydroxide, to remove the traces of acid still present; the substance shortly commenced to crystallise. After standing overnight in contact with the alkali, it was crystallised from dilute alcohol; 3·4 grams of beautiful red needles were obtained.

The alcoholic mother liquor was concentrated, but, as no further crystals separated, the substance in solution was again submitted to

the treatment with 1 per cent. sodium hydroxide, above described. This resulted in a gain of an additional gram of the red needles; thus, in all, the yield of the pure substance amounted to 44 per cent. of the iso-β-lapachol used.

For analysis, the substance was again crystallised from alcohol.

I. 0·2516 gave 0·6875 CO_2 and 0·1111 H_2O. C = 74·52; H = 4·90.
II. 0·1489 „ 0·4091 „ „ 0·0669 „ C = 74·93; H = 4·99.
$C_{15}H_{12}O_3$ requires C = 75·00; H = 5·00 per cent.

The substance has thus the composition $C_{15}H_{12}O_3$, and is otherwise identical with isopropylfuran-β-naphthaquinone. It melts at 94—95°, dissolves in concentrated sulphuric acid with a characteristic blue-green colour, is converted by alkalis into hydroxyisolapachol, and by hydrochloric acid into isopropylfuran-α-naphthaquinone; it gives an azine with orthotolylenediamine, melting at about 132°, thus behaving in all particulars similarly to the isopropylfuran-β-naphthaquinone described above, with which it is, beyond all doubt, identical.

Various attempts were made to isolate the intermediate products in a pure condition, but these have not met with success. The crude substance, which is left in a resinous condition on the evaporation of the chloroform (see above), has doubtless the formula

$$C_{10}H_4\begin{cases} O_2 \\ CHBr\cdot CHBr\cdot CH_7. \\ OH \end{cases}$$

This was treated with 1 per cent. sodium hydroxide in the cold; it dissolved slowly and almost completely. From the solution, impure hydroxyisolapachol was precipitated by the addition of acids.

The condensation of β-hydroxy-α-naphthaquinone with isovaleraldehyde, resulting in the formation of iso-β-lapachol, and the further change of the latter under the influence of bromine into a furfuran derivative of β-naphthaquinone, which can then be converted into the corresponding derivative of α-naphthaquinone, would seem to justify the anticipation that we have in these reactions general methods, firstly, for the preparation of alkylene derivatives of hydroxynaphthaquinone, in which the alkylene chain occupies the β-position next to the hydroxyl group, and, secondly, for the conversion of these compounds into furfuran derivatives of both α- and β-naphthaquinone.

This subject is also of interest as being likely to furnish further material for general deductions regarding the formation of internal anhydrides, and the conversion of ortho- into para- and of para- into ortho-quinone derivatives.

In view of these possibilities, I have felt justified in undertaking a further study of these reactions. The results of my experiments will form the subject of a future paper.

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