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.

82 REMSEN STREET
BROOKLYN, N. Y.

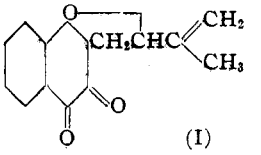
RECEIVED APRIL 3, 1936

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

BY SAMUEL C. HOOKER

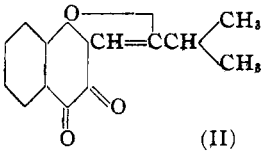
"Isolapachone" was first referred to by Paternò[3] in 1882 in his "Ricerche sull'acido lapacico" (lapachol). It was obtained by the removal of two acetyl groups, followed by spontaneous oxidation, from a compound formed by the action of acetic anhydride and sodium acetate upon lapachol. Seven years later 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)

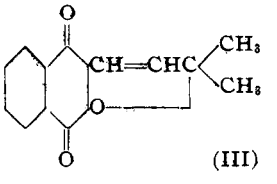
Rennie's Compound



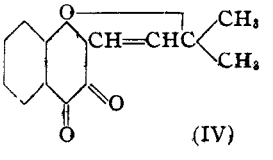
(II)

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).

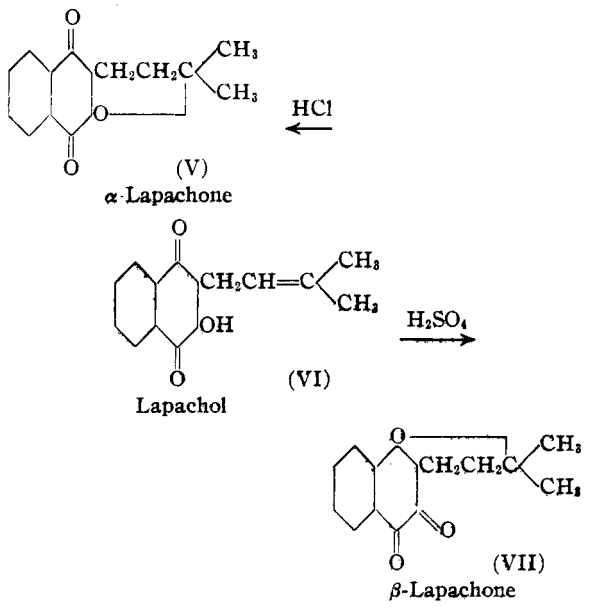
(8) Rennie, *ibid.*, **67**, 786, 792 (1895).

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

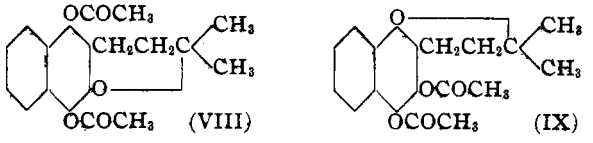
(10) Hooker, THIS JOURNAL, **58**, 1181 (1936).

doned[9] for the reasons stated above, the compound thereafter being referred to as pseudodehydrolapachone. On the basis of the present work the name dehydrolapachone may be assigned to the compound.

When lapachol is submitted to the action of mineral acids it can be converted quantitatively into either α-lapachone or β-lapachone according

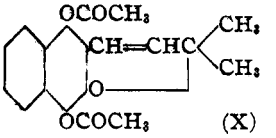


to the conditions under which the experiment is made.[5,7,11] By the action of acetic anhydride in the presence of zinc dust and sodium acetate the lapachones yield the diacetyl derivatives of their hydroquinones, VIII and IX.[4,6] I shall show that no fundamental change has occurred under the in-

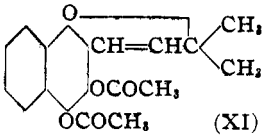


fluence of acetic anhydride, as the removal of the acetyl groups followed by spontaneous oxidation enables the respective lapachones to be again obtained. Now Monti has found[6] that the diacetyl compound from which dehydrolapachone ("isolapachone") was obtained by Paternò can be converted by hydrogenation into VIII, thus substantiating the theory advanced by me.[5] Similarly I have since converted into IX the isomeric diacetyl compound which H. W. Shepard working in my laboratory observed was simultaneously formed when following Paternò's directions for the preparation of the diacetyl compound which he described. Shepard's experiments, mentioned briefly in an earlier communication,[5] are recorded in detail in the experimental part of the present paper. The second diacetyl compound was possibly overlooked by Paternò and by Monti on account of the melting points of both derivatives being almost identical. These compounds can, however, be readily distinguished by their color reactions with concentrated sulfuric acid.

It is evident from the results of the hydrogenations that the isomeric diacetyl compounds must bear the relations to α- and β-lapachone, respectively, which the formulas X and XI indicate.



Paternò's diacetyl compound



Shepard's isomeric compound

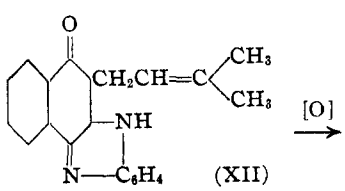
The double bond must occupy the α,β-position in the chain, since no other location is available. It would be natural to expect that these diacetyl derivatives would yield in weak acid solution, followed by spontaneous oxidation, the α- and β-quinones III and IV, respectively, but this is not the case. Only one and the same substance, namely, dehydrolapachone (Paternò's "isolapachone"), has been obtained from each, notwithstanding that the conditions of the experiment have been varied materially. This change, however, is not entirely without precedent as α-lapachone can be converted by the action of sulfuric acid into β-lapachone, and the reverse action can be readily effected with hydrochloric acid.[5] The changes involve the conversion of the α-quinone into the β-quinone group as well as the opening and closing of the side ring. Similarly isopropylfurano-1,2-naphthoquinone (II) can be converted into the corresponding 1,4-naphthoquinone derivative by the action of hydrochloric or sulfuric acid,[7] and still other examples could be cited from my work. Since isomers of this type are not infrequently interconvertible by acids it is not possible to deduce from the above recorded experiments whether dehydrolapachone is a derivative of α- or β-naphthoquinone. Neither does hydrolysis of the diacetyl derivatives in alkaline solution lead to any definite

(11) Monti[6] states that when lapachol is treated with either concentrated sulfuric or hydrochloric acid in the cold β-lapachone is formed, while at higher temperatures α-lapachone is the product, it being entirely a matter of temperature and not of the acid used as was recorded by me.[5] Monti's statements are totally incorrect. On repeating the experiments with lapachol hydrochloric acid was found to give α-lapachone both at room temperature and at 55–60°, while with sulfuric acid β-lapachone was obtained at either 25 or 100°.

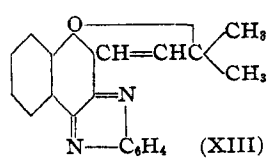
conclusion, as the side ring of compounds of the lapachone type is invariably more or less readily opened by alkalies, leading to the same hydroxynaphthoquinone derivative in both cases.[5]

Since Paternò has showed that dehydrolapachone can be reconverted into the diacetyl compound X from which it was obtained, it is clear that in the removal of the acetyl groups no fundamental change has occurred. This is further demonstrated by the ready conversion, described in the present paper, of dehydrolapachone into α-lapachone by hydrogenation. The following facts therefore would seem to furnish very strong arguments in favor of dehydrolapachone being an α-quinone derivative with the formula III: 1. The diacetyl derivative X can be again obtained from dehydrolapachone. 2. The derivative X can be readily converted by hydrogenation into the diacetyl compound VIII derived from α-lapachone. 3. Dehydrolapachone can be converted directly into α-lapachone (V).

The evidence however is subject to some uncertainty because experiments can be advanced apparently proving almost equally satisfactorily that we are dealing with a derivative of β-napthoquinone. For instance dehydrolapachone gives with *o*-phenylenediamine in good yield an azine (XIII) which can be converted by hydrogenation into the azine of β-lapachone. Also, from lapachol and *o*-phenylenediamine a dark red compound with a metallic reflex can be obtained which has most probably the structure XII,[12] and this



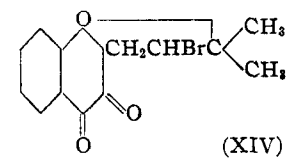
(XII)
Lapeurhodone



(XIII)
Dehydrolapazine

compound, which when treated with concentrated sulfuric acid yields the azine of β-lapachone, is converted into the azine of dehydrolapachone (XIII) by spontaneous oxidation when its ethereal solution is allowed to remain some days in contact with a moderately strong alkaline solution. The change is practically quantitative under proper conditions.

The formation of dehydrolapachone in small quantity in addition to dihydroxyhydrolapachol by the action of dilute sodium hydroxide solution on bromo-β-lapachone (XIV) has already been recorded.[5] At first sight this last method of formation also would seem to suggest the presence of



(XIV)
Bromo-β-lapachone

the β-quinone group, but as the transformation occurred in alkaline solution it is probable that the side ring was opened and again closed on acidifying, but possibly in a different direction.

The several reactions by which dehydrolapachone itself or its derivatives have been obtained lead either to uncertain conclusions or to positively contradictory ones, and the question of whether the compound is an α- or a β-quinone must perhaps remain somewhat uncertain until the isomeric compound has been discovered. The very smooth conversion of dehydrolapachone directly into α-lapachone and also indirectly into the diacetyl derivative of α-lapachone, however, seem to outweigh its conversion into the azine of β-lapachone, as the yield of the intermediate azine of dehydrolapachone, notwithstanding that it is good, nevertheless falls materially below that obtained from other β-quinones in this group. This lower yield may perhaps be due to a preliminary and more or less imperfect change of the α- into the β-quinone before the azine formation occurs.

Perhaps slightly in favor of the α-group, but certainly not at all conclusively so, may also be mentioned the reduction potential determined by Fieser.[13] While this figure varies materially from that of more or less similar heterocyclic α-naphthoquinone substances examined, it falls on the whole better in line with the α-quinones than the β-quinones. The difference, however, is not convincing. The comparison was made by separately averaging the figures given by Fieser for α- and β-naphthoquinone derivatives containing an heterocyclic ring, omitting however the furan derivatives which vary considerably from the other.

It was formerly thought[5] that the orange-red color of dehydrolapachone distinctly favored its

(12) Hooker, *J. Chem. Soc.*, **63**, 1376 (1893).

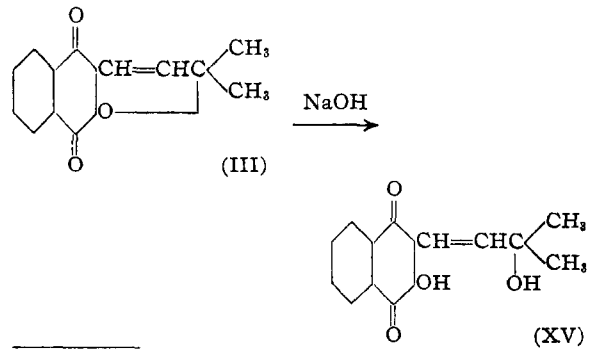
(13) Fieser, THIS JOURNAL, **50**, 450 (1928).

classification as a β-quinone, but in view of the recent recognition that hydroxy-α-naphthoquinone derivatives are usually red or orange-red when they contain a double bond in the α,β-position in the side chain,[14] as is the case with the compound in question, this argument is no longer valid. It would seem, therefore, that the most reliable evidence favors the α-quinone structure III for Paternò's compound and that all of the other observations are capable of being reconciled with this formula.[15]

In regard to the formation of the diacetyl derivatives from which dehydrolapachone is obtained, I am inclined to believe that the first step involved is the closing of the ring through oxidation, the quinone group itself acting as the oxidizing agent. There seems to be a pronounced tendency to form the six-membered ring[10] present in dehydrolapachone, and this can occur only by a shifting of the double bond. The actual mechanism involved must remain in doubt.

Lapachol itself on long standing appears to undergo a corresponding change by spontaneous oxidation and without help from the acetic anhydride. Crude lapachol which had been precipitated from an alkaline extract of Surinam greenheart in 1894 and kept in a wooden box was found after thirty years to be more or less covered with well-formed orange crystals of dehydrolapachone. The crude lapachol after drying had been broken up in moderate sized lumps, and it was in the cavities of these that the crystals had principally formed. In this case there is no positive proof that the dehydrolapachone was really produced directly from lapachol, as it may have had its origin in some other substance present in the crude material, or, as samples of pure lapachol have not been observed to undergo this change, it is also possible that the reaction may have been brought about through the agency of some impurity present. However, in view of the fact that oxidation also occurs in the compound obtained from lapachol and *o*-phenylenediamine (XII) when dissolved in ether and exposed to the air in contact with an alkaline solution, resulting in the azine of dehydrolapachone (XIII), it would seem likely that the orange crystals on the crude lapachol were really derived from lapachol itself.

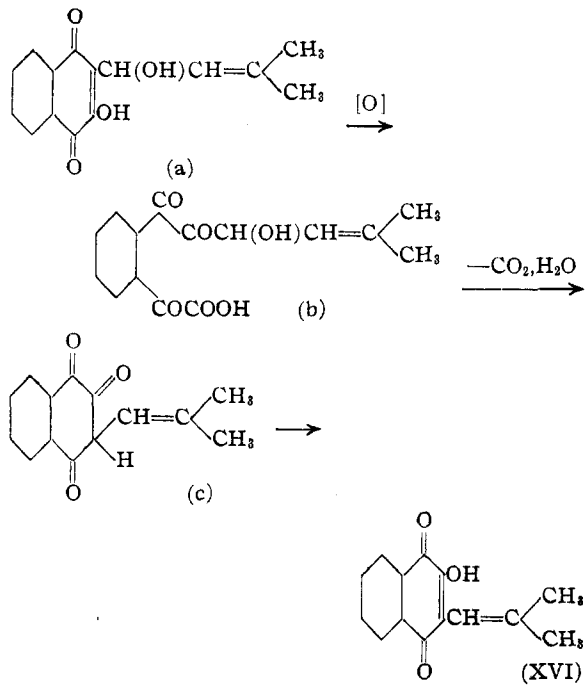
In addition to this type of oxidation, it has been shown in another paper[16] that lapachol is converted by alkaline permanganate in the cold into 2 - β,β - dimethylvinyl - 3 - hydroxy - 1,4 - naphthoquinone (XVI, below), a compound having one less methylene group in the side chain. In the course of the present studies this same substance has been encountered as a product of the oxidation of dehydrolapachone by the air in alkaline solution. As mentioned above, it was found in the earlier work[5] that bromo-β-lapachone is converted by very dilute alkali in part into dehydrolapachone. In repeating the experiment it has now been found that with more concentrated alkali there is formed in place of dehydrolapachone a small amount of the orange-red compound resulting from the permanganate oxidation of lapachol. It seemed likely that dehydrolapachone is formed in all cases along with the main product, dihydroxyhydrolapachol, but that in the more strongly alkaline solution it undergoes further change and is converted by oxidation into the dimethylvinyl compound, and this was established by treating dehydrolapachone directly. When this substance is allowed to stand in contact with cold 10% sodium hydroxide it slowly dissolves to a dark red solution containing the salt of the acidic substance XV. The material which precipitates on acidification consists chiefly of the original substance III in an unchanged condition, but there is present a small percentage of the dimethylvinylhydroxynaphthoquinone XVI. When dehydrolapachone is treated with sodium hydroxide



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

(15) At Dr. Hooker's request in 1931 I tested dehydrolapachone for its ability to form an addition product with sodium bisulfite, a property characteristic of most, if not all, β-quinones. In recently repeated tests it was found that β-lapachone, bromo-β-lapachone and iso-β-lapachone dissolve easily in cold, saturated sodium bisulfite solution when the crystals are crushed to a powder. A colorless, crystalline addition product subsequently separates in each case, and when a dilute solution of the addition product is treated with sodium carbonate the original β-quinone is reprecipitated. Rennie's compound also dissolves in cold bisulfite solution but on adding soda a red solution is obtained, indicating hydrolysis of the side ring. Treated with bisulfite under similar conditions, dehydrolapachone remains undissolved after several hours. The observation supports Dr. Hooker's most recent conclusion (1934) that the substance "almost undoubtedly" is an α-quinone.—L. F. F.

(16) Hooker, THIS JOURNAL, **58**, 1168 (1936).



in the presence of zinc dust, followed by air oxidation of the filtered solution, its conversion into XVI is completed within one hour and a yield of more than 80% can be obtained. The rapidity of the reaction may be due to the fact that the closed ring compound easily passes into solution in the form of the hydroquinone whereas it dissolves very slowly in the absence of the zinc dust.

In the course of this remarkable reaction the double bond migrates to a new position in the chain and a carbon atom is eliminated in the oxidation. In analogy with the recently described[10] conversion of lomatiol into isolomatiol, it appears possible that the migration of the double bond is due to an isomerization of the acidic substance XV to an intermediate of the structure (a). The remaining stages may be accomplished through the opening of the quinone ring (b) and its subsequent closing by oxidation (c), as in the formation of the final product (XVI) in the permanganate oxidation of lapachol.[16,17]

Experimental Part

Preparation of the Diacetyl Compounds X and XI from Lapachol.—A mixture of 40 g. of lapachol, 40 g. of anhydrous sodium acetate and 125 cc. of acetic anhydride was refluxed for fifteen minutes and the resulting green solution was poured into about 1 liter of water. A green oil separated and in the course of a few days it had solidified. After being thoroughly washed and dried, the crude material was fractionally crystallized from alcohol, using 5–6 cc. per gram and employing a liberal quantity of animal charcoal. Needles of Paternò's compound (X) separated first, followed by small crystalline balls of Shepard's compound (XI), the pure, colorless materials being obtained in the following amounts: 20 g. of X and 14 g. of XI. Paternò's compound melted at 131–132°, Shepard's at 128–129°. The first substance (X) dissolves in concentrated sulfuric acid to a light yellowish-green solution which immediately darkens to a deep green with a brownish tinge, while XI gives a garnet color on first contact with the acid and this changes to indigo, or to a very dark green, and finally becomes brown.

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.93; H, 5.52. Found: (X) C, 69.55; H, 5.71; (XI) C, 69.74, 69.73; H, 5.53, 5.57.

Conversion of the Diacetyl Compounds X and XI into α- and β-Lapachone.—Monti[6] hydrogenated Paternò's diacetyl derivative (X) in the presence of palladium and found the product identical with the diacetyl compound VIII, which she prepared by the reductive acetylation of α-lapachone. In the present work Adams catalyst was used for the hydrogenation and the product, obtained in quantitative yield, melted at 169.8–170° and was fully identified by comparison with a sample of VIII prepared according to Monti. Shepard's compound (0.25 g.), XI, hydrogenated in alcoholic solution (35 cc.) using Adams catalyst (thirty minutes), gave colorless crystals (0.21 g.), m. p. at 162–162.6°, which did not depress the melting point of the diacetyl compound IX from β-lapachone prepared according to Monti.

The hydrolysis and oxidation of the saturated diacetyl derivatives VIII and IX was accomplished by dissolving 0.1 g. of the material in 8 cc. of glacial acetic acid, adding to the cooled solution 15 drops of a mixture of 1 cc. of sulfuric acid and 2 cc. of glacial acetic acid, and allowing the solution to stand in an open flask at room temperature for about ten days. On adding 25–60 cc. of water the product was precipitated as an emulsion which became crystalline on standing. The substance obtained from VIII, after recrystallization, melted at 117°, that from IX at 153.5–154°, and these compounds were found identical, by mixed melting point determinations, with α-lapachone and β-lapachone, respectively.

Conversion of the Diacetyl Compounds X and XI into Dehydrolapachone (III).—The hydrolysis and spontaneous oxidation of the unsaturated diacetyl compounds was studied under three sets of conditions, the first of which is the most satisfactory for preparative purposes.

(a) **Sulfuric and Acetic Acids.**—A solution of 2 g. of Shepard's compound (XI) in 25 cc. of warm glacial acetic acid was transferred to a flat dish so as to expose a large surface to the air and 5 cc. of a mixture of one volume of concentrated sulfuric acid with two volumes of water was added to the cooled solution. The solution was allowed to stand uncovered for five days, 40 cc. of glacial acetic acid being added to replace that which evaporated. A small amount of the starting material crystallized at first and later dissolved. Dehydrolapachone was slowly deposited and at the end of the period specified this was collected and purified by crystallization from 80% alcohol, giving 0.44 g. of orange prisms, m. p. 142.5–143°. An additional 0.13 g. of the product was obtained on diluting the acid liquor. The above crystallization of the

(17) Hooker, THIS JOURNAL, **58**, 1174 (1936).

crude material removed a dark brown, granular substance which is insoluble in alcohol and very sparingly soluble in glacial acetic acid. It appears to form a yellow azine with *o*-toluylenediamine.

Treated in the same way, 2 g. of Paternò's diacetyl derivative (X) gave 0.6 g. of dehydrolapachone and none of the brown by-product.

(b) **Aqueous Sodium Hydroxide.**—One gram of either X or XI was finely ground and boiled for about fifteen minutes with 200 cc. of 0.5% sodium hydroxide solution. The solution was filtered from an oily residue (0.23 g.) and on cooling it deposited a reddish oil which soon formed a resinous solid. This was dissolved in hot alcohol and on the addition of water dehydrolapachone was deposited as orange needles. The yields were poor.

(c) **Alcoholic Potassium Hydroxide.**—Ten grams of Shepard's compound (XI) was dissolved in 60 cc. of hot alcohol and the solution was cooled under the tap while 7 g. of solid potassium hydroxide was slowly added and dissolved. A current of air was drawn through the solution for fifteen minutes to ensure complete oxidation to the quinone and the alkali was neutralized with dilute hydrochloric acid (150 cc.). A red oil separated and after several hours it had partially crystallized. The material was removed and allowed to soak with 50 cc. of 1% alkali at room temperature for two days and the solution was poured off and replaced by a fresh portion. The crude residue (4.7 g.) was thoroughly washed with water and crystallized from alcohol, yielding 2.3 g. of pure dehydrolapachone. The combined alkaline extracts on acidification yielded a small amount of 2-β,β-dimethylvinyl-3-hydroxy-1,4-naphthoquinone, which formed orange needles, m. p. 119–120°, from alcohol.

The hydrolysis of Paternò's diacetyl compound (5 g.) by this method proceeded in much the same way, yielding 2.3 g. of crude dehydrolapachone. In the purification small amounts of a colorless and a yellow by-product were observed, but these were not investigated.

Reduction and Hydrogenation of Dehydrolapachone.—Paternò reported[3,4] the conversion of dehydrolapachone by reductive acetylation into the diacetyl derivative X from which he had obtained it, but since he was unaware of the existence of the isomeric compound of Shepard of essentially the same melting point it appeared advisable to repeat the experiment. On boiling for ten minutes a mixture of 0.25 g. of dehydrolapachone, 2.5 g. of zinc dust and 5 cc. of acetic anhydride and pouring the filtered, colorless solution into 30 cc. of water, there was obtained 0.33 g. of product which formed colorless needles, m. p. 130–130.5°, from alcohol. It was found by mixed melting point determination and by the color reaction with sulfuric acid to be identical with Paternò's diacetyl compound X, and there was no indication of the presence of Shepard's compound.

The hydrogenation of dehydrolapachone was conducted in alcoholic solution with Adams catalyst at room temperature for thirty minutes. The filtered solution after exposure to the air was concentrated and the product allowed to crystallize. The material, obtained in 73–80% yield, formed yellow needles, m. p. 117.5–118°, and it was identified as α-lapachone by direct comparison with a known sample. In one experiment the purified product melted at 124.5–125.5° but gave no depression when mixed with a known sample, m. p. 117°, the highest melting point recorded in the literature.

Reductive Acetylation of Isopropylfurano-1,2- and 1,4-naphthoquinone.—Since the isopropylfurano-naphthoquinones[7] such as II are isomeric with dehydrolapachone, they were converted into the diacetyl derivatives of their hydroquinones for comparison with the diacetyl compounds of Paternò and of Shepard. In each case 1 g. of the quinone was refluxed with 20 cc. of acetic anhydride and 10 g. of zinc dust for thirty minutes and the filtered solution was poured into 125 cc. of water. The product crystallized after a few hours and was obtained in each case in quantitative yield. Diacetyl isopropylfurano-1,4-naphthohydroquinone (a) formed colorless needles, m. p. 167–168° from alcohol. It also crystallizes well from glacial acetic acid or benzene. The solution in concentrated sulfuric acid is at first brown, then orange-red and finally a greenish precipitate forms as moisture is absorbed from the atmosphere. Diacetyl isopropylfurano-1,2-naphthohydroquinone (b) crystallizes from alcohol as colorless plates, m. p. 135.5–136.5°. In concentrated sulfuric acid it gives a greenish brown solution changing to dull red on exposure to the air.

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.94; H, 5.52. Found. (a) C, 70.03; H, 5.49; (b) C, 69.34, 69.91; H, 5.37, 5.53:

Dehydrolapazine (XIII).—A mixture of 2 g. of dehydrolapachone, 1.8 g. of *o*-phenylenediamine hydrochloride, 5.4 g. of crystalline sodium acetate and 40 cc. of glacial acetic acid was brought to the boiling point, the solution was filtered to remove salt, and allowed to cool. Dark, shield-shaped crystals of the reaction product separated and were collected after twenty-four hours and washed with alcohol and water and again with alcohol; yield 1.03 g. As examination of the mother liquor showed that it contained unchanged dehydrolapachone it was treated with more of the diamine, yielding an additional 0.4 g. of the azine. The product was purified by crystallization from alcohol and was obtained as brownish yellow scales, m. p. 156.5–157°. The substance imparts to concentrated sulfuric acid a green color which changes to cerise on slight dilution. Its ethereal solution has a strong green fluorescence.

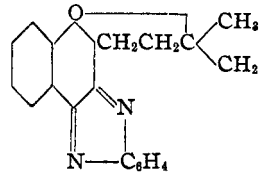
Anal. Calcd. for $C_{21}H_{16}ON_2$: C, 80.76; H, 5.12; N, 8.97. Found (Hooker): C, 80.73; H, 5.43; N, 8.98.

Lapeurhodone (XII).—This was prepared from lapachol (20 g.) by essentially the method described above except that less solvent was employed (200 cc.) and the mixture was heated for two hours on the steam-bath. To this was then added 100 cc. of hot water and on cooling the solution deposited dark prisms of the reaction product. The collected material was washed successively with 50% acetic acid, with water, with 150 cc. of cold 1% alkali to remove unchanged lapachol and with water. The yield was 25.6 g. (97%). The substance crystallized from alcohol in the form of small, diamond-shaped scales with a metallic dark green reflex, m. p. 161.5–162.5°. From acetic acid it crystallizes both in the above form and as wooly, dark magenta colored needles. Cold 1% alkali dissolves the diamond-shaped crystals slowly and the needles more rapidly, giving a bright crimson colored solution. The solution in concentrated sulfuric acid is

bright green, and water precipitates orange crystals of the sulfate.

Anal. Calcd. for $C_{21}H_{18}ON_2$: C, 80.25; H, 5.73; N, 8.91. Found (Hooker): C, 79.86; H, 5.80; N, 9.09.

Lapazine.—



The azine was prepared by each of the following methods and the samples were all compared and found to be identical.

(a) **From β-Lapachone.**—A mixture of 5 g. of the quinone, 13 g. of crystalline sodium acetate, 5 g. of *o*-phenylenediamine hydrochloride and 90 cc. of glacial acetic acid was heated on the steam-bath for two hours and the red-brown solution was diluted with water and allowed to stand overnight, the resulting oil slowly crystallizing during this time. The yellow globular masses of micro scales were washed with 50% acetic acid and with water; yield, quantitative. Crystallized from alcohol, lapazine was obtained either as yellow scales melting at 130.5–131.5°, or as yellow needles which melt at 121.5–122.5° to a clear liquid which then becomes opaque as the temperature rises and finally clears again at 130.5–131.5°. Either variety can be obtained by merely dissolving the crystals in hot alcohol and seeding with the type desired. No difference could be detected in the action of concentrated sulfuric acid on the two varieties, both dissolving to a deep green solution which became orange on slight dilution.

Anal. Calcd. for $C_{21}H_{18}ON_2$: N, 8.91. Found: N, 8.94.

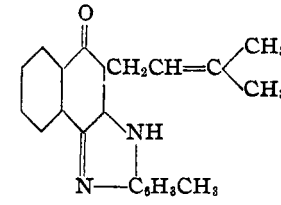
(b) **From Lapeurhodone (XII).**—A solution of 0.1 g. of lapeurhodone in 5 cc. of cold concentrated sulfuric acid was allowed to stand at room temperature for ten minutes and poured into 100 cc. of cold water. A brownish-red, flocculent precipitate formed and on being washed with water it became more crystalline and changed to a yellow color. The yield of lapazine was quantitative.

(c) **From Dehydrolapazine (XIII).**—Dehydrolapazine (0.05 g.) was hydrogenated in alcoholic solution (35 cc.) with Adams catalyst (forty-five minutes) and the filtered solution after exposure to the air was concentrated to a volume of 10 cc. The product, identified as lapazine, was deposited as extremely fine yellow needles mixed with yellow scales, the two forms having the properties recorded above.

Oxidation of Lapeurhodone (XII) to Dehydrolapazine (XIII).—A solution of 5 g. of lapeurhodone in 600 cc. of ether was transferred to a separatory funnel containing 250 cc. of 5% sodium hydroxide. The funnel was plugged with cotton and the mixture let stand at room temperature for eight days. The aqueous layer at the outset gradually turned red in color due to the presence of dissolved lapeurhodone. At the end of the period both layers had become lighter in color, the ether layer developing a strong green fluorescence and depositing some yellow crystals. The aqueous layer was discarded and the ethereal solution on evaporation yielded 3.4 g. of dehydrolapazine. The substance crystallized from alcohol in the form of brownish-yellow scales melting at 156.5–157°. It gave no depression when mixed with the azine from Paternò's dehydrolapachone and gave the same color reactions.

The above change also occurred when a solution of 0.1 g. of lapeurhodone in 20 cc. of 1% sodium hydroxide solution was refluxed for about twenty-four hours, the dehydrolapazine depositing from the alkaline solution as a yellow oil which solidified on cooling. The yield was good but the product was less satisfactory than that obtained by the other method.

Oxidation of Methyllapeurhodone.—Six grams of methyllapeurhodone (from lapachol and *o*-toluylenediamine)[12] was dissolved in 500 cc. of ether, 500 cc. of 5%



sodium hydroxide solution was added and the mixture was allowed to stand in a loosely stoppered flask for two days. Evaporation of the ether layer yielded 4.5 g. of a mixture of yellow needles and yellow scales. The two substances, which appear to be isomers differing in the location of the methyl group, were separated by fractional crystallization from alcohol, the needle-form separating first. The needles melted at 149–151.5°, the scales at 169.5–171.5°. Both substances give a green solution in concentrated sulfuric acid, the solution becoming carmine on dilution and depositing red needles of a salt.

Anal. Calcd. for $C_{22}H_{18}ON_2$: C, 80.98; H, 5.52; N, 8.59. Found: (needles) C, 80.74; H, 5.45; N, 8.55; (scales) C, 81.12; H, 5.60; N, 8.56.

By condensing dehydrolapachone with *o*-toluylenediamine in the usual way and fractionally crystallizing the product from alcohol, two methyldehydrolapazines were obtained having properties identical with those of the compounds described above and giving no depression in melting point when mixed with these substances.

Action of Sodium Hydroxide on Bromo-β-lapachone (XIV). (a) **1% Alkali.**—Finely ground bromo-β-lapachone was allowed to stand at room temperature with 1% sodium hydroxide solution for ten days and the crimson colored solution was filtered from unattacked material and acidified. Orange-yellow crystals of dihydroxyhydrolapachol,[5] m. p. 184–185°, were deposited, and the aqueous mother liquor slowly yielded an additional crop of crystals which were found to consist chiefly of dihydroxyhydrolapachol and an extremely small amount of material insoluble in cold dilute alkali and identified as dehydrolapachone.

(b) **5% Alkali.**—Treated as above, but with stronger alkali, the substance was attacked more rapidly. After one week the alkaline solution was filtered from unchanged material and acidified. The crystalline product consisted of a mixture of dihydroxyhydrolapachol (60–65% by weight) and the lapachol oxidation product XVI (5% by weight), m. p. 119–120°. A separation was accomplished by reprecipitation from an alkaline solution, the oxidation

product separating rapidly while dihydroxyhydrolapachol is deposited slowly.

Conversion of Dehydrolapachone (III) into 2-β,β-Dimethylvinyl-3-hydroxy-1,4-naphthoquinone (XVI). — (a) Finely ground dehydrolapachone was allowed to stand in contact with 10% sodium hydroxide solution at room temperature and after one day the alkaline solution was filtered from unattacked material and acidified. The precipitate consisted largely of dehydrolapachone, but a small amount of an acidic substance was isolated by soaking the crude material with dilute alkali, which leaves the dehydrolapachone largely, if not entirely, undissolved, and reprecipitating with acid. The dimethylvinyl compound XVI was identified by melting point (119–120°), mixed melting point, and by its reaction with concentrated sulfuric acid.

(b) Ten grams of dehydrolapachone was ground to a paste with 200 cc. of water, this was treated with a solution of 50 g. of sodium hydroxide in 300 cc. of water, 50 g. of zinc dust was added and the container was stoppered and shaken at intervals. The substance dissolved within a few minutes owing to its rapid conversion to the hydroquinone, as indicated by the change in the color of the solution from crimson to yellow. After one hour the mixture was poured into 2.5 liters of water, the color changing at once to red and the dilute alkaline solution was filtered to remove the zinc. Air was drawn through the solution for a few minutes to ensure complete oxidation and the solution was then acidified by pouring it into dilute hydrochloric acid (a better product was obtained than when the acid was added to the alkaline solution). The crude material contained some unchanged dehydrolapachone, but this was largely left as a residue on extracting the product with 700 cc. of 0.5% alkali and filtering immediately. On acidification the reddish-purple filtrate yielded 6.7 g. of 2-β,β-dimethylvinyl-3-hydroxy-1,4-naphthoquinone in the form of red prismatic needles. Extraction of the mother liquor gave 1.3 g. more of the material. The purified product melted at 119–120° and was identical with that obtained by the permanganate oxidation of lapachol.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.26. Found: C, 73.49; H, 5.54.

Action of Acetic Anhydride and Sodium Acetate on 2-Allyl-3-hydroxy-1,4-naphthoquinone.—It was observed by Fieser[18] that the allyl compound behaves in the acetylation reaction like lapachol, and he reported the isolation of a substance of m. p. 220–221°, dec., analogous to Paternò's diacetyl compound X. A further investigation of the reaction was undertaken with Dr. Steyermark in the hope of obtaining the parent quinone of which dehydrolapachone (III) is the dimethyl derivative, but the work was not completed. A second isomer, probably corresponding to Shepard's compound XI, was isolated from the reaction mixture by fractional crystallization from alcohol. From 1 g. of the allyl compound there was obtained 0.5 g. of Fieser's diacetyl compound, which after recrystallization melted at 223.5–224.5°, dec., and 0.4 g. of the new compound. The latter formed feather-shaped needles, m. p. 178.5–179.5°.

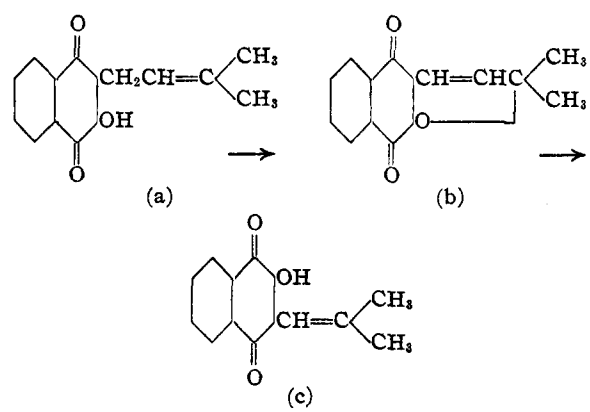
Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.43; H, 4.73. Found: C, 68.71; H, 4.70.

Fieser's compound on acid hydrolysis and exposure to the air gave a red quinone resembling dehydrolapachone, but the substance was not fully characterized.

(18) Fieser, THIS JOURNAL, **48**, 3201 (1926).

Summary

It is shown in this paper that Paternò's "isolapachone" is in reality a dehydro derivative of α-lapachone in which the double bond occupies the α,β-position in the chain. Under certain conditions lapachol (a) or its derivatives can be transformed both directly and indirectly into Paternò's compound (b), or the corresponding derivatives of this substance. The actual mechanism of the



change is still in doubt. Conditions also have been defined under which dehydro-α-lapachone (b) can be transformed by air oxidation in the presence of alkali into a substance (c) previously obtained by the oxidation of lapachol with alkaline potassium permanganate.

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RECEIVED APRIL 3, 1936