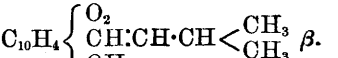
## LVII.—*The Constitution of "Lapachic Acid" (Lapachol) and its Derivatives.*

By SAMUEL C. HOOKER, Ph.D. (Munich).

THE experiments of E. Paternò, published in 1882 (*Gazzetta*, **12**, 337) enabled him to assign to "lapachic acid,"* with a considerable degree of probability, the following formula:—



Amylenehydroxynaphthaquinone.

The formula was mainly deduced from the following observations:—

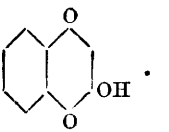
1. "Lapachic acid," on distillation with zinc-dust, yields naphthalene and isobutylene.
2. Oxidation with nitric acid gives rise to the formation of phthalic acid in considerable quantity, showing clearly that all the side groups are situated in the same benzene nucleus.
3. On reduction with hydrogen iodide, a hydrocarbon, having the composition of an amylnaphthalene, is formed, differing from the $\alpha$-amylnaphthylene obtained by Leone (*Gazzetta*, **12**, 209). The amylene chain, therefore, probably occupies the $\beta$-position.

* Lapachic acid is found in a crystalline condition in the grain of a number of South American woods: the lapacho tree, from which the acid derives its name, grows plentifully in the Argentine Republic, yielding a wood which is said to contain as much as 7 per cent. of the acid. The Surinam greenheart, from which the material used in this investigation was mostly obtained, contained a much smaller quantity, probably not more than 1 per cent.

4. "Lapachic acid" forms a monacetyl derivative.
5. Although possessing sufficiently strongly acid properties to expel carbon dioxide from carbonates, experiments failed to reveal the presence of the COOH group.
6. "Lapachic acid," which is yellow, is easily converted by reducing agents into a colourless hydro-derivative. This compound is unstable, absorbs oxygen readily, and becomes reconverted into "lapachic acid."

Although Paternò's experiments did not enable him to decide as to whether lapachol ("lapachic acid") contained the $\alpha$- or $\beta$-quinone group, he expressed himself, in a subsequent publication (*Gazzetta*, **12**, 622), in favour of the former supposition, because lapachone, an isomeric substance, into which lapachol is readily converted, resembled, in his opinion, $\alpha$- rather than $\beta$-naphthaquinone. While Paternò was almost certainly right in assigning the $\alpha$-quinone group to lapachol, his reason for doing so was insufficient, as I shall show that lapachone is a derivative of $\beta$-naphthaquinone, and that, in the conversion of lapachol into lapachone, a change in the quinone group simultaneously occurs. There are, however, several facts which point to the existence of the $\alpha$-quinone group in lapachol, which Paternò has not advanced, and which it may be well at once to refer to:—

1. Lapachol very closely resembles hydroxy-$\alpha$-naphthaquinone (naphthalenic acid), which has the following constitution:—

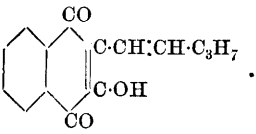



2. Lapachol, like hydroxy-$\alpha$-naphthaquinone, is *yellow*, whereas $\beta$-naphthaquinone and all its simple derivatives are *orange-red*.
3. Lapachol volatilises with steam, although with some difficulty.

It is, therefore, extremely probable that lapachol is a derivative of hydroxy-$\alpha$-naphthaquinone.

All the experiments to be recorded in this paper point directly and indirectly to the correctness of this conclusion, and justify the substitution of the name lapachol.

The evidence available in regard to the position of the double bond in the amylene side-chain, is at present very limited. It is assumed, however, in this paper, as is most probable, that it is situated as shown in the following formula:—



While much light was thrown by Paternò's investigation on the constitution of lapachol, many of its reactions received no satisfactory explanation. One of the most interesting of the changes which it undergoes is that brought about by concentrated sulphuric acid, which converts it, quantitatively, into the isomeric substance, lapachone, which is entirely devoid of acid properties. This change was first explained by Paternò, by the assumption that 2 mols. of lapachol had combined to form one of the isomeric product; but this view was afterwards shown to be untenable by Paternò and Nasini (*Gazzetta*, **19**, 333), in an investigation on Raoult's law, as the molecular weights of lapachol and lapachone were found, experimentally, to be the same. It was not until some time after the publication of these last experiments that the interaction was first satisfactorily explained by Hooker and Greene (*Amer. Chem. J.*, **11**, 395) in a preliminary paper. It was then shown that the change occurred in two stages, as follows:—

$$C_{10}H_4\begin{cases}O_2\\CH{:}CH\cdot C_3H_7\\OH\end{cases} + H_2O = C_{10}H_4\begin{cases}O_2\\CH_2\cdot CH(OH)\cdot C_3H_7\\OH\end{cases}$$

Hydroxyhydrolapachol.

$$= C_{10}H_4\begin{cases}O_2\\CH_2\cdot CH\cdot C_3H_7\\O\end{cases} + H_2O.$$

Lapachone.

The formation of lapachone from lapachol, as shown in the above equations, rendered it extremely probable that several other changes observed by Paternò occurred in a precisely analogous manner. By the action of bromine on lapachol, Paternò obtained a compound which he believed to be a bromo-derivative of the following constitution, $C_{10}H_4\begin{cases}O_2\\CH{:}CH\cdot C_3H_7\\OBr\end{cases}$.

This compound, which is insoluble in alkalis, and can be dissolved in, and reprecipitated from, concentrated sulphuric acid in an unaltered condition, was considered by Hooker and Greene (*Amer. Chem. J.*, **11**, 397) to be a lapachone and not a lapachol derivative, the formation of which could be readily explained as follows:—

$$C_{10}H_4\begin{cases}O_2\\CH{:}CH\cdot C_3H_7\\OH\end{cases} + Br_2 = C_{10}H_4\begin{cases}O_2\\CHBr\cdot CHBr\cdot C_3H_7\\OH\end{cases}$$

Dibromhydrolapachol.

$$= C_{10}H_4\begin{cases}O_2\\CHBr\cdot CH\cdot C_3H_7\\O\text{——}\end{cases} + HBr.$$

Bromolapachone.

In a paper published some months later, Paternò and Minunni (*Gazzetta*, **19**, 601) adopted this explanation of the formation of lapachone, and recorded some additional facts which they believed added to its weight; but, while admitting that the bromolapachone formula for Paternò's so-called bromolapachic acid had some strong points in its favour, they were not prepared to consider it, on the whole, as probable (*Gazzetta*, **19**, 623).

Finally, in a paper published last year (*Gazzetta*, **21**, 374), Paternò and Caberti positively reject the above explanation of the formation of so-called bromolapachic acid, and emphatically assert that the compound cannot be a lapachone derivative. I shall show that Paternò and Caberti have allowed a change which they did not fully understand, and which appeared to be much simpler than was really the case, to mislead their judgment in coming to this decision. The experiments recorded in this paper prove that Paternò's bromolapachic acid is in reality bromolapachone: the compound will, therefore, in future be referred to by the latter name.

The analogy existing between lapachone and bromolapachone is strikingly shown in several reactions: I describe in the following pages the preparation and properties of two compounds obtained by the direct addition of hydrogen chloride and bromide respectively to lapachol, viz.:—

$$C_{10}H_4\begin{cases}O_2\\CH_2\cdot CHCl\cdot C_3H_7\\OH\end{cases},$$

Chlorhydrolapachol.

$$C_{10}H_4\begin{cases}O_2\\CHBr\cdot CHBr\cdot C_3H_7\\OH\end{cases}.$$

Dibromhydrolapachol.

These compounds in contact with concentrated sulphuric acid are converted into lapachone and bromolapachone respectively, thus:—

$$C_{10}H_4\begin{cases}O_2\\CH_2\cdot CHCl\cdot C_3H_7\\OH\end{cases} = C_{10}H_4\begin{cases}O_2\\CH_2\cdot CH\cdot C_3H_7\\O\text{——}\end{cases} + HCl.$$

Lapachone.

$$C_{10}H_4\begin{cases}O_2\\CHBr\cdot CHBr\cdot C_3H_7\\OH\end{cases} = C_{10}H_4\begin{cases}O_2\\CHBr\cdot CH\cdot C_3H_7\\O\text{——}\end{cases} + HBr.$$

Bromolapachone
(Paternò's bromolapachic acid).

Apart from these changes, the importance of which in deciding the point at issue is readily seen, there are others to which I shall now refer, and which are scarcely less satisfactory or convincing. Boiling aqueous potash converts lapachone into hydroxyhydrolapachol, thus:—

$$C_{10}H_4\begin{cases}O_2\\CH_2\cdot CH\cdot C_3H_7\\O\end{cases} + H_2O = C_{10}H_4\begin{cases}O_2\\CH_2\cdot CH(OH)\cdot C_3H_7.\\OH\end{cases}$$

and a precisely analogous change occurs in the case of bromolapachone, which it would be difficult, if not impossible, to explain satisfactorily by Paternò's bromolapachic acid formula.

$$C_{10}H_4\begin{cases}O_2\\CHBr\cdot CH\cdot C_3H_7\\O\end{cases} + 2H_2O = C_{10}H_4\begin{cases}O_2\\CH(OH)\cdot CH(OH)\cdot C_3H_7\\OH\end{cases} + HBr.$$

Bromlapachone. Dihydroxyhydrolapachol.

In order to distinguish between the formulæ

$$C_{10}H_4\begin{cases}O_2\\CH{:}CH\cdot C_3H_7\\OBr\end{cases} \quad \text{and} \quad C_{10}H_4\begin{cases}O_2\\CHBr\cdot CH\cdot C_3H_7,\\O\end{cases}$$

Paternò and Caberti (*Gazzetta*, **21**, 374) submitted the compound to the action of reducing agents, and found that lapachol, and not lapachone, was formed by the removal of the bromine, thus confirming in their mind the correctness of the bromolapachic acid formula. This reaction, while at first sight apparently antagonistic to the bromolapachone theory, is not, however, really so. The changes as they undoubtedly occur are shown in the following equations: lapachol is not formed by the simple removal of the bromine, but is the result of a secondary change. The change takes place in two stages, thus:—

$$C_{10}H_4\begin{cases}O_2\\CHBr\cdot CH\cdot C_3H_7\\O\end{cases} + H_2 = C_{10}H_4\begin{cases}O_2\\CHBr\cdot CH_2\cdot C_3H_7,\\OH\end{cases}$$

$$\text{and } C_{10}H_4\begin{cases}O_2\\CHBr\cdot CH_2\cdot C_3H_7\\OH\end{cases} + KHO = C_{10}H_4\begin{cases}O_2\\CH{:}CH\cdot C_3H_7\\OH\end{cases} + KBr.$$

That this is indeed the true explanation of the reconversion of bromolapachone into lapachol is supported by at least two very important facts: 1. Bromolapachone cannot be converted into lapachol by reducing agents in *acid* solution, as Paternò and Caberti themselves found, the alkali being obviously necessary for the removal of the hydrogen

bromide in the second stage of the change. 2. Lapachone itself can be reconverted into lapachol by an entirely analogous change. Concentrated aqueous hydrochloric acid readily dissolves lapachone, and under proper conditions soon deposits crystals of chlorhydrolapachol:—

$$C_{10}H_4\begin{cases}O_2\\CH_2CH\cdot C_3H_7\\O\end{cases} + HCl = C_{10}H_4\begin{cases}O_2\\CH_2\cdot CHCl\cdot C_3H_7,\\OH\end{cases}$$

and this compound is instantly converted, in part at least,* into lapachol by the action of dilute sodic hydrate:—

$$C_{10}H_4\begin{cases}O_2\\CH_2\cdot CHCl\cdot C_3H_7\\OH\end{cases} + NaOH = C_{10}H_4\begin{cases}O_2\\CH{:}CH\cdot C_3H_7\\OH\end{cases} + NaCl + H_2O.$$

So readily is the hydrogen chloride removed, that the change is instantly effected in the cold by a 1 per cent. solution of sodic hydrate.

Paternò's remaining argument in favour of the formula

$$C_{10}H_4\begin{cases}O_2\\CH{:}CH\cdot C_3H_7\\OBr\end{cases}$$

is based on the formation of bromolapachone by the action of bromine on the acetyl derivative of lapachol. According to Paternò, action occurs as follows:—

$$C_{10}H_4\begin{cases}O_2\\CH{:}CH\cdot C_3H_7\\O\cdot C_2H_3O\end{cases} + Br_2 = C_{10}H_4\begin{cases}O_2\\CH{:}CH\cdot C_3H_7\\OBr\end{cases} + C_2H_3OBr.$$

but it is at once obvious that the change can be explained equally satisfactorily as shown in the equation:—

$$C_{10}H_4\begin{cases}O_2\\CH{:}CH\cdot C_3H_7\\O\cdot C_2H_3O\end{cases} + Br_2 = C_{10}H_4\begin{cases}O_2\\CHBr\cdot CHBr\cdot C_3H_7\\O\cdot C_2H_3O\end{cases}$$

$$= C_{10}H_4\begin{cases}O_2\\CHBr\cdot CH\cdot C_3H_7\\O\end{cases} + C_2H_3OBr.$$

I have already shown in the commencement of this paper that there exist strong reasons for regarding lapachol as a derivative of $\alpha$-naphthaquinone. I shall now enumerate the evidence which is

* Hydroxyhydrolapachol and lapachone are simultaneously formed.

conclusive, showing that lapachone and bromolapachone are derivatives of $\beta$-naphthaquinone.

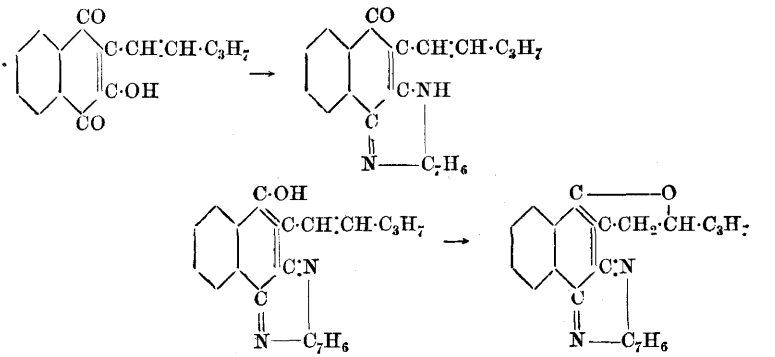
I. Like $\beta$-naphthaquinone, lapachone and bromolapachone are *orange-red* substances, whereas $\alpha$-naphthaquinone, like lapachol, is *yellow*.

II. Lapachone and bromolapachone are readily acted on by orthotoluylenediamine, forming compounds having all the characteristic properties of the azines.*

III. Unlike lapachol, lapachone† and bromolapachone do not volatilise with steam.

IV. Lapachone and bromolapachone are acted on by thiophen and sulphuric acid, giving the characteristic dark-blue compounds similar to those formed under like conditions from orthoquinones (*Gazzetta*, **21**, 377).

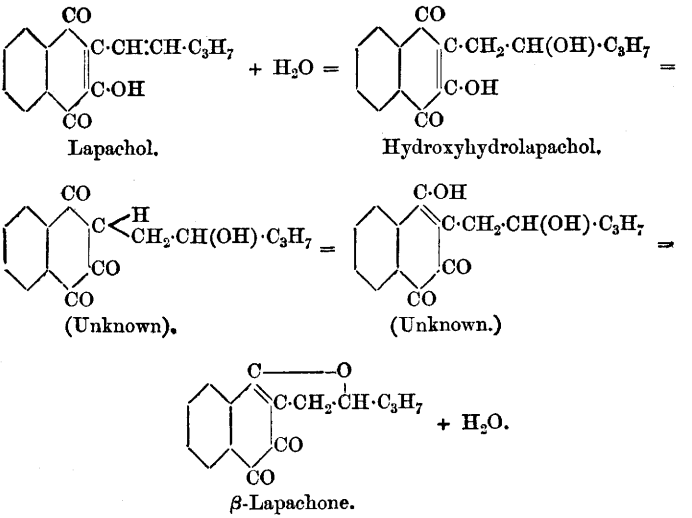
The equations therefore, given above, representing the conversion of lapachol and its derivatives into lapachone and its derivatives, while essentially correct as far as they go, do not express the complete change which really occurs. Thus in the conversion of lapachol into lapachone by the action of concentrated sulphuric acid, the change probably occurs in the following steps:—



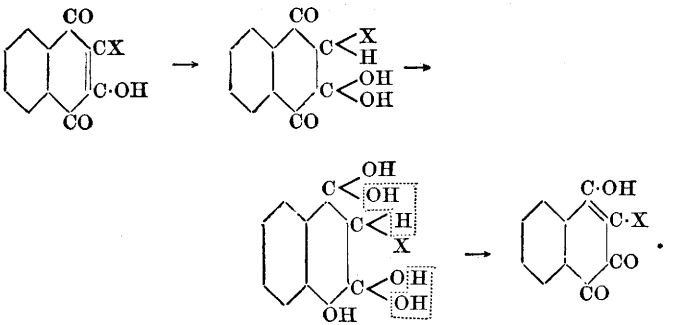
* Lapachol yields a compound with orthotoluylenediamine, which crystallises in red needles. This compound is insoluble in alkalis, but, on boiling with dilute sodic hydrate, is converted into a carmine-red substance, probably an eurhodol, soluble in alkaline solutions in the cold, and capable of forming salts with mineral acids. This substance is apparently converted by the action of concentrated sulphuric acid into the same azine as that derived from $\beta$-lapachone. These changes are probably correctly illustrated as follows:—

These compounds will be studied in detail and described in a subsequent paper.

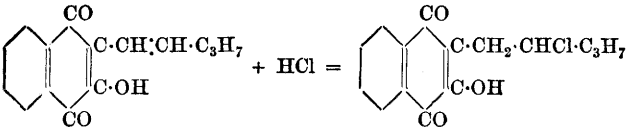
† The distillate obtained, in the case of lapachone, is, however, slightly coloured, but no crystals of lapachone separate. With $\beta$-naphthaquinone, Liebermann and Jacobson (*Annalen*, 211, 69) also obtained a slightly coloured distillate.



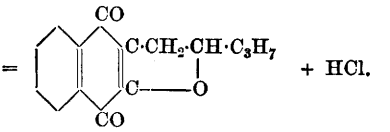

Or possibly the change from hydroxyhydrolapachol to the corresponding $\beta$-quinone derivative involves the addition and subsequent splitting off of water, as follows:—




Starting, therefore, with lapachol, a derivative of $\alpha$-naphthaquinone, it is converted by the action of concentrated sulphuric acid into lapachone, a derivative of $\beta$-naphthaquinone. It will be necessary to refer to this compound in future as *$\beta$-lapachone*, for the reason that by the action of concentrated hydrochloric acid on lapachol an isomeric product, *$\alpha$-lapachone*, may be obtained. The difference in the behaviour of concentrated sulphuric acid and hydrochloric acid is indeed a remarkable one, especially as the reactions take place in both cases apparently quantitatively. The action of the hydrogen chloride is as follows:—



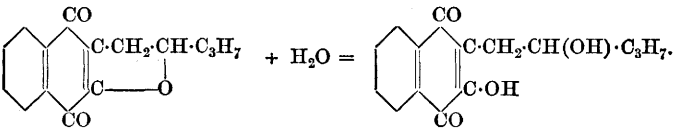
Chlorhydrolapachol.



α-Lapachone.

With concentrated nitric acid,* both α- and β-lapachone are formed; the latter, however, considerably predominates.

The action of boiling alkalis on α- and β-lapachone is extremely interesting. In the case of α-lapachone, the change shown in the following equation occurs:—



α-Lapachone. Hydroxyhydrolapachol.

With β-lapachone, the same hydroxyhydrolapachol is formed†—

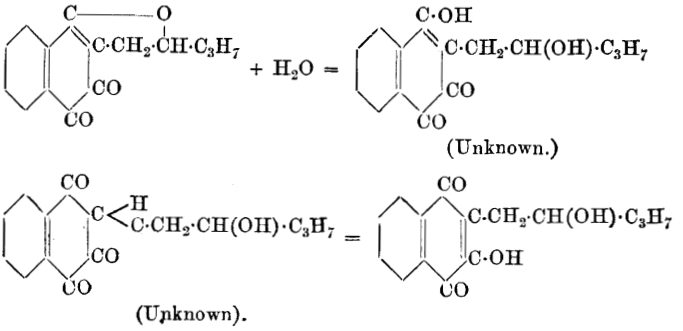
* α-Lapachone was first obtained by Paternò (*Gazzetta*, **12**, 371) in small quantity by the action of nitric acid on lapachol: it was also subsequently obtained in traces by Paternò and Minunni (*Gazzetta*, **19**, 616), and by Paternò and Caberti (*Gazzetta*, **21**, 379) in several reactions, in which hydrogen chloride and lapachol or lapachone had taken part. The compound was found by Paternò to be isomeric with β-lapachone. In his earlier papers, no constitution was assigned to it, but subsequent to the publication of Hooker and Greene's investigation (*Amer. Chem. J.*, **11**, 393) explaining the formation of β-lapachone, Paternò and Minunni suggested a similar method of formation for α-lapachone, thus:—

$$C_{10}H_4\begin{cases}O_2\\ CH{:}CH\cdot C_3H_7\\ OH\end{cases} + H_2O = C_{10}H_4\begin{cases}O_2\\ CH(OH)\cdot CH_2\cdot C_3H_7\\ OH\end{cases}$$

$$= C_{10}H_4\begin{cases}O_2\\ CH\\ O\end{cases}\!\!>CH_2\cdot C_3H_7 + H_2O.$$

As α- and β-lapachone are, however, converted by boiling alkalis into the same acid, it is obvious that this explanation is not the true one.

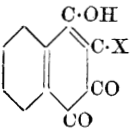
† Nor is this interaction an isolated one: the author has obtained several β-lapachone derivatives, each undoubtedly containing the β-quinone group, and readily convertible by the action of boiling dilute caustic soda or potash into derivatives of lapachol, which, like the latter, contain the α-quinone group.



(Unknown.)

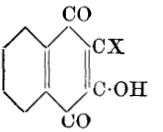
(Unknown).

The conversion of both $\alpha$- and $\beta$-lapachone into the same hydroxyhydrolapachol is in accordance with what appears to be a general rule, namely, that compounds of the general formula



(1)

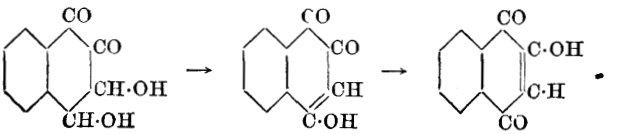
are unstable in contact with alkalis, being rapidly converted into corresponding derivatives of $\alpha$-naphthaquinone having the general formula



(2).

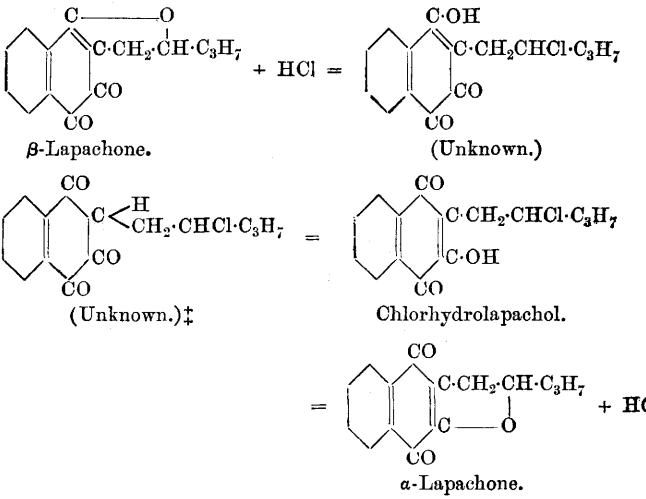
Zincke has shown (*Ber.*, **19**, 2495, 2498) that both $\beta$-bromo- and $\beta$-chloro-$\beta$-naphthaquinone are readily converted into derivatives of $\alpha$-naphthaquinone by the action of dilute caustic alkalis in the cold. In this case, the halogen-$\beta$-naphthaquinone is undoubtedly first oxidised in contact with the alkali, a compound of the general formula (1) given above, being thus produced; and this, in accordance with the rule here laid down, is immediately converted into the corresponding $\alpha$-naphthaquinone derivative.*

* Since this paragraph was written, Zincke has recorded (*Ber.*, **25**, 1171) the conversion of $\alpha$-hydroxy-$\beta$-naphthaquinone into $\beta$-hydroxy-$\alpha$-naphthaquinone by the action of caustic soda, thus giving one more instance in accordance with the above rule. The $\alpha$-hydroxy-$\beta$-naphthaquinone was not isolated, but undoubtedly existed as an intermediate product in the conversion of dihydroxydiketotetrahydronaphthalene into $\beta$-hydroxy-$\alpha$-naphthaquinone, thus :—



While the ease with which lapachol can be converted quantitatively into either $\alpha$- or $\beta$-lapachone is very remarkable, the fact that these two compounds can be converted into each other, also apparently quantitatively, is still more so. If, for instance, $\alpha$-lapachone is dissolved in concentrated sulphuric acid, and the solution allowed to stand for a few minutes, water precipitates $\beta$-lapachone from it. Similarly, if $\beta$-lapachone is dissolved in a comparatively large volume of concentrated hydrochloric acid, $\alpha$-lapachone* is slowly deposited, until finally, after a few days, little or nothing remains in solution.†

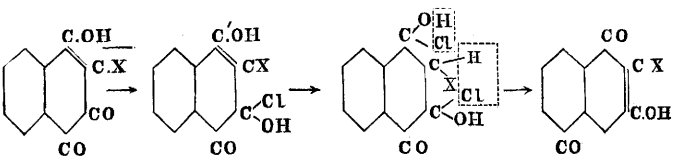
In the conversion of $\beta$-lapachone into $\alpha$-lapachone by hydrogen chloride, I have been fortunate in isolating one of the intermediate products, namely, chlorhydrolapachol,




* By slightly warming the acid solution, the separation may be considerably hastened. The compound actually deposited is $\alpha$-lapachone, $x$HCl, which is immediately decomposed by water into $\alpha$-lapachone and hydrogen chloride. No importance can be attached to the presence of hydrogen chloride in the compound, as $\alpha$-lapachone when immersed in concentrated hydrochloric acid forms the same addition product.

† This remarkable difference in the behaviour of sulphuric and hydrochloric acid is not confined, as I shall show in a subsequent paper, to the action of these acids on $\alpha$- and $\beta$-lapachone, but is common to certain derivatives of these compounds.

‡ The conversion of the $\beta$-quinone into the $\alpha$-quinone group may be possibly effected by the successive addition and elimination of hydrogen chloride, thus:—



The importance of the isolation of chlorhydrolapachol and its subsequent conversion into α-lapachone is self-evident. Proof is thereby furnished that in the transformation of β- into α-lapachone the side ring *is opened*, which is entirely in accordance with the above-given theoretical explanation of the change.

That α-lapachone and β-lapachone are really isomers and not polymeric substances, has been proved by the approximate determination of their molecular weights by Raoult's method. Under precisely similar conditions, the figure 265 was obtained for α-lapachone and 261 for β-lapachone.

Like α-naphthaquinone, α-lapachone is yellow, and volatilises with steam.

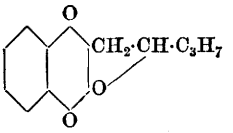
Like β-naphthaquinone, β-lapachone is red, and does not volatilise with steam.

α-Lapachone does not interact with orthotoluylenediamine, but β-lapachone does so readily.

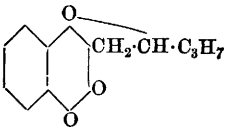
α-Lapachone melts at 117°, β-lapachone at 154°.

The above evidence would seem sufficient to establish the fact absolutely that lapachol and α-lapachone are derivatives of α-naphthaquinone, and that β-lapachone is a derivative of β-naphthaquinone. It is necessary, however, to discuss the matter somewhat more in detail, as the above conclusions do not accord with Paternò's views. Thus, while Paternò gives preference to the α-quinone group for lapachol, he does so, not because of its behaviour, but because of a supposed resemblance of β-lapachone to α-naphthaquinone. Paternò, who has studied the action of hydroxylamine on β-lapachone, was only able to obtain from it a monhydroxime; and as Paternò believed that α-naphthaquinone had only given a monhydroxime, whereas β-naphthaquinone had given a dihydroxime as well, he found in the behaviour of β-lapachone a greater resemblance to that of α- than of β-naphthaquinone. This argument would not, under any circumstances, carry great weight, as Paternò himself realised, but it is deprived of any value whatever by the fact that at the time Paternò wrote (*Gazzetta*, **19**, 622, September, 1889), the dihydroxime of α-naphthaquinone (*Ber.*, **21**, 433, 1888) had, apparently unknown to him, already been discovered.

There is, however, in the work of Paternò, a difficulty apparently more real than the above, which must be explained. By the action of acetic anhydride and sodic acetate on lapachol, Paternò obtained a compound which, on hydrolysis, followed by spontaneous oxidation, gave a quinone (differing from α-lapachone) which he believed to be isomeric with β-lapachone. We have, therefore, β-lapachone and isolapachone most probably, according to Paternò, with the following formulæ, respectively (*Gazzetta*, **19**, 622):—



Formula accepted by Paternò as most probable for $\beta$-lapachone.



Probable formula for isolapachone (Paternò).

It is at once obvious that the existence of an isolapachone, other than $\alpha$-lapachone, bearing the relation to $\beta$-lapachone shown above, is at variance with the theoretical considerations already discussed. It is easy, however, to prove that Paternò's isolapachone is not related to $\beta$-lapachone in this simple way.

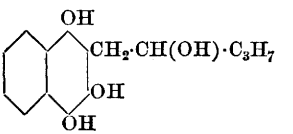
It has been already mentioned that when $\beta$-lapachone is treated with boiling alkalis, it is converted into hydroxyhydrolapachol, as follows :—

$$C_{10}H_4\begin{cases}O_2\\CH_2\cdot CH\cdot C_3H_7\\O\end{cases} + H_2O = C_{10}H_4\begin{cases}O_2\\CH_2\cdot CH(OH)\cdot C_3H_7.\\OH\end{cases}$$

Similarly by the action of boiling alkalis on Paternò's isolapachone an intensely red solution is obtained, containing the salt of an acid substance. That the isolapachone is not simply dissolved unaltered, is proved by the fact that ether, in which the isolapachone is readily soluble, does not extract a trace of this substance from the alkaline solution. Hence, if isolapachone has the formula suggested by Paternò, it is necessary to conclude by analogy that the acid substance existing in the alkaline solution has also the composition

$$C_{10}H_4\begin{cases}O_2\\CH_2\cdot CH(OH)\cdot C_3H_7,\\OH\end{cases}$$

being isomeric with that derived from $\beta$-lapachone, and differing only in the nature of its quinone group and the position of its hydroxyl. On treating the two alkaline solutions with zinc-dust, it is evident that, if reduction occur, the same compound must be obtained from both, namely :—



Experiment has shown, however, that this is not the case. After both the solutions were thoroughly reduced, as shown by the entire loss of their intense red colour, they were filtered off from the zinc-dust, and allowed to oxidise spontaneously by absorbing atmospheric

oxygen. Acetic acid then precipitated hydroxyhydrolapachol from the solution obtained from β-lapachone, and isolapachone unchanged from the other solution, showing that in the latter case the acid substance first formed probably immediately loses water when liberated from its salts, becoming converted into its internal anhydride; be this as it may, the experiment renders it very improbable that isolapachone possesses the formula assigned to it by Paternò.

An examination of Paternò's analyses of the so-called isolapachone reveals the fact that they agree far better with the formula $C_{15}H_{12}O_3$ than with $C_{15}H_{14}O_3$.

| | | | | | Calculated. | |
|---|---|---|---|---|---|---|
| | I. | II. | III. | Mean. | $C_{15}H_{12}O_3$. | $C_{15}H_{14}O_3$. |
| C.... | 74·38 | 75·02 | 74·46 | 74·62 | 75·00 | 74·38 |
| H.... | 4·98 | 5·05 | 5·22 | 5·08 | 5·00 | 5·78 |

It is at first, indeed, difficult to understand why, in the face of such concordant analyses of a compound easy to purify, Paternò should have chosen the latter formula, in which the theoretical hydrogen is 0·7 per cent. higher than the mean of the analytical results. On comparing the analyses of the diacetyl compound from which isolapachone was obtained, there is the same evidence in favour of the formula $C_{15}H_{12}O_3$, but the results, as stated by Paternò and Minunni (*Gazzetta*, **19**, 607), owing to an error in the theoretical figures, are entirely misleading; and it is probably this error, doubtless due to an accidental interchange of figures subsequent to calculation, which led Paternò and Minunni to select the formula making isolapachone isomeric with β-lapachone.

The mean of Paternò's analysis is given as follows:—

$$C = 69{\cdot}68$$
$$H = 5{\cdot}77$$

and above this are given, as the theoretical figures for

$$C_{15}H_{14}O(OC_2H_3O)_2,$$

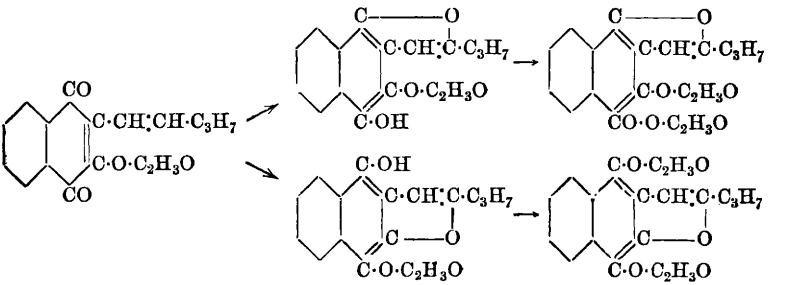
$$C = 69{\cdot}93$$
$$H = 5{\cdot}52$$

These figures are, however, in reality those required for a compound containing two hydrogen atoms less, namely, $C_{15}H_{12}O(OC_2H_3O)_2$.

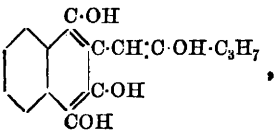
The analyses, therefore, of both isolapachone itself and also of the diacetyl compound show clearly that the substances contain two hydrogen atoms less than are present in the formula assigned to them by Paternò and Minunni. Isolapachone is not, therefore, isomeric with lapachone, and the apparent difficulty is thus entirely removed, which the existence of isolapachone, as such, offered to the

acceptance of the theory advanced in this paper regarding the relations existing between lapachol, $\alpha$-lapachone, and $\beta$-lapachone.

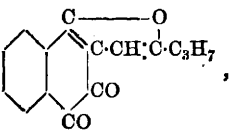
The formation of Paternò's isolapachone can be explained as follows:—By the action of acetic anhydride on lapachol a simple acetyl derivative is first formed, as shown by Paternò (*Gazzetta*, **12**, 358). This compound, in the presence of acetic anhydride and sodic acetate, then probably undergoes the following changes:—



Paternò describes only one acetyl derivative, but Mr. H. W. Shepard, in conjunction with whom I have studied the constitution of isolapachone, has, by following the directions given by Paternò, obtained two isomeric compounds, probably bearing the relation to each other shown in the above formulæ, and, being thus connected in precisely the same way as $\alpha$- and $\beta$-lapachone. On treating the acetyl compounds with caustic alkalis, they both probably yield the same acid substance,



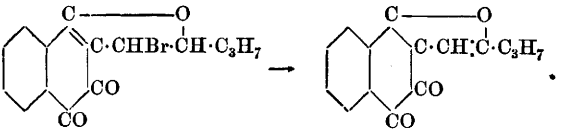
which is, however, spontaneously oxidised, and on acidifying $\beta$-naphthaquinonepropylfurfuran,



the so-called isolapachone is obtained.

That this compound is derived from $\beta$- and not from $\alpha$-naphthaquinone, can be at once inferred from its orange-red colour and its general striking resemblance to $\beta$-lapachone. We have succeeded in obtaining additional experimental evidence in support of the above formula.

By the action of dilute caustic soda on bromo-$\beta$-lapachone, the constitution of which has been fully discussed in the opening pages of this paper, we have obtained, in addition to dihydroxyhydrolapachol, small quantities of Paternò's isolapachone. Thus :—



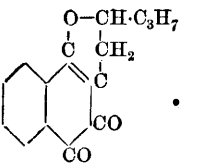
In accepting this formula, the best possible interpretation would seem to be given of the experimental results so far at our disposal; but when it is remembered that not more than 0·8 per cent. of the compound is formed from bromo-$\beta$-lapachone, under the most favourable circumstances, and, further, that all attempts so far made to obtain bromo-$\beta$-lapachone from the so-called isolapachone have failed, the formula must be accepted with some caution until it is based on further experimental evidence. The compound is still being studied in my laboratory, and I shall hope to communicate shortly further details of interest concerning it.

## *Experimental Part.*

The lapachol used in this investigation was principally obtained from Surinam greenheart: a small quantity was also extracted from Bethabarra wood (*Amer. Chem. J.*, **11**, 267).

Surinam greenheart, specially selected from a number of samples for the richness of its yellow grain, was obtained for me from Holland by Messrs. Godfrey S. Saunders and Co., of London, to whom I am much indebted for their trouble and courtesy. The wood, reduced to a fine meal by passage through a disintegrator, was extracted in a 10-gallon percolator essentially as described by the author in conjunction with Dr. Greene in the *American Chemical Journal* (**11**, 268).

Lapachol is formed in small quantity by the action of dilute aqueous alkalis on chlorhydrolapachol (see p. 635); and also by the action of zinc-dust in alkaline solution on bromo-$\beta$-lapachone (see p. 642; *Gazzetta*, **21**, 375).

$\beta$-*Lapachone*, 

In a preliminary paper published in conjunction with Dr. W. H. Greene (*Amer. Chem. J.*, **11**, 395), it was shown that the conver-

sion of lapachol into lapachone (*Gazzetta*, **12**, 372) by the action of concentrated sulphuric acid probably occurs in two stages, but, as already stated in the introduction to this paper, I have since found that the action is far more complicated than was then supposed, owing to a change which takes place in the quinone group.

Although the intermediate product, hydroxyhydrolapachol, cannot be isolated, it can nevertheless be obtained indirectly by the action of boiling aqueous alkalis on β-lapachone. In contact with dilute mineral acids, it is reconverted into β-lapachone. β-Lapachone is also formed by the action of alkalis, or of concentrated sulphuric acid on chlorhydrolapachol (see pp. 634, 635), and further by the action of concentrated sulphuric acid on α-lapachone (see p. 638).

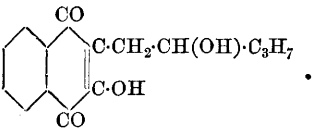
β-Lapachone is best prepared by dissolving 1 part of lapachol in 5 parts of concentrated sulphuric acid essentially as described by Paternò; as soon as dissolution is complete, the whole is poured into a large volume of water. β-Lapachone separates in a crystalline condition, and can be obtained pure by one crystallisation from alcohol. The yield is quantitative.

When crystallised from alcohol, β-lapachone usually separates in heavy needles of a brilliant orange-red colour; it is also occasionally deposited from concentrated solutions in irregular, diamond-shaped plates, the surfaces of which are very much striated. The following properties of β-lapachone have not been given by Paternò. β-Lapachone forms two distinct compounds with ammonia, differing from each other in the colour and stability of their salts. These compounds will be studied somewhat more in detail and described at length in a subsequent paper. β-Lapachone readily dissolves in a warm solution of sodium hydrogen sulphite; white, crystalline leaflets are deposited, from which acids and alkalis liberate the original substance.

Concentrated hydrochloric acid dissolves β-lapachone with great readiness, forming an intensely orange-red solution, from which, if not too dilute, first chlorhydrolapachol, and then α-lapachone, is deposited. If water is added to the freshly prepared solution, β-lapachone is reprecipitated for the most part unchanged.

β-Lapachone darkens gradually when exposed to bright daylight. A few minutes exposure to direct sunlight is sufficient to very materially affect its colour.

*o*-Toluylenediamine and β-lapachone very readily interact in alcoholic solution. The azine thus obtained melts at about 134°; it crystallises readily in bright-yellow needles, and its alcoholic solution exhibits a yellow-green fluorescence. This compound will be described more in detail in a subsequent paper.

*Hydroxyhydrolapachol,* 

The action of aqueous potash on lapachone has been studied by Paternò (*Gazzetta*, **12**, 372) who writes as follows:—"Lapachone does not dissolve in cold aqueous potash of medium concentration; on heating, it dissolves, forming a fine purple-red solution, which, filtered while hot, deposits, on cooling, beautiful, orange needles of silky lustre, recognised by their melting point (154—155°) to be lapachone. On the addition of hydrochloric acid, the alkaline filtrate yields a precipitate, which, purified by recrystallisation, was similarly found to be lapachone."

This statement is incorrect. The facts are these:—Lapachone dissolves with some difficulty in hot aqueous potash, but in so doing undergoes a change. A new acid compound is formed, and this, and not lapachone, exists in the solution obtained. If hydrochloric acid, in very slight excess, is added to the cold alkaline solution, the new compound separates as a yellow oil, which gradually assumes a crystalline form. If, however, a large quantity of hydrochloric acid be employed, the colour of the turbid solution is seen gradually to change. The bright-yellow gives place to orange, and finally red crystals of lapachone may be observed floating in the liquid.

The new compound has, in fact, been reconverted into lapachone by the excess of hydrochloric acid employed. The experiment has been repeated a number of times, but the author has not once observed the separation of crystals of lapachone from the alkaline solution as described by Paternò.

The action of potash on lapachone is shown in the following equation:—

$$C_{10}H_4\begin{cases} O_2\alpha\beta \\ CH_2\cdot CH\cdot C_3H_7 \\ O\!\!-\!\!\alpha \end{cases} + H_2O = C_{10}H_4\begin{cases} O_2\alpha\alpha \\ CH_2\cdot CHOH\cdot C_3H_7. \\ OH\beta \end{cases}$$

β-Lapachone. Hydroxyhydrolapachol.

In order to prepare hydroxyhydrolapachol, 8 grams of lapachone, 4 grams of caustic potash, and 150 c.c. of water are heated together. If the crystals of lapachone be large, they should be first powdered. As the lapachone is dissolved, the colour of the solution becomes very intense, being similar to that of the salts of lapachol.

After boiling several minutes, the solution is filtered to remove any crystals which may have escaped the action of the potash, and an excess of acetic acid is then added. A yellow oil is immediately

precipitated, which collects at the bottom of the beaker, and then appears considerably darker than when first seen in a fine state of division. In the course of an hour or so, it solidifies to a yellow, crystalline mass, which, after some hours, may be separated and washed with water. The compound as thus obtained, though slightly coloured at the surface, is in a very nearly pure condition, and can be rendered pure by crystallisation once or twice from alcohol, in which it dissolves very readily and from which it separates slowly in large, yellow, monosymmetric crystals. The yield is theoretical; 8 grams of lapachone gave 8·4 grams of the crude product; that required by theory being 8·59 grams.

The following figures were obtained on analysis:—

I. 0·1965 gram of substance gave 0·4970 $CO_2$ and — $H_2O$.
II. 0·4932 „ „ 1·2510 $CO_2$ „ 0·2743 $H_2O$.
III. 0·2093 „ „ 0·5306 $CO_2$ „ 0·1160 $H_2O$.

| | Found. | | | Calculated for $C_{15}H_{16}O_4$. |
|---|---|---|---|---|
| | I. | II. | III. | |
| C..... | 68·96 | 69·18 | 69·13 | 69·23 |
| H..... | lost | 6·18 | 6·15 | 6·15 |

Hydroxyhydrolapachol melts at 125°. It is readily soluble in most of the ordinary solvents, from which it crystallises after standing some time; if, however, the solvent be allowed to evaporate rapidly, the acid is left as a yellow oil. Under ordinary conditions, it is a very stable substance, and can be crystallised from acetic acid unchanged; but in contact with dilute mineral acids, it is readily converted into $\beta$-lapachone, which was identified by its fusing point and other properties, and by analysis.

The barium salt is extremely characteristic, separating from a claret-coloured solution in bright *orange*, silky needles, grouped together in wavy tufts. In order to prepare it, the substance was dissolved in a solution of baric hydrate, from which the excess of barium was precipitated at the boiling temperature by means of carbon dioxide. The solution was then concentrated to the crystallising point. As the evaporation proceeded, a film of the salt, in an amorphous condition, and of the *same* colour as the solution, formed at the edge of the liquid, on the evaporating basin. The salt is much more soluble in hot than in cold water. After recrystallisation, the orange needles gave the following figures on analysis:—

I. 0·2152 gram of substance gave 0·0744 $BaSO_4$.
II. 0·2883 „ „ 0·0987 „
III. 0·2478 „ „ 0·0854 „

| | Found. | | | Calculated for | |
|---|---|---|---|---|---|
| | I. | II. | III. | $(C_{15}H_{15}O_4)_2Ba,H_2O$. | $(C_{15}H_{15}O_4)_2Ba$. |
| Ba (p. c.).. | 20·32 | 20·12 | 20·26 | 20·35 | 20·91 |

The above figures were obtained from different preparations, dried over sulphuric acid, and also at 110°.

The salt evidently contains 1 mol. of water of crystallisation, although the attempts to determine this by loss were unsuccessful. Heated at 110° for several hours, no change in weight occurred, and decomposition commenced at somewhat higher temperatures. It was, however, observed that the orange crystals, when rubbed, became dark *magenta-red*, and analysis proved the altered salt, dried at 105—110°, to be anhydrous. Under the microscope, it showed no definite structure, and, when moistened with water, it immediately became *orange*, at the same time swelling up, and then passing into solution. On evaporation, the characteristic orange needles of the salt, as above described, were again obtained.

The anhydrous salt was prepared for analysis by thoroughly grinding the orange crystals, in small quantities at a time, in an agate mortar. The conversion was not easily accomplished, and it seemed as if a resinous substance were being dealt with. The powdered substance was heated at 110° until constant in weight.

I. 0·3368 gram of substance gave 0·1182 $BaSO_4$.
II. 0·2834 „ „ 0·1002 „

| | Found. | | Calculated for |
|---|---|---|---|
| | I. | II. | $(C_{15}H_{15}O_4)Ba$. |
| Ba ..... | 20·63 | 20·78 p. c. | 20·91 p. c. |

The two determinations were made with different preparations.

The calcium salt is entirely different from the barium salt just described. It separates from its solution on evaporation in small, dark-red crystals, and is only very sparingly soluble either in hot or in cold water. After drying over sulphuric acid, it did not lose in weight when exposed for over an hour to a temperature of 105—110°. Analysis shows it to be anhydrous.

I. 0·3113 gram of substance gave 0·0808 $CaSO_4$.
II. 0·2594 „ „ 0·0635 „

| | Found. | | Calculated for |
|---|---|---|---|
| | I. | II. | $(C_{15}H_{15}O_4)_2Ca$. |
| Ca..... | 7·63 | 7·19 p. c. | 7·16 p. c. |

The preparations analysed were different: I was obtained by adding

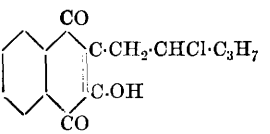
the theoretical quantity of calcium chloride to the slightly ammoniacal solution of the acid; on expelling the excess of ammonia by heat, the salt separated; II was prepared in the same manner as the above described orange variety of the barium salt.

The silver salt was obtained by precipitating a concentrated neutral solution of the ammonium salt with the calculated quantity of silver nitrate. It separates in a semi-resinous condition, becoming granular after some time. It is decidedly soluble in water, also in dilute alcohol, from which it separates, on spontaneous evaporation, in small, dark-red needles. The figures it gave on analysis lie between those required for $C_{15}H_{15}O_4Ag$ and $C_{15}H_{15}O_4Ag + H_2O$. It is probable, therefore, that the compound was not obtained in a pure condition.

Hydroxyhydrolapachol is readily dissolved by concentrated hydrochloric acid; the solution, however, becomes almost immediately turbid, and crystals of chlorhydrolapachol are formed. One gram of the finely powdered substance was added to 10 c.c. of hydrochloric acid, sp. gr. 1·10. The lumps which formed at first were thoroughly broken up with a glass rod. After 10 minutes, the temperature was raised to about 50°, and, 15 minutes from the time of mixing, the substance was thrown on to a funnel provided with a perforated platinum cone, and washed first with concentrated hydrochloric acid, and then with water. The heating must not be prolonged beyond the time given, or $\alpha$-lapachone + $x$HCl (see p. 636) will crystallise out. Rather more than 50 per cent. of the substance operated on was thus obtained as pure chlorhydrolapachol, which, when once crystallised from alcohol, melted sharply at 113°. It will be shown subsequently (p. 637) that chlorhydrolapachol is also formed by the action of concentrated hydrochloric acid on $\beta$-lapachone; but as hydroxyhydrolapachol is much more readily converted into chlorhydrolapachol than $\beta$-lapachone, although the latter dissolves in the concentrated acid with great readiness, the conversion is undoubtedly brought about by the direct interchange of –OH for –Cl, and not by the formation of $\beta$-lapachone in the first stage of the reaction.

Concentrated sulphuric acid dissolves hydroxyhydrolapachol, forming an orange-red solution, from which water precipitates $\beta$-lapachone.

*Chlorhydrolapachol,*




This substance is formed (1) by the direct addition of hydrogen chloride to lapachol; (2) by the action of concentrated hydrochloric

acid on hydroxyhydrolapachol; (3) by the action of the hydrochloric acid on β-lapachone. It is most conveniently prepared directly from lapachol.

Paternò and Caberti (*Gazzetta*, **21**, 379) have studied the action of hydrogen chloride on lapachol. They passed the dry gas through an acetic acid solution of lapachol in the cold, and obtained as a result a mixture of three substances, which they believed to be lapachone, unchanged lapachol, and the substance (α-lapachone) melting at 116—117°, which Paternò (*Gazzetta*, **12**, 371) had previously obtained in small quantity, by the action of concentrated nitric acid on lapachol. Of these three substances, the former was said to predominate, whilst the third-mentioned compound was present in traces only. The substances were not isolated, and were identified only by their appearance under the microscope.

I subsequently made a more thorough study of the action of hydrogen chloride with a view to the isolation of chlorhydrolapachol, the existence of which as an intermediate compound in the conversion of lapachol into lapachone, Paternò does not seem to have suspected. At the time that these experiments were made, the presence of the double bond in the amylene chain had not been demonstrated by the formation of a simple addition compound; the isolation of chlorhydrolapachol was of additional importance on this account.

After numerous trials, the following method of preparation was finally adopted:—

Twenty grams of lapachol are dissolved by the aid of heat in 300 c.c. of acetic acid. The solution is cooled to 50°, and 100 c.c. of concentrated hydrochloric acid, of sp. gr. 1·20, are then added. A precipitate, consisting of unchanged lapachol, is immediately formed, but this speedily redissolves, and crystals of chlorhydrolapachol are gradually deposited. The solution may now be completely cooled, and concentrated hydrochloric acid added at intervals, in small quantities, until 400 c.c. in all have been used. The larger portion of the acid is added to complete the precipitation of the chlorhydrolapachol, which is almost entirely insoluble in acetic acid containing large quantities of hydrochloric acid. It is added gradually, so that better developed crystals may be formed and the subsequent washing of the compound facilitated. As chlorhydrolapachol is, under these conditions, easily resolved into β-lapachone and hydrogen chloride, a considerable quantity of β-lapachone is invariably produced, even under the most favourable circumstances; this, however, remains entirely in solution, β-lapachone being very readily soluble in concentrated hydrochloric acid. The acid having been added, the crystals are thrown on to a funnel containing a plug of glass-wool resting on a platinum cone, and thoroughly washed with the aid of a pump, first

with concentrated hydrochloric acid and then with water; the water must not, however, be used until all the mother liquor has been completely displaced, or otherwise β-lapachone will be precipitated. By following these directions, about 50 per cent. of the weight of the lapachol employed is obtained as chlorhydrolapachol in a very pure form.

As β-lapachone may, under suitable conditions, be converted into chlorhydrolapachol, it seemed desirable to demonstrate that in the method of preparation just described chlorhydrolapachol results from the direct addition of hydrogen chloride to lapachol, and that the latter is not first converted into β-lapachone. On substituting β-lapachone for lapachol and following the directions above given, no chlorhydrolapachol was obtained.

Chlorhydrolapachol was purified for analysis by crystallisation from alcohol; prolonged or unnecessary heating of the alcoholic solution should be avoided, as under such conditions hydrogen chloride is slowly liberated and α- and β-lapachone and other substances are formed. Chlorhydrolapachol usually separates from its alcoholic solution in small, crystalline plates which, when seen in contact with the mother liquor, strikingly resemble in form and external characteristics the crystals of lapachol. When dry, however, the compound lacks the golden tint which pure lapachol exhibits, being more of a canary yellow. In this form the compound undergoes a remarkable change when allowed to remain in contact with its saturated mother liquor; the crystalline plates gradually redissolve and are replaced by irregular bundles of flattened prisms, the change being usually complete in the course of 24 hours or so. Both forms of crystals have the same melting point, 113°. On analysis, the compound gave the following figures:—

I. 0·2489 gram of substance gave 0·5848 gram $CO_2$ and 0·1228 gram $H_2O$.

II. 0·2505 gram of substance gave 0·1276 gram AgCl.

| | Calculated for $C_{15}H_{15}O_3Cl$. | Found. I. | Found. II. |
|---|---|---|---|
| C..... | 64·63 | 64·07 | — |
| H ..... | 5·38 | 5·48 | — |
| Cl..... | 12·74 | — | 12·59 |

If the formulæ of lapachol and hydroxyhydrolapachol have been correctly given in respect to the side chain, the behaviour of chlorhydrolapachol clearly indicates that it has the formula

$$C_{10}H_4\begin{cases}O_2\\CH_2\cdot CHCl\cdot C_3H_7,\\OH\end{cases}$$ and not $$C_{10}H_4\begin{cases}O_2\\CHCl\cdot CH_2\cdot C_3H_7.\\OH\end{cases}$$

Concentrated sulphuric acid dissolves chlorhydrolapachol, forming an intensely orange-red solution, with simultaneous evolution of hydrogen chloride. 0·7 gram was dissolved in 10 c.c. of concentrated sulphuric acid; the solution was allowed to stand 10 minutes, and then poured into a relatively large volume of water; an orange, crystalline precipitate, consisting of a neutral substance, was obtained. Although apparently pure, it did not fuse sharply until three times crystallised from alcohol. Its melting point was then 152—153°. The compound was, therefore, lapachone, which was further identified by conversion into hydroxyhydrolapachol, this, in turn, being recognised by its physical properties and its very characteristic orange barium salt.

Chlorhydrolapachol is slowly decomposed by prolonged heating with alcohol, but is far more readily decomposed on heating with acetic acid. The solution becomes perceptibly darker almost immediately, hydrogen chloride is evolved on boiling, and if the heating be continued for an hour or so, the addition of water produces an orange, crystalline precipitate which no longer reddens potassic hydrate. This precipitate consists of a mixture of two substances, $\alpha$- and $\beta$-lapachone, the former resulting, as will be subsequently shown, from the action of the liberated hydrogen chloride on chlorhydrolapachol. It was found impossible to separate the two substances by fractional crystallisation, owing to the small quantity operated on and the great solubility of both compounds. Advantage was, however, taken of the fact that an alcoholic solution of $\beta$-lapachone very readily yields a sparingly soluble hydroxime, whilst $\alpha$-lapachone, under the same conditions, remains unchanged. The mixed substances were dissolved in sufficient dilute alcohol to retain them in solution even after standing some time. An excess of hydroxylamine hydrochloride was then added and the solution warmed; golden needles of $\beta$-lapachone monohydroxime were soon deposited, which, when once crystallised from alcohol, fused sharply at 166—167°. The mother liquor from which the $\beta$-lapachone hydroxime was filtered off, was slightly diluted with water and allowed to stand for an hour or two; the precipitate, consisting of a mixture of $\beta$-lapachone monhydroxime and $\alpha$-lapachone, was discarded. The solution was again diluted, this time considerably. The yellow crystals collected on the following morning, when once recrystallised from dilute alcohol, melted sharply at 114°, and resembled, in other respects, $\alpha$-lapachone.

The behaviour of chlorhydrolapachol, in contact with dilute caustic alkalis is very instructive, as lapachol, hydroxyhydrolapachol, and $\alpha$- and $\beta$-lapachone are simultaneously formed.

The formation of $\beta$-lapachone, a $\beta$-quinone derivative, from chlorhydrolapachol, unquestionably an $\alpha$-quinone derivative, by the action

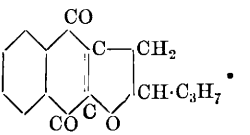
of caustic alkalis, would seem to be an exception to the general rule previously referred to.

Chlorhydrolapachol dissolves readily in dilute caustic potash, giving an intensely red solution which is at first bright, but almost immediately becomes turbid, and rapidly deposits small, orange needles. 1 gram of the finely-powdered substance was treated with 140 c.c. of a cold, 1 per cent. solution of potassic hydrate, and the whole thoroughly stirred for a few minutes. The orange crystals were then collected, and, when dry, were found to be about half the weight of the chlorhydrolapachol taken. The mother liquor, which still remained intensely red, on being acidified with acetic acid, became turbid, and soon deposited a yellow, crystalline substance, which, when purified by recrystallisation from alcohol, melted at 134—137°, and otherwise resembled lapachol, giving its characteristic barium salt. The solution from which lapachol was filtered off was allowed to stand several days, when crystals of hydroxyhydrolapachol were found to have separated. This substance was recognised by its crystalline form, by its melting point, 124°, and by conversion into its barium salt, which, by loss of water of crystallisation, on slight friction changed from bright-orange to dark-red.

Attempts were made to purify the orange needles obtained from the alkaline solution as above described, by recrystallising them from alcohol, but, as after repeating the operation several times the melting point of the substance covered a wide range, a microscopic examination was made which revealed the presence of yellow needles. The two compounds were separated, as described above, by means of hydroxylamine hydrochloride, and $\beta$-lapachone monoxime and $\alpha$-lapachone were obtained.

Concentrated hydrochloric acid in the cold appears to exert little or no action on chlorhydrolapachol, but when heated with it for a short time at about 100° in a sealed tube, a complete conversion into $\alpha$-lapachone is effected. The same change takes place on dissolving the substance in acetic acid containing hydrogen chloride, and heating the solution for about an hour on a water-bath.

*$\alpha$-Lapachone,*




$\alpha$-Lapachone may be conveniently prepared as follows:—2 grams of lapachol are dissolved in a mixture of 20 c.c. of acetic acid and 5 c.c. of concentrated hydrochloric acid, sp. gr. 1·20, and the solution heated on a water-bath for one hour and a quarter; $\alpha$-lapachone is

then precipitated in a crystalline condition by the gradual addition of water to the acid solution. This precipitate, after being washed with water, is partially or completely dried, and redissolved in about 15 c.c. of acetic acid, to which 0·1 gram of chromic acid dissolved in a small quantity of water is added, for the purpose of destroying a trace of colouring matter which it is difficult to remove by crystallisation alone; the solution is then boiled for two or three minutes until quite green, and water is slowly added until the whole of the α-lapachone has crystallised out. α-Lapachone is thus obtained in a very pure condition. The yield is almost quantitative.

The mechanism of the change appears to be the following:—The lapachol is first converted into chlorhydrolapachol, which is then, for the most part, immediately changed into β-lapachone; at higher temperatures, the β-lapachone is slowly reconverted into chlorhydrolapachol, and from this α-lapachone is directly formed. Both β-lapachone and chlorhydrolapachol can be shown to be present in the solution in considerable quantities during the early stage of the change, so that, for the reason given, either of these substances can be substituted for lapachol in the preparation of α-lapachone.

The above method is extremely satisfactory, and succeeds equally well with large or small quantities. α-Lapachone may also be prepared by the following method, which gives almost quantitative results, and is as convenient as that described above.

Five grams of β-lapachone are dissolved in 150 c.c. of concentrated hydrochloric acid, sp. gr. 1·2; the flask containing the solution is loosely corked, and it is then immersed in warm water, the temperature of which is kept at 50° to 55°, for one hour, when it is gradually increased to 65°, and maintained at this point for about half an hour. The separation is then complete, and the solution is filled with yellow crystals consisting of an addition product of α-lapachone and hydrogen chloride; these are thrown on to a funnel containing a perforated platinum cone, and washed first with concentrated hydrochloric acid* and then with water. The addition compound is decomposed by the water, and α-lapachone is thus obtained in minute clusters of microscopic needles. The compound is then once crystallised from alcohol or dilute acetic acid.

Lapachol cannot be substituted for β-lapachone in the method just described, as it is not sufficiently soluble in concentrated hydrochloric acid, action taking place much more readily in a sealed tube at 70—80°.

If in the preparation of α-lapachone from β-lapachone a consider-

* The use of hydrochloric acid for washing is precautionary, as, should there be any unchanged β-lapachone in the mother liquor, this would be precipitated by water, and thus render the α-lapachone impure.

ably smaller quantity of hydrochloric acid than that given above be used, chlorhydrolapachol will crystallise out in the course of a few minutes. Its existence as an intermediate product is thus demonstrated. The formation of chlorhydrolapachol from $\beta$-lapachone is theoretically important, and for this reason the conditions to be observed in obtaining it are given in detail below.

Ten grams of finely-powdered $\beta$-lapachone are dissolved in 20 c.c. of concentrated hydrochloric acid, sp. gr. 1·20, and immediately after mixing, the solution is gently warmed by immersion in warm water, the temperature being kept at 48—52°; the $\beta$-lapachone dissolves very readily to an intensely orange-red solution, and in a few minutes crystalline leaflets begin to separate. When the heating has continued precisely 20 minutes from the moment of mixing, an additional 20 c.c. of concentrated hydrochloric acid is added, and the whole is immediately thrown on to a funnel provided with a platinum cone, and the hydrochloric acid mother liquor filtered off as rapidly as possible. Concentrated hydrochloric acid, in which chlorhydrolapachol is almost insoluble, is freely used to wash out all traces of the mother liquor; the acid is then in turn displaced by water. Rather more than 2 grams are thus obtained in a pure condition. The above directions must be carefully followed or a mixture of chlorhydrolapachol and $\alpha$-lapachone will be obtained. The length of the time of heating is perhaps of the most importance, and should this be increased by two or three minutes, there will be considerable danger of obtaining an admixture of $\alpha$-lapachone. The purity of the compound can be readily tested; it should leave no unchanged yellow particles after being moistened with dilute sodic hydrate, and the crystalline leaflets, subsequent to being thoroughly washed with hydrochloric acid, should remain unchanged on the addition of water. This observation should be made with the aid of the microscope.

In the course of some experiments on the oxidation of $\beta$-lapachone by dilute nitric acid, I have also observed the formation of $\alpha$-lapachone. 1 gram of finely-powdered $\beta$-lapachone was suspended in 200 c.c. of dilute nitric acid, sp. gr. 1·045, the solution boiled for 40 minutes, and then rapidly cooled and filtered; $\alpha$-lapachone separated from the filtrate, but the quantity did not exceed 6 to 7 per cent. of the weight of the $\beta$-lapachone employed.

The formation of $\alpha$-lapachone in small quantity from lapachol by the action of concentrated nitric acid in the cold has already been recorded by Paternò (*Gazzetta*, **12**, 371).

The following analyses show that $\alpha$-lapachone is isomeric with $\beta$-lapachone:—

0·1496 gram of substance gave 0·4062 $CO_2$ and 0·0787 $H_2O$

| | Found. | Paternò found. | Calculated for $C_{15}H_{14}O_3$. |
|---|---|---|---|
| C..... | 74·05 | 74·16 | 74·38 |
| H..... | 5·84 | 5·87 | 5·78 |

The molecular weight of α-lapachone was found by Raoult's method to be 265; this figure represents the mean of two determinations, and agrees sufficiently closely with the formula $C_{15}H_{14}O_3$, which requires a molecular weight of 242.

α-Lapachone melts at 117°. It is readily soluble in most of the ordinary solvents, but only very slightly in water. It crystallises well from dilute acetic acid, and also from alcohol, being deposited as pale-yellow needles. It volatilises with difficulty with steam.

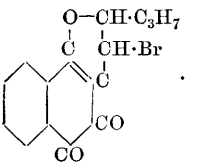
On distillation with zinc-dust, α-lapachone apparently yields the same products as lapachol (Paternò). Heated with acetic anhydride even in the presence of sodic acetate, α-lapachone does not appear to form any acetyl derivative; if sodic acetate is present, greenish, resinous substances are formed. My experiments were conducted at ordinary pressures.

Crystals of α-lapachone become opaque when immersed in concentrated hydrochloric acid, owing to the formation of an addition product. The opaque substance when examined under the microscope is found to be covered with minute crystals, which, on the addition of water, disappear, and are replaced by hair-like needles of α-lapachone. The addition compound also gives off hydrogen chloride when exposed to the air, or when immersed in concentrated sulphuric acid.

Concentrated sulphuric acid dissolves α-lapachone readily, and if water be added immediately, it is, in part at least, reprecipitated unchanged; if, however, the solution be allowed to stand for a few minutes, the α-lapachone is completely converted into β-lapachone.

α-Lapachone is insoluble in alkalis in the cold, but is gradually dissolved by a boiling 1 per cent. solution of sodic hydrate to an intensely coloured solution, somewhat of a claret-red. Acetic acid precipitates from this solution hydroxyhydrolapachol, which is obtained under similar circumstances from β-lapachone.

*Bromo-β-lapachone* (*Paternò's Bromolapachic Acid*),




Paternò obtained his so-called bromolapachic acid by the action of bromine on "lapachic acid" in acetic acid solution (*Gazzetta*, **12**, 353).

In the directions given by him for the preparation of the compound, stress is laid upon the necessity of adding the bromine to the lapachol as rapidly as possible, in order to obtain a good yield. With the constitution which Paternò assigned to bromlapachone, no reason suggests itself for the considerable difference in yield brought about by the slow or rapid addition of the bromine; but, nevertheless, the desirability of observing Paternò's instructions in this respect was confirmed by my own experiments. The same difference was also observed when chloroform was substituted for acetic acid. As soon as the bromlapachone formula suggested itself, the reactions involved became clearer, and the differences brought about by the variation in the method of adding the bromine could be then readily explained.

On the addition of bromine to lapachol, the following action first occurs :—

$$C_{10}H_4\begin{cases}O_2\alpha_1\alpha_1\\ CH{:}CH\cdot C_3H_7\beta\\ OH\beta\end{cases} + Br_2 = C_{10}H_4\begin{cases}O_2\alpha_1\alpha_1\\ CHBr\cdot CHBr\cdot C_3H_7\beta\\ OH\beta\end{cases}$$

$$= C_{10}H_4\begin{cases}O_2\alpha\beta\\ CHBr\cdot CH\cdot C_3H_7\beta\\ O\overset{\alpha}{\frown}\end{cases} + HBr.$$

If the bromine is added slowly, the lapachol is in excess throughout the operation, and the hydrogen bromide which, as the equation indicates, is liberated, will form bromhydrolapachol, which in turn gives off hydrogen bromide, with the formation of $\beta$-lapachone.

$$C_{10}H_4\begin{cases}O_2\alpha\alpha\\ CH{:}CH\cdot C_3H_7\\ OH\beta\end{cases} + HBr = C_{10}H_4\begin{cases}O_2\alpha\alpha\\ CH_2\cdot CHBr\cdot C_3H_7\\ OH\beta\end{cases}$$

$$= C_{10}H_4\begin{cases}O_2\alpha_1\beta_1\\ CH_2CH\cdot C_3H_7\\ O\overset{\alpha}{\frown}\end{cases} + HBr.$$

As the hydrogen bromide is thus regenerated, it is obvious that a very small quantity only is necessary to transform the whole of the lapachol into $\beta$-lapachone; and the extent to which this is effected will depend on the length of time given to the hydrogen bromide to act. Hence, the more slowly the addition of the bromine is brought about, the more $\beta$-lapachone, and consequently the less bromolapachone, will be obtained.

The conversion of lapachol into $\beta$-lapachone can be readily shown by passing dry hydrogen bromide gas through the chloroform solution of lapachol, but it is necessary to guard against an excess of hydrogen bromide, as $\beta$-lapachone may be readily changed by its action into other substances. The perfectly analogous action of hydrogen

chloride has been already described, and in this case it was found possible to isolate the intermediate chlorhydrolapachol, which was subsequently converted into β-lapachone. From the above considerations, it is obvious that in order to reduce the formation of β-lapachone to a minimum, or to prevent it altogether, the bromine, and *not* the lapachol, should be in excess; hence it is desirable to add the lapachol to the bromine, and not bromine to the lapachol. Far better results were obtained after the importance of this was realised, and better results were thus obtained than by brominating in the presence of mercuric oxide.

The following method of preparing bromo-β-lapachone will be found to furnish a considerably larger yield of the compound than that given by Paternò. A solution of 30 grams of lapachol in 400 c.c. of chloroform is added at one operation to 22 grams of bromine in 200 c.c. of chloroform; both solutions should be ice-cold, and it is well to keep the flask containing the bromine immersed in water cooled by ice, until the whole of the lapachol has been added. The flask is then immediately transferred to a water-bath, and the chloroform distilled off completely; the distillation must not be delayed, or the yield of bromolapachone will be diminished; as the chloroform distils over, bromine and hydrogen bromide accompany the first portions. The residue, an orange oil, is dissolved in 75 c.c. of alcohol. In a short time bromo-β-lapachone commences to crystallise out, and after 12 hours or more it is filtered off, and washed with a little alcohol. From 25 to 26 grams are thus obtained in a very pure condition. The mother liquor and alcohol washings are evaporated to about 35 c.c., a crystal of bromo-β-lapachone is then added, and the solution covered to prevent evaporation, and set aside for a day or two to crystallise. From this, the bromo-β-lapachone separates in a dense crystalline mass, upon the surface of which compact yellow rosettes of dibromhydrolapachol are deposited. The crystals of the latter are scraped off as thoroughly as possible, and the partial mechanical separation thus effected renders easy the subsequent purification of the bromolapachone by crystallisation from alcohol. The total yield of bromo-β-lapachone is usually rather more than the weight of the lapachol operated on. It occasionally happens that a small quantity of dibromo-β-lapachone* is deposited from the mother liquor after evaporation, together with the other compounds. Dibromo-β-lapachone is readily distinguished by its physical properties; it is obtained under these conditions as microscopic needles of a light orange colour, which, owing to their slight solubility in alcohol, can be readily separated.

* Mr. A. D. Gray has made a detailed study of the preparation and properties of this compound in my laboratory. The results obtained will shortly be published.

The bromolapachone was first carefully compared with that prepared as directed by Paternò, and in all particulars was found to be identical. A bromine estimation was made, with the following result:—

0·2588 gram of substance gave 0·1502 AgBr.

| | Found. | Calculated for $C_{15}H_{13}BrO_3$. |
|---|---|---|
| Br ..... | 24·69 | 24·92 |

Bromolapachone has been observed by Paternò to separate from its solution in alcohol in orange-red, crystalline plates. While able to confirm this observation, the author has also obtained it, when in a pure condition, crystallised in tufts of fine needles, and the ease with which either form of crystal may be obtained is one of the most striking characteristics of this compound.

The conditions under which both varieties of crystals are formed may be stated generally as follows:—

From slightly impure alcoholic solutions, bromolapachone separates in plates, this being the case whether the solution is allowed to remain at perfect rest or be disturbed while crystallisation is proceeding. From pure concentrated solutions, bromolapachone can be readily obtained in plates by keeping the solution slightly in motion while the compound is crystallising out. If the compound, crystallised in plates and still in contact with its saturated mother liquor, be allowed to stand one or more weeks, the plates will be gradually replaced by tufts of needles. This change is believed to occur only when the compound is in a very pure condition. The observation was first accidentally made, and the experiment was then repeated several times.

Pure solutions protected from dust and allowed to stand absolutely at rest frequently deposit the compound crystallised entirely in tufts of needles. By observing only partially the above conditions, both varieties of crystals may often be obtained in the same solution. A saturated solution can be made to deposit the compound entirely in needles or plates by introducing the desired form of crystal to start crystallisation.

The above remarks apply to all alcoholic solutions of bromolapachone, whether obtained from needles or plates.

The melting points of the two varieties of crystals differ only very slightly, if at all. That of the plates was found to be 138·5°; that of the needles, 138°.

A combustion of the needles gave the following results:—

0·2399 gram of substance gave 0·4932 gram $CO_2$ and 0·0870 gram $H_2O$.

| | Found. | Calculated for $C_{15}H_{13}BrO_3$. |
|---|---|---|
| C ..... | 56·06 | 56·07 |
| H ..... | 4·02 | 4·04 |

Bromo-β-lapachone does not form an addition product with bromine, as it might be expected to do if it were in reality bromolapachol as suggested by Paternò. The author has allowed it to remain for several days in contact with the theoretical quantity of bromine in chloroform solution, but has not observed the formation of any addition compound. Bromolapachone was recovered unchanged.

Bromo-β-lapachone does, however, form unstable addition products with hydrogen chloride and bromide. In order to prepare the bromine compound, bromolapachone is immersed in concentrated aqueous hydrobromic acid, in which it dissolves readily. In the course of a few minutes the addition compound separates in orange needles. The compound may be washed with concentrated hydrobromic acid and dried on a porous plate, but it commences to decompose almost as soon as it is removed from the acid solution, giving off hydrogen bromide, and becoming reconverted into bromo-β-lapachone. The compound is immediately decomposed by contact with water. The chlorine compound is similar, but less easy to prepare, owing to bromo-β-lapachone being much less soluble in hydrochloric than in hydrobromic acid. The very instability of these compounds is sufficient evidence that they are not such as would be required to give support to Paternò's bromolapachol formula; nevertheless it is desirable that their existence should be recorded. The compounds were not analysed.

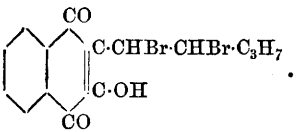
Bromo-β-lapachone is readily converted into lapachol by the action of zinc-dust in alkaline solution (compare Paternò and Caberti, *Gazzetta*, **21**, 374). This is best accomplished as follows:—To 1 gram of finely powdered bromo-β-lapachone small quantities of 10 per cent. sodic hydrate are gradually added, and the substance is simultaneously carefully mixed until the whole is thoroughly moistened and no longer repels the alkaline solution. The quantity of sodic hydrate used is then increased to 15 c.c., and 1 gram of zinc-dust is added. The solution is allowed to stand for about 40 minutes in a loosely corked flask, being slightly agitated at intervals, and is then diluted with about 100 c.c. of water. After the zinc-dust has completely separated, the solution is poured off, and air is drawn through it for an hour or two until thoroughly oxidised. It is then filtered and poured into an excess of dilute hydrochloric acid; lapachol separates entirely free from resin, and equal in quantity to at least 75 per

cent. of the theoretical yield. This action, which is full of theoretical interest, has been already discussed in the opening pages of this paper.

Bromo-$\beta$-lapachone dissolves readily in a warm solution of acid sodic sulphite, from which colourless crystalline leaflets are deposited.

Orthotoluylenediamine and bromolapachone readily react in alcoholic solution: the azine obtained will be described in detail in a subsequent paper.

That the bromine of bromo-$\beta$-lapachone is not situated in the naphthalene nucleus is abundantly proved by the formation of phthalic acid on oxidation (Paternò), and further by the ease with which it is removed by dilute alkalis.

*Dibromhydrolapachol,* 


The yellow substance obtained from the mother liquor in the preparation of bromolapachone (see p. 640), and still mixed with some of the latter, is purified by repeated recrystallisation.* The mixture is dissolved in a small quantity of alcohol, and crystallisation started by the addition of a crystal of bromolapachone or of the dibromo-compound, according as the one or the other of these is present in the larger quantity. It will be found possible by the successive introduction of crystals of the two substances into the same solution to obtain first the one compound and then the other, each in a comparatively pure condition. The mother liquor may then be concentrated by evaporation, and the crystallising operation repeated. After preliminary separation in this manner, no difficulty will be experienced in obtaining the substance quite pure by several recrystallisations from alcohol.

Dibromhydrolapachol as thus prepared forms yellow, crystalline plates closely resembling lapachol and chlorhydrolapachol in appearance. The crystals effloresce, however, on exposure to the air, and were found on analysis to contain alcohol of crystallisation. Only a small portion of the alcohol is lost at ordinary temperatures, and even prolonged exposure at 80° was found insufficient to completely expel it. At 100° the alcohol is all given off.

* Dibromhydrolapachol cannot be separated from the admixed bromolapachone by extraction with sodic or potassic hydrate: even a very dilute solution of the alkali decomposes it with elimination of the bromine.

I. 0·8074 gram of substance heated to 100° until constant in weight lost 0·0291 gram.

II. 0·2403 gram gave 0·3988 gram $CO_2$ and 0·0855 gram $H_2O$.

III. 0·2332 „ 0·2084 „ AgBr.

| | Calculated for $3C_{15}H_{14}Br_2O_3,C_2H_6O$. | Found. I. | II. | III. |
|---|---|---|---|---|
| $C_2H_6O$ ..... | 3·67 | 3·60 | — | — |
| C ..... | 45·04 | — | 45·06 | — |
| H ..... | 3·83 | — | 3·95 | — |
| Br ..... | 38·33 | — | — | 38·02 |

The substance, heated at 100° until constant in weight, was also analysed with the following results:—

I. 0·2278 gram gave 0·3707 gram $CO_2$ and 0·0684 gram $H_2O$.

II. 0·2698 „ 0·2491 „ AgBr.

| | Calculated for $C_{15}H_{14}Br_2O_3$. | Found. I. | II. |
|---|---|---|---|
| C ..... | 44·77 | 44·38 | — |
| H ..... | 3·48 | 3·33 | — |
| Br ..... | 39·80 | — | 39·28 |

Finally, the substance, previously completely purified by crystallisation from alcohol, was dissolved in benzene, and after the addition of light petroleum, set aside to crystallise. It was thus obtained in plates, resembling those deposited from alcohol, but entirely free from alcohol, benzene, &c.

0·2307 gram of substance gave 0·3782 gram $CO_2$ and 0·0742 $H_2O$.

| | Calculated for $C_{15}H_{14}Br_2O_3$. | Found. |
|---|---|---|
| C ..... | 44·77 | 44·70 |
| H ..... | 3·48 | 3·57 |

Dibromhydrolapachol dissolves readily in boiling alcohol, benzene, chloroform, acetone, acetic acid, &c. The crystals deposited from acetic acid, like those from alcohol, effloresce on exposure to the air.

When crystallised from benzene and light petroleum, it melts at 132°; when containing alcohol of crystallisation, the melting point is slightly lower.

Dibromhydrolapachol is formed by the direct addition of bromine to lapachol, thus :—

$$C_{10}H_4\begin{cases}O_2\\CH{:}CH\cdot C_3H_7\\OH\end{cases} + Br_2 = C_{10}H_4\begin{cases}O_2\\CHBr\cdot CHBr\cdot C_3H_7\\OH\end{cases};$$

by far the greater part of the latter, however, is immediately converted into bromo-$\beta$-lapachone with elimination of hydrogen bromide.* This is all the more surprising, as, contrary to expectation, dibromhydrolapachol, in a pure condition, exhibits but a very slight tendency to pass into bromo-$\beta$-lapachone. It might at first be supposed that the hydrogen bromide or bromine present played some important part in bringing about this change; but dibromhydrolapachol has been proved by the experiments given below, to be perfectly stable in contact with these substances in chloroform solution, and hence it is difficult to explain why the transformation into bromo-$\beta$-lapachone occurs.

It is not impossible that the whole of the dibromhydrolapachol first formed may, under the conditions of the experiment, at the moment of formation, pass into bromolapachone; and later, the conditions having changed, that the bromolapachone may be in part reconverted by the hydrogen bromide present, into dibromhydrolapachol, thus :—

$$C_{10}H_4\begin{cases}O_2\\CHBr\cdot CH\cdot C_3H_7\\O\text{—————}\end{cases} + HBr = C_{10}H_4\begin{cases}O_2\\CHBr\cdot CHBr\cdot C_3H_7.\\OH\end{cases}$$

Owing to the readiness with which hydrogen bromide attacks bromolapachone in chloroform solution, with the formation of a variety of products, I have not, so far, been able to obtain any conclusive experimental evidence in corroboration or refutation of this view; but there is an almost exact parallel in the case of chlorhydrolapachol, which can be obtained from, or converted into, $\beta$-lapachone, by the action of hydrochloric acid under varying conditions.

A small quantity was dissolved in chloroform, and hydrogen bromide passed through the solution, the light-yellow colour of which remained unchanged: there was no indication of the formation of bromo-$\beta$-lapachone.

The solution, saturated with hydrogen bromide, was still yellow, after standing 12 hours, and the residue left on the evaporation of

* Only about 3 per cent. of the lapachol used in the preparation of bromo-$\beta$-lapachone was obtained as dibromhydrolapachol. Many variations were made in the method of brominating without increasing the yield. The presence of mercuric oxide exerted no beneficial effect.

the chloroform was completely soluble in dilute sodic hydrate, and hence contained no bromo-$\beta$-lapachone.

A solution of 0·33 gram of bromine in 10 c.c. of chloroform was gradually added to 0·83 gram of dibromhydrolapachol (the whole at that time available), also dissolved in 10 c.c. of chloroform. The solution was set aside to evaporate spontaneously; the residue once crystallised from alcohol was recognised as the unchanged substance by its melting point, by its solubility in dilute sodic hydrate, and other properties.

Concentrated sulphuric acid dissolves dibromhydrolapachol to an orange-red solution, and slowly converts it, with evolution of hydrogen bromide, into bromo-$\beta$-lapachone, thus:—

$$C_{10}H_4\begin{cases}O_2\alpha_1\alpha_1\\ CHBr\cdot CHBr\cdot C_3H_7\\ OH\beta\end{cases} = C_{10}H_4\begin{cases}O_2\alpha\beta\\ CHBr\cdot CH\cdot C_3H_7\\ O\overline{\quad\alpha}\end{cases} + HBr.$$

0·5 gram was dissolved in 2 c.c. of concentrated sulphuric acid; the solution soon commenced to fume slightly, but the evolution of hydrogen bromide was not sufficiently rapid to cause the formation and escape of bubbles of the gas. Soon after the compound had completely dissolved, the sulphuric acid solution was poured into about 100 c.c. of water. An orange-coloured precipitate formed, which collected into a lump, and soon hardened; this proved to be the unchanged substance, accompanied by a small quantity of an orange compound, and when once crystallised from alcohol it melted sharply at 130—131°. It was redissolved in about the same quantity of concentrated sulphuric acid, and this time allowed to stand 16 hours; when poured into water, an orange precipitate was formed, which became crystalline on standing. Crystallised from alcohol, the compound was found to be no longer soluble in sodic hydrate; it was orange in colour, and was recognised by its melting point and other properties to be bromo-$\beta$-lapachone, crystallising like this compound in the two characteristic forms described above.

The action of dilute alkalis on dibromhydrolapachol is interesting, as it gives additional evidence of the relation existing between it and bromo-$\beta$-lapachone. It will be shown in the following pages that boiling aqueous alkalis convert bromo-$\beta$-lapachone into dihydroxyhydrolapachol, as indicated in the following equation:—

$$C_{10}H_4\begin{cases}O_2\alpha\beta\\ CHBr\cdot CH\cdot C_3H_7\\ O\overline{\quad\alpha}\end{cases} + 2H_2O = C_{10}H_4\begin{cases}O_2\alpha_1\alpha_1\\ CH\cdot OH\cdot CH(OH)\cdot C_3H_7\\ OH\beta\end{cases} + HBr.$$

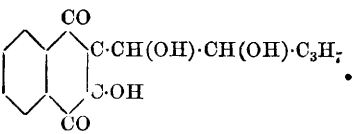
Similarly, dihydroxyhydrolapachol is also formed by the action of alkalis on dibromhydrolapachol.

$$C_{10}H_4\begin{cases}O_2\alpha\alpha\\ CHBr\cdot CHBr\cdot C_3H_7\\ OH\beta\end{cases} + 2H_2O = C_{10}H_4\begin{cases}O_2\alpha_1\alpha_1\\ CH(OH)\cdot CH(OH)\cdot C_3H_7\\ OH\beta\end{cases} + 2HBr.$$

One gram of the finely powdered substance was immersed in 50 c.c. of a 1 per cent. solution of sodic hydrate; it dissolved readily, giving an intensely red solution, which, although at first bright, became turbid after a few minutes from the separation of a very small quantity of an orange-red substance, which was filtered off shortly afterwards. The alkaline filtrate was then allowed to stand about 12 hours, during which time a slight additional deposit of a greenish colour was formed. The solution, once more filtered, was acidified with acetic acid, and a compound was thus obtained, on standing, having all the properties of dihydroxyhydrolapachol. When crystallised from alcohol, it still contained slight traces of bromine, and was, therefore, once more dissolved in dilute sodic hydrate and reprecipitated. After crystallisation from acetic acid, all traces of bromine had disappeared, and the compound proved to be pure dihydroxyhydrolapachol.

It is an interesting fact that, while dibromhydrolapachol dissolves with great readiness in dilute caustic soda, it is but slowly dissolved by a moderately concentrated solution.

*Dihydroxyhydrolapachol,*




This compound is formed by the action of caustic alkalis on bromo-$\beta$-lapachone, or on hydroxy-$\beta$-lapachone, and also on dibromhydrolapachol. It is best prepared as follows:—12 grams of finely powdered bromolapachone and 900 c.c. of a 1 per cent. solution of caustic soda are boiled together with a reflux condenser. The bromolapachone dissolves slowly to an intense carmine-red solution. At the end of 15 minutes the boiling is discontinued and the solution filtered. Stray crystals of bromolapachone which have escaped grinding and are consequently able to resist the action of the potash for a long time, are thus removed; a small quantity of a green substance, formed by the action of the soda, is also retained on the filter paper. A slight excess of acetic acid is added to the filtered solution when cold, resulting in the immediate formation of a precipitate in small quantity, consisting of a brownish substance. This is removed as quickly as possible by filtration through a folded paper of compara-

tively large size. The filtration must be promptly accomplished, otherwise the substance will commence to crystallise out before the separation of the brown impurity has been effected. In a very few minutes after acidifying, the dihydroxy-derivative commences to be deposited from the now orange-red solution in compact, yellow, crystalline grains. The separation occurs slowly, the solution becoming simultaneously lighter in colour. In the course of 24 hours the crystallisation, which can be considerably promoted by vigorous stirring, is complete, and the compound can be collected, washed well with water, and dried. The compound, as thus obtained, is almost pure:* 12 grams of bromolapachone give rather more than 8 grams of the new product. It can be obtained pure by one crystallisation from acetic acid. For analysis it was crystallised from alcohol, in which it is not very soluble. A qualitative test showed that the bromine had been removed.

0·1867 gram gave 0·4442 $CO_2$ + 0·0989 $H_2O$.

| | Found. | Calculated for $C_{15}H_{16}O_5$. |
|---|---|---|
| C ..... | 64·88 | 65·21 |
| H ..... | 5·88 | 5·79 |

Dihydroxyhydrolapachol melts at 181—182°. Like bromolapachone, it crystallises from 95 per cent. alcohol in two apparently different forms. No special experiments were made to determine the conditions governing the formation of each variety of crystal, and sometimes the one form, sometimes the other, would be obtained under apparently similar conditions. One modification (that analysed) consists of small, prismatic crystals, often grouped together in the form of compact stars; the other, of very fine, long needles, crystallising in tufts.

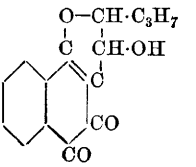
Like hydroxyhydrolapachol and lapachol, it forms stable metallic derivatives which are not decomposed by carbon dioxide. The colour of their solutions is similar to that of those of lapachol. The strontia compound is the only one of those examined which can be readily obtained in a crystalline form. It consists of very small, dark-red needles. The lime, barium, and silver compounds were obtained as amorphous films only.

* If the crude substance be dissolved in a very slight excess of 1 per cent. sodic hydrate and immediately filtered, orange crystals consisting of Paternò's isolapachone will be retained on the filter-paper. This substance was most carefully identified by its fusing point and by a variety of reactions as yet unpublished, which Mr. Shepard has found to be characteristic of the compound prepared as described by Paternò.

The action of concentrated sulphuric acid on dihydroxyhydrolapachol is being studied at the present time in my laboratory. Some interesting results have been obtained.

Concentrated hydrochloric acid dissolves dihydroxyhydrolapachol slowly, simultaneously converting it into hydroxy-$\beta$-lapachone

*Hydroxy-$\beta$-lapachone,*




Hydroxy-$\beta$-lapachone is readily formed by the action of dilute mineral acids on dihydroxyhydrolapachol. The compound was prepared for analysis as follows:—

To a solution of 1·36 grams in the smallest possible quantity of boiling 95 per cent. alcohol, 5 c.c. of concentrated hydrochloric acid were added: the colour of the solution changed to an intense orange-red. After boiling for one or two minutes, the solution was diluted with water as long as a precipitate was produced; in this way a considerable portion of the hydroxylapachone was obtained in small, orange-red needles. The filtrate, still orange in colour, was evaporated until a crust of crystals had formed upon its surface, and these were separated from the solution when cool. Total yield, 1·15 grams. The substance, on being purified by crystallisation from dilute alcohol, separated in red needles, melting at 201·5°, and closely resembling $\beta$-lapachone in appearance.

0·2507 gram gave 0·6401 $CO_2$ + 0·1228 $H_2O$.

| | Found. | Calculated for $C_{15}H_{14}O_4$. |
|---|---|---|
| C..... | 69·63 | 69·76 |
| H..... | 5·44 | 5·42 |

Although the above method of preparing hydroxy-$\beta$-lapachone is entirely satisfactory in operating with small quantities, it is not so well adapted to the preparation of the compound on a larger scale, owing to the comparatively large volume of alcohol needed to dissolve the dihydroxyhydrolapachol.

The following method, which was subsequently discovered, will be found generally far more convenient, and is probably equally well adapted to the preparation of the compound in large or small quantities. 2 grams of finely powdered dihydroxyhydrolapachol were immersed in 5 c.c. of concentrated hydrochloric acid, sp. gr. 1·20.

After standing in a corked flask for about an hour, the compound was found to have completely dissolved. The acid solution was then poured into about 100 c.c. of water, when hydroxy-$\beta$-lapachone separated in a very pure form. Yield, 1·72 grams. The filtrate and aqueous washings were evaporated on a water-bath, and a further yield of about 0·08 gram was obtained, making in all 1·80 grams. The yield is therefore theoretical, the calculated figures being 1·86.

Hydroxy-$\beta$-lapachone, like $\beta$-lapachone and bromo-$\beta$-lapachone, is almost insoluble in alkalis in the cold; on boiling, however, it readily passes into solution. 35 c.c. of 1 per cent. solution of caustic potash and 1·35 grams of hydroxylapachone were heated for several minutes at the boiling point. The solution was then filtered, cooled, and acidified with acetic acid. Crystals commenced to form almost immediately, but the separation was not complete for some hours. After crystallisation from alcohol, the compound melted at 181—182°, and in other respects was found to be identical with dihydroxyhydrolapachol obtained as above described from bromolapachone. The yield of the substance was almost theoretical; 1·35 grams gave 1·36 grams of the dihydroxy-derivative, 1·45 being required by theory.

0·1834 gram gave 0·4390 $CO_2$ + 0·0958 $H_2O$.

| | Found. | Calculated for $C_{15}H_{16}O_5$. |
|---|---|---|
| C ..... | 65·28 | 65·21 |
| H ..... | 5·80 | 5·79 |