The chief interest in this series of compounds lies in its biological rather than in its chemical importance. Of the groups hexylresorcinol stands out as the most interesting product because of its importance as a therapeutic agent.

BALTIMORE, MARYLAND

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

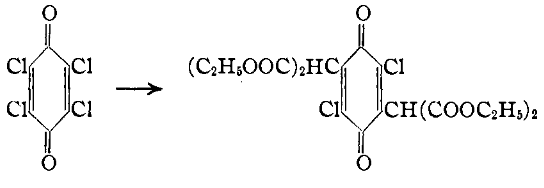
THE REACTION BETWEEN DUROQUINONE AND SODIUM MALONIC ESTERS[1]

BY LEE IRVIN SMITH AND FRANK J. DOBROVOLNY

RECEIVED FEBRUARY 23, 1926 PUBLISHED JUNE 5, 1926

Malonic ester has been added to a great many α,β-unsaturated carbonyl systems, and the results of these reactions have been interpreted variously by Michael, Vorlander, Thiele and others. Perhaps the most complex α,β-carbonyl systems may be found in benzoquinone and its derivatives, for in such a substance there are two independent, and four dependent, conjugated systems, of four atoms each, two conjugated systems of six atoms each, besides the two carbonyl groups and the two double bonds, which might function independently of each other. Hence, the addition of such a reagent as malonic ester to a *p*-benzoquinone should lead to some very interesting results.

A review of the literature shows that very little work has been done on the reaction between malonic ester and benzoquinone derivatives. Practically all the work reported has been carried out with halogenated quinones such as bromanil, and the results can be explained in more than one way. Thus, Stieglitz,[2] in an attempt to prepare benzoquinone carboxylic acids, allowed sodium malonic ester to react with chloranil, obtaining a small yield of the *p*-dichlorodimalonic diethyl ester of benzoquinone. Later, C. L. Jackson and his co-workers[3] replaced the halogen atoms in chloranil and bromanil with malonic ester and various alkoxyl groups, but only two of the halogen atoms could be so replaced. Liebermann and his



---

[1] Abstracted from a thesis by F. J. Dobrovolny, presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Stieglitz, *Am. Chem. J.*, **13**, 38 (1891).

[3] Jackson and co-workers, *Am. Chem. J.*, **17**, 597 (1895). *Proc. Am. Acad. Sci.*, **30**, 409 (1894).

students[4] have studied the action of sodium malonic ester and its derivatives on the mono- and di-halogenated indones and naphthoquinones. All of these reactions can be explained either as Würtz-Fittig syntheses, or as additions to the conjugated system followed by elimination of sodium halide. In every case deeply colored intermediate products were formed, and since there was a great tendency to form tars the products were purified with difficulty, and the yields were usually quite low.

There is in the literature no report of the addition of sodium malonic ester to a simple benzoquinone which does not contain halogen, and the most comprehensive report on the addition of any metallic derivative to benzoquinones is the work of Bamberger and Blangey[5] on the addition of methylmagnesium iodide to benzoquinone, toluquinone, and xyloquinone. Their results may be summed up very briefly as follows. Benzoquinone gave no products that could be characterized, toluquinone gave very little in the way of definite products, while xyloquinone yielded a great variety of products. They succeeded in isolating and identifying six solid reaction products, but these accounted for less than half the material used. Most of the reaction product was either oily or amorphous.

In Bamberger's work, the large number of products may be at least partially due to the hydrogen atoms attached to the nucleus of the quinones used. Once anything is added to the quinone it is no longer a true quinone, but becomes an unsaturated compound of the enolic type and, in the unsubstituted quinones, the products are capable of a keto-enol shift in several different ways because of the hydrogen atoms attached originally to the nucleus. If a fully substituted quinone were used, these keto-enol shifts would be limited to those hydrogen atoms added in the reaction, and so the number of side reactions and possible products should be decreased.

To achieve this end, and also to avoid the possibility that the Würtz reaction would take place, we decided to use duroquinone, tetramethyl-*p*-benzoquinone, as the starting material.[6] When duroquinone was treated with the sodium derivative of malonic ester in absolute alcohol, and the reaction mixture decomposed with dilute acid, two products resulted. One of these, melting at 207°, was orange in color and was diduroquinone, a substance discovered by v. Pechmann,[7] and investigated also by Rügheimer and Hankel.[8] The substance has the composition of duroquinone, but twice its molecular weight, and an hydroxy group is present. The other substance is yellow and, when carefully purified,

---

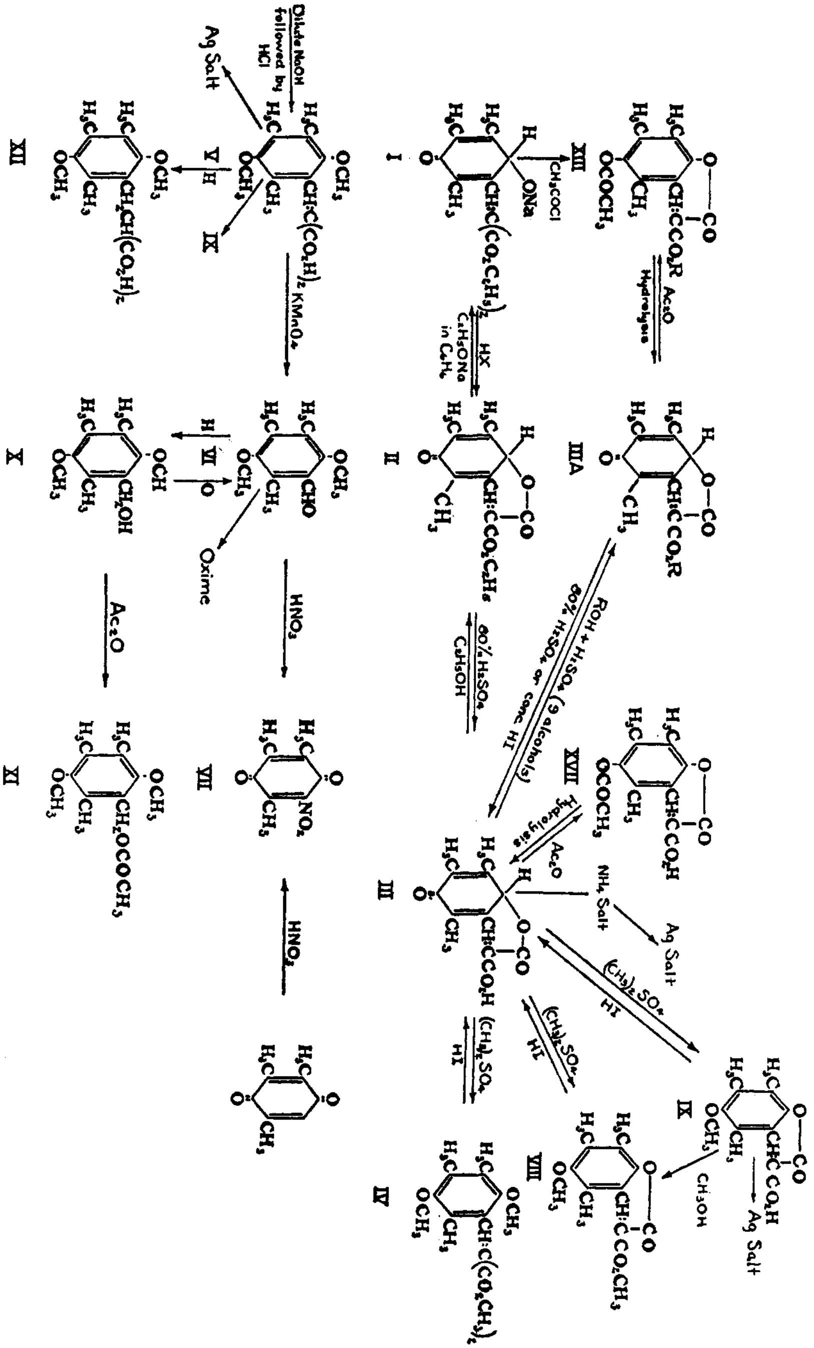
[4] Liebermann and students, *Ber.*, **31**, 2906 (1898); **32**, 264, 916 (1899); **33**, 566, 2402, 2412 (1900).

[5] Bamberger and Blangey, *Ann.*, **384**, 272 (1911).

[6] The manufacture of durene, and the preparation of duroquinone from it are described in a previous paper, THIS JOURNAL, **48**, 1420 (1926).

[7] v. Pechmann, *Ber.*, **22**, 2115 (1889).

[8] Rügheimer and Hankel, *Ber.*, **29**, 2176 (1896).


XIII
Ac₂O
Hydrolysis
CH₃COCl
IIIA
I
HX
C₂H₅ONa in C₆H₆
II
80% H₂SO₄
C₂H₅OH
ROH + H₂SO₄ (9 alcohols)
80% H₂SO₄ or conc. HI
XVII
Ac₂O
Hydrolysis
NH₄ Salt
Ag Salt
III
(CH₃)₂SO₄
HI
(CH₃)₂SO₄
HI
(CH₃)₂SO₄
HI
IX
CH₃OH
Ag Salt
VIII
IV
Dilute NaOH followed by HCl
Ag Salt
V
H
IX
XII
KMnO₄
VI
H
O
Oxime
X
HNO₃
VII
HNO₃
Ac₂O
XI

melts at 184°. The separation of the two compounds is very tedious and, therefore, we carried out our reaction under conditions which avoided the formation of the polymer of duroquinone. This was accomplished by causing the reaction to take place in dry benzene.

The reaction between duroquinone and the sodium derivative of malonic ester in dry benzene requires at least a week to give good yields of the product. The primary product is a very stable, red solid, I (roman numerals refer to the chart, p. 1695) which contains sodium, and which, with acids, gives the yellow 184° compound. The composition of this substance is given by the formula $C_{15}H_{16}O_5$, and it represents the addition of one molecule of malonic ester to one molecule of the quinone, accompanied by the loss of a molecule of alcohol and two atoms of hydrogen. If the addition is carried out in an inert atmosphere, hydroduroquinone is found in molecular amounts, proving that the quinone itself is the oxidizing agent. The equation for the reaction (omitting the intermediate steps) may, therefore, be written as follows.

$$\underset{\text{Duroquinone}}{2\ C_{10}H_{12}O_2} + \underset{\text{malonic ester}}{CH_2(COOC_2H_5)_2} \longrightarrow C_2H_5OH + \underset{\text{hydroquinone}}{C_{10}H_{14}O_2} + \underset{184^\circ\text{ compound}}{C_{15}H_{16}O_5}$$

This accounts for the time necessary to complete the reaction under ordinary conditions, for hydroduroquinone does not react with sodium malonic ester and it is necessary for the atmospheric oxygen to oxidize the hydroquinone back to the quinone before it can react to completion. When the flask is shaken vigorously, or when air is bubbled through during the reaction, less time is required.

Discussion of the Reaction Products

The Yellow 184° Compound.—The yellow compound II is an ester, for it can be hydrolyzed to an acid, m. p. 260°, which in turn can be esterified with any alcohol to give a product IIIA, identical with that obtained by adding the appropriate malonic ester directly to duroquinone. Either a free or an enolic hydroxyl grouping is present in the ester, for it forms an acetyl derivative and, from the determination of the acetyl value and the molecular weight, only one such hydroxyl group is present. The acetyl compound is nearly colorless, and this indicates that the fixing of the hydroxyl group involves some structure change in the yellow ester.

A lactone ring is indicated by a consideration of the results of the analysis, the ethoxyl determination and the molecular-weight determination, which gives about 275. From this it follows that only one molecule of malonic ester and one of duroquinone are involved, and the net loss in the reaction is a molecule of alcohol and two hydrogen atoms. Carbon dioxide could not have been lost, therefore, and since two carboxyl groups were originally present in malonic ester, there should be two such groups in the addition compound. The compound is a mono-ester, which accounts for one carboxyl group, and the other must be involved in the formation of a lactone ring.

The 260° Yellow Acid.—When the yellow ester is hydrolyzed, it gives a yellow acid III, m. p. 260°, the formula for which is $C_{13}H_{12}O_5$. The analysis of the ammonium and silver salts of this acid show it to be monobasic; hence, the lactone ring is not affected by the hydrolysis. The color of this 260° acid in alkali is deep red, and it becomes deeper with increasing concentration of the alkali. When the compound is acetylated, one hydroxyl group becomes fixed, resulting in a colorless, monobasic acid XVII.

Methylation Products.—When the yellow ester or the yellow acid is methylated, three different methyl derivatives result, depending upon the conditions of the reaction. The complete methylation of the yellow compounds gives a colorless tetramethyl derivative IV, m. p. 93°, $C_{17}H_{22}O_6$. The composition indicates that in addition to the entry of four CH_2 groups into the molecule of the acid, a molecule of water has also been added, and since the hydrolysis of this tetramethyl derivative gives a diether diacid, the original lactone ring in the yellow acid must have been opened.

If the methylation is not complete, a mono- and a di-methyl derivative result. The analysis of the monomethyl derivative IX, m. p. 195°, indicates the addition of one CH_2 group to the acid; its formation, therefore, involves methylation of one hydroxyl group, and since the substance is colorless, the same hydroxyl must be involved in methylation as in acetylation. One free carboxyl is shown by the formation and analysis of the silver salt. The dimethyl derivative VIII, m. p. 153–154°, is simply the methyl ester of the 195° monomethyl derivative, for it can be made from the 195° monomethyl ester almost quantitatively.

Oxidation Products.—When the 188° diether diacid V is oxidized with alkaline permanganate, the products are carbon dioxide, manganous oxalate, and a white solid VI, m. p. 85°, which turns yellow in the light.[9] The analysis and molecular-weight determinations give the formula $C_{12}H_{16}O_3$, and the methoxyl value shows that it contains two OCH_3 groups. This 85° compound is insoluble in dilute alkalies and is not hydrolyzed by these reagents. It also does not acetylate. It is, therefore, not an ester, nor an hydroxyl compound, but must be a dimethyl ether, and the two ether linkages must be the same as those that are present in the 188° diether diacid, and in the 93° tetramethyl derivative.

When VI was warmed with nitric acid, there resulted a yellow nitro compound VII, of the composition $C_9H_9O_4N$, m. p. 112–113°, which was proved to be identical in every respect with the trimethyl nitrobenzoquinone prepared by Nef.[10] When this was mixed with a sample of nitrotrimethyl-

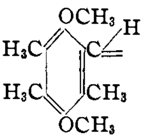
---

[9] This substance turns yellow rather rapidly in the light, and in the dark slowly loses the yellow color.

[10] Nef, *Ann.*, **237**, 17 (1887).

quinone, m. p. 112–113°, made by nitrating pseudocumoquinone, the melting point showed no depression. The formation of this nitro quinone from VI by oxidation shows that the benzene nucleus is intact in VI, and that there are three methyl groups attached to the nucleus. If this is the case, then the substance cannot be a ketone, and the only possible structure for it is that of an aldehyde, 2,5-dimethoxy-3,4,6-trimethylbenzaldehyde. This is supported by the fact that VI can be reduced to an hydroxyl compound X, $C_{12}H_{18}O_3$, that it forms an oxime and that it gives a positive test with Tollens' reagent. It was not possible, however, to oxidize VI in such a way as to form the corresponding acid; all oxidizing agents, except nitric acid, either do not attack it at all, or else oxidize it completely.[11]

Structure of the Diacid V.—If, then, the duroquinone skeleton of 10 carbon atoms, with two methoxyl groups and three methyl groups joined to this nucleus, is present in the diether diacid V, it is necessary only to account for that part of the structure of V which is attached to that modified methyl group that appears as an aldehyde in the oxidation product, for the presence of the bivalent radical has been established. This radical has the composition $C_{12}H_{16}O_2$, while the diacid V is $C_{15}H_{18}O_6$. The difference in composition is $C_3H_2O_4$. Compound V is a dibasic acid, and so two carboxyl groups must be present. This leaves one carbon atom for which to account. The two carboxyl groups cannot, therefore, be directly attached to this radical. Neither is it possible to attach one carboxyl group to the bivalent radical and then attach the extra carbon atom to the second valence of this radical, for this would leave three free valence bonds on the one carbon atom. The only arrangement possible is to attach the extra carbon atom to the bivalent radical by a double bond, and then to attach the two carboxyl groups to this carbon atom. Therefore, the structure of the diacid must be represented by V, 2,5-dimethoxy-3,4,6-trimethyl-benzalmalonic acid. Such a structure is in complete agreement with the experimental facts. The loss of one molecule of methyl alcohol should, and does lead to the formation of a lactone. This lactone should be, and is, a monomethyl ether and a monobasic acid IX. Although there is an aliphatic double bond in this diether diacid, the addition of bromine would not be



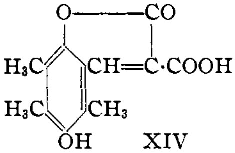
---

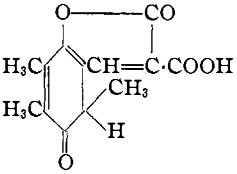
[11] This rather striking behavior of an aldehyde towards oxidizing agents is paralleled by the behavior of some of the other derivatives of the highly methylated benzenes. Thus Jacobsen [*Ber.*, **22**, 1215 (1889)] made pentamethylbenzyl alcohol and found that it could not be oxidized to the corresponding acid; chromic trioxide gave a polybasic acid, nitric acid gave oily resinous products and potassium permanganate either destroys it completely or else does not attack it at all. Nef (Ref. 10, p. 1) found the same sort of behavior in the case of dihydroxy-pyromellitic acid $C_6(OH)_2(COOH)_4$. This acid cannot be oxidized to the corresponding quinone acid. Nitric acid, potassium dichromate, potassium permanganate or chromic trioxide either do not attack it or else destroy it completely.

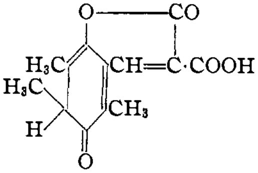
expected, because of the presence of two carboxyl groups and the phenyl group about the double bond.[12] On reduction, V takes up two atoms of hydrogen giving XII and, on oxidation, V should react at the double bond giving an aldehyde, and mesoxalic acid or its oxidation products. An aldehyde, carbon dioxide and oxalic acid are actually obtained.

The structure of the tetramethyl derivative IV follows at once from that of V. It is the dimethyl ester of 2,5-dimethoxy-3,4,6-trimethylbenzalmalonic acid.

Structure of the Yellow Acid, III.—The hydrolysis of V by concd. hydriodic acid leads to III, the 260° yellow acid. The reaction is $C_{15}H_{18}O_6 + H_2O \longrightarrow C_{13}H_{12}O_5 + 2CH_3OH$, and indicates that V, on hydrolysis, loses two CH_2 groups and a molecule of water. This shows that a lactone must have been formed. Knowing the structure of V, it might be concluded that the product of hydrolysis would be XIV. But this structure does not account for two important facts. First, the substance III is deep yellow, while IV and V are white. Second, III with alkali gives a red solution which becomes more deeply colored as the concentration of the alkali increases. Further, the simple acetyl derivative XIII and the monomethyl ether IX are colorless, and these facts indicate that the yellow acid is subject to some structure change which is responsible for the yellow color of the acid and all of its esters, while the acetyl derivatives and the methyl ethers are colorless. The simplest assumption to make is that the structure given by XIV is an "enol" form, and that the acetyl and methyl derivatives are the results of the "fixing" of this enol form. The derivatives of the enol form would be colorless, while the yellow color of the acid and its esters would be due to their existence in the "keto" form. Of the possible keto forms for the enol XIV, one is a *para* derivative III, and the other two are *ortho*, XV and XVI.


XIV


XV

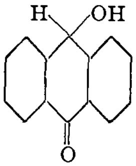

XVI

There is only indirect evidence to decide between these but, in general, *o*-quinoid groupings give rise to a deeper color than yellow, usually red, while *p*-quinoid forms are usually yellow. There is also evidence for the existence of this type of compounds among the reduction products of anthraquinone. When anthraquinone is reduced under proper conditions,

---

[12] Nef, *Ann.*, **298**, 208 (1897). Bauer, *Ber.*, **37**, 3488 (1904).

the solution of the reduction product gives a deep red with alkali, and contains oxanthrol XVIII. This substance is yellow when freshly precipitated from the red alkali solution, and is very sensitive to oxidizing agents. The acetyl derivative is colorless and is a derivative of hydro-anthraquinone.[13]



XVIII

For these reasons, we have assigned Structure III to the yellow acid, though any one of III, XV or XVI will explain all of the experimental facts equally well. III is, therefore, the *para* keto form of 2-lactone of 2,5-dihydroxy-3,4,6-trimethyl-benzalmalonic acid. A series of nine esters has been made from this acid. All are yellow and their acetyl derivatives are colorless (IIIA and XIII).

The Red Sodium Compound.—The primary product of the reaction is a red solid (I), containing sodium. It is very stable and can be filtered off, washed with water, alcohol and ether, or heated to 100°, without decomposition. Three of these red sodium compounds were made by adding dimethyl, diethyl and di*iso*propyl malonates; all behaved alike. Because it was not possible to purify these compounds, the analyses are not concordant, and about the only conclusion that can be drawn from the results is that one molecule of duroquinone and one of sodium malonic ester are involved in the reaction. That the oxidation has taken place before the formation of the red compound, is indicated by the stability of the substance, and by the fact that it reacts with acids to give the yellow ester-lactone (II), and with acetyl chloride to give the colorless acetyl derivative XIII. Both these reactions take place very rapidly, and there is no evidence of the formation of any intermediate compounds which could be oxidized to the compounds actually obtained. If the yellow ethyl ester II is treated with sodium alcoholate in benzene (but not in alcohol) the red compound precipitates almost at once, though the reaction is not fully complete for a day or so. The same reaction takes place when sodium powder in benzene is used, although at a much slower rate. Under these circumstances the red compound does not appear in an appreciable amount until after three days' refluxing, and it requires two months' standing to reach the same point as that reached with sodium alcoholate in a day. Because of this, we assume that the molecule of alcohol has not been eliminated, and that there is no lactone ring in the red compound I. In view of these facts, we have assigned Structure I to this compound, and regard it at present as the 2-sodium derivative of the *para*-keto form of 2,5-dihydroxy-3,4,6-trimethyl-benzalmalonic diethyl ester. This structure accounts for the deep red color, and the compound may be considered as the analog of the red sodium salt of oxanthrol XVIII,

---

[13] Liebermann, *Ann.*, **212**, 1, 63 (1882). Graebe and Liebermann, *Ann.*, **160**, 127 (1871). Schulze, *Ber.*, **18**, 3036 (1885).

which is known only in solution, but which on treatment with acids results in the formation of a yellow, unstable substance that easily rearranges to give hydo-anthraquinone.

It has not been possible, as yet, to determine the mechanism of this reaction between duroquinone and malonic ester. Work is now in progress on the addition of the Grignard reagents to duroquinone, and on the addition of malonic ester to some other quinones and systems which contain essentially the same, though somewhat less complex, linkages than the quinones. It may be noted, however, that benzoquinone, when treated with malonic ester in exactly the same way as duroquinone, gives only a hopeless tar. It is expected that the work now in progress will enable us to fix the mechanism of this reaction, and this we shall report in later papers.

Experimental Part

Addition of Diethyl Malonate to Duroquinone.—Formation of the *para*-keto form of 2-lactone of 2,5-dihydroxy-3,4,6-trimethyl-benzalmalonic ethyl ester II and its red sodium derivative I.

Thirteen g. of powdered sodium is covered with 1 liter of dry benzene in a 3-liter flask, connected with an efficient reflux condenser; 95 g. of diethyl malonate is added through the condenser in three or four portions during a half-hour period. The mixture is refluxed on the steam-bath for two or three hours, and vigorously shaken at intervals of 20 to 40 minutes. The viscous, jelly-like white mass of the sodium derivative now fills the flask. Thirty-five g. of duroquinone, dissolved in 300 to 500 cc. of dry benzene, is added through the condenser and the mixture is heated for eight or ten days. It is necessary to shake the flask vigorously every few hours, and if an adhering layer forms in the bottom of the flask, it should be pried loose with a strong stirring rod. The mixture becomes darker after a few hours and slowly changes to a deep red with the formation of an amorphous red precipitate, which is the metallic derivative I. It is filtered off, triturated successively with two or three portions each of benzene, ethyl alcohol and water. It is then dried at 80° for several hours when it is an amorphous red powder which cannot be dissolved in any of the common solvents. Acids cause immediate decomposition with the formation of the yellow lactone ester II. Since this red substance could not be further purified, it was then analyzed.

Anal. Calcd. for $C_{17}H_{21}O_6Na$: C, 59.3; H, 6.11; Na, 6.68. Calcd. for $C_{15}H_{15}O_5Na$: C, 60.5; H, 5.04; Na 7.2. Found: C, 58.3, 58.15; H, 4.98, 5.49; Na, 6.93, 6.82.

The yellow ester II may be isolated in either of two ways; first, the red sodium compound is filtered off and then treated with benzene, alcohol and water, and finally decomposed by glacial acetic acid; second, the reaction mixture is decomposed with either acetic acid or hydrochloric acid, the yellow product filtered off and extracted with benzene to remove duroquinone and tarry by-products.

The first method is tedious, but the yellow addition compound is procured in a fairly pure condition after one or two recrystallizations from alcohol or glacial acetic acid. The second method is much more rapid, but the product is not so pure, due to the fact that it has not been exposed to atmospheric oxygen and is thus always contaminated by small amounts of hydroduroquinone, which are only slowly converted into duroquinone.

The yellow addition compound crystallizes in matted, felted, small needles from either acetic acid or alcohol. When carefully purified, it melts at 184–185° to give a yellow liquid which decomposes slowly. The substance is practically insoluble in water, benzene, ether, chloroform and other halogenated hydrocarbons. For this reason it was rather difficult to obtain accurate molecular weights.[14]

TABLE I

MOLECULAR-WEIGHT DETERMINATIONS

Solvent	Volume, cc.	Sample, g.	Δt, °C.	K	Mol. wt.	Method
Benzene.......	32.8	0.3251	0.115	32.0	276	Boiling point
Benzene.......	36.75	.3251	.085	32.0	333	Boiling point
Alcohol.......	30.2	1.2596	.265	15.6	269	Boiling point
Alcohol.......	31.2	1.2596	.251	15.6	251	Boiling point
Camphor......	0.1877 g.	0.129	10.0	400.0	275	Freezing point
	0.1877 g.	.129	10.7	400.0	257	Freezing point

Anal. Calcd. for $C_{15}H_{16}O_6$: C, 65.1; H, 5.8; OC_2H_5, 16.3; mol. wt.. 276. Found: C, 65.11, 64.90; H, 5.96, 5.80; OC_2H_5, 16.01, 16.09.

Addition in an Inert Atmosphere.—The addition was carried out in a current of nitrogen, and when complete, acetyl chloride was added to decompose the red sodium compound. This is necessary, because the hydroquinone formed oxidizes in the air rather easily.

Sodium powder (1.3 g.) was placed in a 200cc. round-bottomed flask with a wide neck 50 cm. long. To the flask a side tube was sealed with a small separatory funnel. Ten g. of malonic ester with 100 cc. of dry, pure benzene was added. The end of the neck of the flask was tightly fitted with a rubber stopper through which a glass stopcock passed. Air, which was passed with ammonia vapors over heated copper in a long tube and dried with sulfuric acid and phosphorus pentoxide, was admitted through the glass stopcock. The system was thoroughly swept out for several hours to remove all traces of water and oxygen. Then 4 g. of duroquinone dissolved in 30 cc. of benzene was added through the separatory funnel, no air being admitted. The flask was heated, but there was no reaction for about 30 minutes, when the contents became darker. At the end of several days the flask was filled with a black-to-red mass. After this mixture had cooled, acetyl chloride in small portions was admitted through the side tube, without admitting air. The red gave place to a pale yellow with a white suspension (sodium chloride) and evolution of heat. The flask was then opened, the benzene evaporated and the residue washed out of the flask with water and filtered. The residue was then extracted with ether. The ether on evaporation gave an oil (10 g.) from which 1.8 g. of quinone was isolated. The oil was malonic ester. The washed residue (2.6 g.), consisting of the acetyl derivative XIII and the diacetate of hydroduroquinone, was pure white and melted over a large range above and below 170°. On crystallization

---

[14] Many of the compounds described in this paper were exceedingly difficult to burn completely, and no consistent results could be obtained, using the ordinary Liebig method. After several modifications of the ordinary method had been tried without success, a semi-micro method was developed by one of us (F. J. D.) and Dr. W. M. Lauer. This method gave excellent results.

from dil. acetic acid, the material melted over a large range (some above 182°). This material (about 2 g.) was then boiled for ten minutes with 57% hydriodic acid. This hydrolyzed the two acetyl compounds, giving a mixture of II and hydroduroquinone. After half an hour, the solution was diluted with water and the yellow precipitate filtered off, washed with water and dried (1.8 g.); m. p., 200–230°. This material was oxidized at this stage by suspending it in a solution of ferric chloride; the product was then filtered off and extracted with ether. The ether on evaporation gave 0.83 g. of duroquinone melting at 110°. The ether-insoluble residue weighed 0.9 g., melted at 260°, and was the acid III.

Reaction between the Ethyl Ester and Sodium.—One-tenth g. of powdered sodium suspended in dry benzene was refluxed with 1.0 g. of the yellow 184° addition compound. After three days there was a slight coating of red about the sodium particles, but most of the yellow 184° compound on cooling crystallized from the benzene in large, rhombic crystals. The mixture was then allowed to stand for two months, at the end of which time practically no yellow 184° compound remained in the benzene, all seemingly having reacted with the sodium to form the insoluble "red."

Reaction between the Ethyl Ester and Sodium Ethylate.—About 0.15 g. of powdered sodium was suspended in dry benzene and 10 cc. of absolute alcohol added. After the reaction the excess of alcohol was boiled off. More benzene was added, the solution again boiled, and 1 g. of the yellow 184° compound added. The flask at once became filled with a dark red precipitate, adhering to the walls. The mixture was refluxed for two days, filtered and the precipitate washed with benzene and alcohol. The "red" so formed is not soluble in alcohol and behaves exactly as the "red" obtained by the direct addition of sodium malonic ester and duroquinone; yield, 0.9 g. of "red" (dried at 80° for a day), and 0.2 g. of unchanged material melting at 180°.

Hydrolysis of the Ethyl Ester. *para*-Keto Form of 2-Lactone of 2,5-Dihydroxy-3,4,6-trimethyl-benzalmalonic Acid III.—The yellow 184° addition compound of malonic ester and duroquinone is hydrolyzed by strong acid or alkali. The hydrolysis is best carried out by dissolving the substance in warm 80% sulfuric acid, allowing the solution to stand for a few hours and then adding ice. The hydrolysis product separates almost quantitatively. If the yellow 184° compound is impure, then the hydrolysis produces tarry by-products which are removed from the hydrolysis compound with great difficulty. The following experiment was carried out quantitatively.

The yellow 184° compound (2.137 g.) was hydrolyzed and the product precipitated with water, filtered on a Gooch crucible and dried to constant weight; yield, 1.884 g. of hydrolysis product. The loss in weight was 0.253 g., or 10.1% of C_2H_4. That calculated for $C_{15}H_{16}O_6$ was 11.3%. There was no evolution of carbon dioxide.

The hydrolysis compound when carefully purified melts at 260° with decomposition. Very small traces of impurities lower the melting point 5° to 10°. The substance is very insoluble in all of the usual organic solvents, and only slightly soluble in boiling glacial acetic acid, from which it crystallizes in small, blunt, yellow, prismatic needles. It dissolves in alkalies, giving a red solution.

Anal. Calcd. for $C_{13}H_{12}O_6$ (248): C, 62.90; H, 4.80. Found: C, 62.82, 62.94; H, 4.68, 4.95.

AMMONIUM SALT.—The ammonium salt of the 260° hydrolysis compound is prepared by dissolving the latter in a small volume of dil. ammonium hydroxide and boiling. On cooling the solution in ice, the yellow ammonium salt separates. The precipitate is washed with a very small quantity of ice water, dried and analyzed. The substance crystallizes in ill-defined needles.

Anal. Calcd. for $C_{13}H_{15}O_6N$: C, 58.8; H, 5.7; N, 5.3. Found: C, 58.5, 58.2; H, 5.31, 5.43; N. 4.99, 4.88.

SILVER SALT.—The silver salt is made by dissolving the 260° hydrolysis compound in dil. ammonium hydroxide and boiling the solution until the odor of ammonia is not perceptible. The solution is cooled to room temperature, filtered and a dilute solution of silver nitrate added. The silver salt precipitates out as a curdy green jell which is very sensitive to light and heat and difficult to filter. The salt is washed as well as possible and then dried. It is a greenish-yellow powder.

Anal. Calcd. for $C_{13}H_{11}O_6Ag$ (355): C, 43.96; H, 3.10; Ag, 30.4. Found: C, 41.39, 41.52; H, 3.17, 3.10; Ag, 32.12, 32.19.

ANILIDE—The yellow acid III is treated with thionyl chloride, the excess of thionylchloride boiled off, and aniline, diluted with benzene, is added. The anilide separates out as an amorphous yellow powder, which melts above 200° with decomposition.

Anal. Calcd. for $C_{19}H_{17}O_4N$: C, 70.6; H, 5.3; N, 4.3. Found: C, 70.12, 70.28; H, 5.52, 5.51; N, 4.91, 4.95.

Acetylation of III.—The yellow acid III is dissolved in a small amount of acetic anhydride, and a drop of sulfuric acid added. The white acetyl derivative soon separates in good yield. Upon one crystallization from glacial acetic acid, the substance is analytically pure. The acetyl derivative separates in a network of very fine, slender needles, colorless, and melts at 218°. The substance is easily electrified.

Anal. Calcd. for $C_{15}H_{14}O_6$ (290): H, 4.8; C, 62.1; acetyl (one), 14.4 (Wenzel). Found: C, 62.07, 62.42; H, 5.08, 4.81; acetyl, 15.98, 16.72.

Esterification.—Nine different esters (IIIA) of the acid III have been made, and in three cases, the esters have also been made by adding the appropriate malonic ester directly to duroquinone. The three which have been made by both ways are the methyl, ethyl and *iso*propyl esters. In making the esters directly from duroquinone, the procedure was the same as that followed in the addition of diethyl malonate. In making the esters from the acid, essentially the same procedure was followed in all cases, so that the preparation of only one ester will be described in detail. The esters were all recrystallized from the same alcohol used in making them. The acetyl derivatives of most of the esters were also made, and the procedure was exactly the same as that used for the acetylation of the acid III and need not be described again.

METHYL ESTER.—The yellow 260° acid III is treated with a large excess of dry methyl alcohol and a few drops of sulfuric acid and then refluxed for two days. The yellow crystalline product melts at 214° and is identical with the addition compound of duroquinone and sodium dimethyl malonate.

Anal. Calcd. for $C_{14}H_{14}O_6$ (262): C, 64.1; H, 5.3; OCH_3 (one), 11.83. Found: C, 64.32, 64.44; H, 5.37, 5.16; OCH_3, 11.49, 11.65.

The *acetyl derivative* was colorless; m. p., 190°.

Anal. Calcd. for $C_{16}H_{16}O_6$ (304): C, 63.2; H, 5.2; OCH_3 (one), 10.10. Found: C, 63.17, 62.64; H, 5.21, 5.31; OCH_3, 10.08, 10.03.

ETHYL ESTER.—M. p., 184°. This has already been described.

The *acetyl derivative* crystallizes in the form of colorless needles; m. p., 177°.

Mol. wt. Subs., 0.0224; camphor, 0.1797; D, 14.9°, 15.5°, 15.7°. Calcd. for $C_{17}H_{18}O_6$: 318. Found: 335, 322, 318.

Anal. Calcd. for $C_{17}H_{18}O_6$: C, 64.2; H, 5.6; OC_2H_5 (one), 14.1. Found: C, 63.93, 64.30; H, 5.78, 6.10; OC_2H_5, 13.04, 13.75.

n-PROPYL ESTER.—Yellow; m. p., 175°.

Anal. Calcd. for $C_{16}H_{18}O_5$ (290): C, 66.2; H, 6.2; OC_3H_7, 20.35. Found: C, 66.29, 66.16; H, 6.34, 6.32; OC_3H_7, 19.32, 19.32.

The *acetyl derivative* is colorless; m. p., 179°.

Anal. Calcd. for $C_{18}H_{20}O_6$ (322): C, 65.1; H, 6.0; OC_3H_7 (one), 17.77. Found: C, 64.55, 64.94; H, 6.22, 6.05; OC_3H_7, 16.99.

*iso*PROPYL ESTER—Yellow; m. p., 170°.

Anal. Calcd. for $C_{16}H_{18}O_5$ (290): C, 66.2; H, 6.2. Found: C, 66.34, 65.52; H, 6.5, 6.1.

n-BUTYL ESTER.—Yellow; m. p., 168°.

Anal. Calcd. for $C_{17}H_{20}O_5$ (304): C, 67.1; H, 6.6; OC_4H_9 (one), 24.01. Found: C, 66.90, 66.63; H, 6.63, 6.65; OC_4H_9, 23.54.

The *acetyl derivative* is colorless; m. p., 134°.

Anal. Calcd. for $C_{19}H_{22}O_6$ (346): C, 65.9; H, 6.3; OC_4H_9, 21.1. Found: C, 66.01, 66.24; H, 6.49, 6.55; OC_4H_9, 20.72.

*iso*AMYL ESTER.—Yellow; m. p., 149°.

Anal. Calcd. for $C_{18}H_{22}O_5$ (318): C, 67.9; H, 6.9; OC_5H_{11} (one), 27.3. Found: C, 67.98, 68.13; H, 7.01, 7.15; OC_5H_{11}, 25.16.

GLYCERYL ESTER.—Yellow; m. p., 155° with decomposition. It does not crystallize well.

Anal. Calcd. for $C_{16}H_{18}O_7$ (322): C, 59.60; H, 5.60. Found: C, 58.63, 59.05; H, 5.55, 5.63.

ETHYLENE CHLOROHYDRIN ESTER.—Yellow needles; m. p., 229.

Anal. Calcd. for $C_{15}H_{15}O_5Cl$ (310.5): C, 57.98; H, 4.84; Cl, 11.43. Found: C, 58.45, 58.08; H, 4.89, 4.70; Cl, 11.13, 11.17.

ETHYLENE BROMOHYDRIN ESTER.—Yellow; m. p., 234–236° with decomp.

Anal. Calcd. for $C_{15}H_{15}O_5Br$ (355): C, 50.71; H, 4.25; Br, 22.54. Found: C, 50.51, 50.81; H, 4.10; Br, 22.45, 22.50.

Methylation of III.—The methylation of the acid III, or of the methyl or ethyl esters IIIA, leads to the same products. Since the ethyl ester IIIA was the direct product of the reaction between the quinone and malonic ester, it was usually the starting material for the preparation of these methyl derivatives. The methylation, however, requires great care. When the substance is shaken with an excess of dimethyl sulfate, and dilute alkali is added in small portions, with waiting before each addition until the deep red precipitate disappears, a good yield of the 195° monomethyl derivative IX results. If care is taken to complete the methylation in a neutral solution, at room temperature, there results a mixture of two substances which may be separated by fractional crystallization from methyl alcohol. One is the 195° monomethyl derivative IX and the other is a dimethyl derivative VIII, melting at 153-154°. If the yellow ethyl ester IIIA is dissolved in a large excess of dimethyl sulfate, and concd. potassium hydroxide solution is added in small portions through a reflux condenser, the mixture boils violently, and after a time, a clear solution results that separates into two layers. When nearly all of the dimethyl sulfate has been used up, the reaction mixture is cooled and the methylation is completed by adding alternately alkali and dimethyl sulfate, keeping the contents as nearly neutral as possible. Water is then added in excess, and the white mass is filtered off after being thoroughly cooled. The product is mainly the 93° tetramethyl derivative IV. It is best extracted with ether, the ether being then filtered and evaporated. The oily solid is taken up in a small volume of warm methyl alcohol and warm water added just to cloudiness. On cooling, the white substance crystallizes. The 195° and 153° derivatives are usually present, but are removed by the ether extraction because of their slight solubility in ether. All of these methyl derivatives, when heated with concd. aqueous hydriodic acid, give the original acid III.

MONOMETHYL DERIVATIVE. 2-Lactone of 2-Hydroxy-5-methoxy-3,4,6-trimethylbenzalmalonic Acid IX.—The substance is recrystallized from acetic acid. It forms long slender needles, almost colorless, melting at 195° without decomposition. It is not very soluble in the ordinary solvents, but dissolves in alkali and in aqueous ammonia without hydrolysis, giving a very pale yellow solution. It is isomeric with the yellow 214° methyl ester IIIA.

Anal. Calcd. for $C_{14}H_{14}O_5$ (262): C, 64.1; H, 5.3; OCH_3 (one), 11.8. Found: C, 63.94, 63.95; H, 5.32, 5.26; OCH_3, 11.55, 11.75.

SILVER SALT.—This is prepared by dissolving the 195° derivative in dil. ammonia, boiling off the excess ammonia and adding a solution of silver nitrate to the cooled solution. The salt precipitates as a pale yellow substance, and coagulates well, so that it is easily filtered off and washed.

Anal. Calcd. for $C_{14}H_{13}O_5Ag$: C, 45.6; H, 3.52; Ag, 29.3; OCH_3 (one), 8.40. Found: C, 45.19, 45.08; H, 3.40, 3.51; Ag, 28.79, 28.82; OCH_3, 8.23, 8.22.

Esterification.—When the 195° compound is dissolved in an excess of dry alcohol and a few drops of sulfuric acid, the solution refluxed for a day and then allowed to stand for another day, esterification takes place and the ester crystallizes on cooling. It may be recrystallized from the appropriate alcohol or from acetic acid.

METHYL ESTER VIII.—This melts at 153-154° without decomposition. It is very pale yellow and is soluble in most organic solvents. It is identical with the 153-154° dimethyl derivative obtained by the action of dimethyl sulfate on the acid III, the yellow 214° methyl ester, or the yellow 184° ethyl ester (IIIA). Alkalies hydrolyze it to the 195° derivative. This methyl ether-methyl ester is isomeric with the yellow ethyl ester (IIIA).

Anal. Calcd. for $C_{15}H_{16}O_5$ (276): C, 65.1; H, 5.8; OCH_3 (two), 22.46. Found: C, 64.96, 65.03; H, 5.92, 5.96; OCH_3, 22.64, 22.70.

ETHYL ESTER.—This is colorless and melts at 108°.

Anal. Calcd. for $C_{16}H_{18}O_5$ (290): C, 66.2; H, 6.2; $^1/_2$ (OCH_3 + OC_2H_5), 26.20. Found: C, 66.13, 66.08; H, 6.22, 6.21; OR, 25.6.

TETRAMETHYL DERIVATIVE. 2,5-Dimethoxy-3,4,6-trimethyl-benzalmalonic Dimethyl Ester IV.—This crystallizes from dil. methyl alcohol as short, heavy, colorles- prisms, which tend to form clusters; m. p., 93°. For most of the reactions involving this substance, samples were used which melted at 90–91°. When the substance is recrystallized from ethyl alcohol, it melts sharply at 88–89° and retains this melting point, even after several recrystallizations from methyl alcohol. The substance does not react with bromine, either in acetic acid or carbon tetrachloride.

Mol. ut. Subs., 0. 4650, 0.9895: Benzene, 15.16, 12.66; D, 0.514°, 1.338°; *K*, 5.12; mol. wt., 306, 299.

Anal. Calcd. for $C_{17}H_{22}O_6$ (322): C, 63.3; H, 6.8; OCH_3 (four), 38.5. Found: C, 63.59, 63.26; H, 6.75, 6.80; OCH_3, 37.30, 37.40.

The Diether Diacid (V). 2,5-Dimethoxy-3,4,6-trimethyl-benzalmalonic Acid.—The 93° tetramethyl derivative is heated for two hours on the steam-bath with a dilute alcoholic solution of sodium hydroxide. The solution is deep red and, when cool, acid is added in slight excess; the product precipitates as an oil which hardens on standing for a few hours. It is then filtered off and recrystallized from dil. alcohol, from which it forms long, blunt, colorless needles, melting at 188° with decomposition. It is slightly soluble in water and the mother liquor should be extracted with ether to prevent loss of material.

Anal. Calcd. for $C_{15}H_{18}O_6$ (294): C, 61.2; H, 6.10; OCH_3 (two), 21.1. Found: C, 60.90, 60.80; H, 5.95, 6.19; OCH_3, 21.05.

SILVER SALT.—This was prepared by the usual method of making the ammonium salt and adding silver nitrate solution to it. It is slightly soluble in water, and is stable to light and a temperature of 100°.

Anal. Calcd. for $C_{15}H_{16}O_6Ag_2$ (508): C, 35.40; H, 3.15; Ag, 42.50. Found: C, 34.44; H, 3.63, 3.37; Ag, 41.10, 40.80.

Alkali Fusion.—An attempt was made to eliminate a carboxyl group from the diacid by fusing it with about 20 times its weight of a mixture of moist sodium and potassium hydroxides. The temperature was held at 290°, during constant stirring for several hours. Then the cooled mixture was dissolved in water, the solution neutralized with acid, and the white precipitate filtered off and crystallized from dil. acetic acid. It was the 195° monomethyl derivative, and the same product was obtained when the diacid was heated with moist lime, or simply heated alone at its melting point. On heating the acid at its melting point and passing the evolved gas through phosphorus pentoxide, 1.071 g. of substance lost 0.1182 g., or 11.1%; and 0.1476 g. of substance, lost 0.0145 g. or 9.8%. Calculated loss for $C_{15}H_{18}O_6$ (one molecular proportion of methyl alcohol), 10.8%. Constant boiling hydriodic acid reacts with the diacid, giving the 260° yellow acid III.

Reduction. 2,5-Dimethoxy-3,4,6-trimethyl-benzylmalonic Acid XII.—One g. of the 188° diether-diacid was dissolved in about 50 cc. of glacial acetic and zinc dust added to the boiling solution. The excess of zinc was dissolved with dil. sulfuric acid after the mixture had been diluted. A white precipitate formed, which on recrystallization from acetic acid melted at 154–155°.

Anal. Calcd. for $C_{15}H_{20}O_6$: C, 60.8; H, 6.7. Found: C, 61.3, 61.4; H, 6.9, 6.8.

Oxidation. 2,5-Dimethoxy-3,4,6-trimethyl-benzaldehyde VI.—The 188° diether diacid was dissolved in sodium bicarbonate (about 10%), cooled in an ice-bath, and slightly more than its own weight of potassium permanganate in solution was added in several portions during two hours. After standing for a few hours, the mixture was acidified with dil. sulfuric acid, and then just enough bisulfite added to dissolve the precipitated oxides of manganese. The yellow precipitate was filtered off and recrystallized from methyl alcohol diluted with thrice its volume of water. The yellow plates melted at 84–85° without decomposition. The oxidation product is phototropic. In the dark it slowly loses its yellow color, which rapidly returns in sunlight.

Mol. wt. Subs., 1.022, 1.022: Benzene, 22.08, 27.23; D, 1.131°, 0.927°; *K*, 5.12. Calcd. for $C_{12}H_{16}O_3$: mol. wt., 208. Found: 209, 207.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.2; H, 7.70; OCH_3 (two), 29.8. Found: C, 69.03, 68.86; H, 7.90, 7.94; OCH_3, 29.5. 29.2.

On standing for a day, the original reaction mixture deposited a fine, white, crystalline powder, which was filtered off and washed. This gave a test for manganese, and the substance was apparently a manganese salt of some organic acid. The properties agree with those of the dihydrate of manganous oxalate[15] in color, crystalline structure and solubility, and the analysis also checks this substance.

Anal. Calcd. for $C_2O_4Mn.2H_2O$: C, 13.4; H, 2.23; Mn, 30.7. Found: C, 13.6, 13.4; H, 2.05, 2.23; Mn, 32.4, 32.3.

Attempts were made to oxidize the aldehyde with potassium dichromate and chromic trioxide in both glacial acetic acid and water. In the cold, no reaction took place, while on heating, the substance was attacked but no solid products could be isolated. The aldehyde gave a silver mirror with alkaline silver nitrate (Tollens' reagent) on standing for 12 hours.

OXIME.—This was made by heating the aldehyde with hydroxylamine hydrochloride in large excess (4 to 5 equivalents), sodium acetate (5 equivalents) in absolute methyl alcohol on the steam-bath for a day, and then allowing the mixture to stand for three days. On dilution with water and a few drops of hydrochloric acid, a pale yellow precipitate formed which, when recrystallized from dil. methyl alcohol, formed very pale yellow, squarely cut prisms, melting at 132–134° without decomposition. The oxime deflagrates violently when heated on a platinum foil, and because of this must not be heated too rapidly during analysis. It gave a qualitative test for nitrogen.

Anal. Calcd. for $C_{12}H_{17}O_3N$: C, 64.60; H, 7.60. Found: C, 64.50, 64.40; H, 7.57, 7.50.

Reduction. 2,5-Dimethoxy-3,4,6-trimethyl-benzyl Alcohol X.—The aldehyde was dissolved in pure methyl alcohol, and the solution shaken with an excess of 2% sodium amalgam, a few drops of hydrochloric acid being added from time to time. There soon appeared a gray-to-white precipitate which was filtered off and recrystallized from 30% acetic acid. It was white, m. p. 242–244°, and was not investigated further. It accounts for about one-third of the material. The filtrate from the reaction mixture on dilution with water deposited white crystals, which on recrystallization from dil. methyl alcohol melted at 115–116°. When this is oxidized with chromic trioxide in acetic acid, the product is the aldehyde VI.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.60; H, 8.60. Found: C, 68.61, 68.50; H, 8.58, 8.00.

Acetylated with acetic anhydride and a drop of concd. sulfuric acid, this alcohol gave

---

[15] Abegg, "Handbuch der Anorg. Chem.," S. Hirzel, Leipzig, 1913, Vol. IV, Pt. 2, p. 782.

a purple solution, which on dilution yielded white needles, m. p. 65–66°. This was the 2,5-dimethoxy-3,4,6-trimethyl-benzyl ester of acetic acid XI.

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.70; H, 7.90. Found: C, 66.3; H, 7.62.

Trimethyl-nitrobenzoquinone (VII).—When the 85° aldehyde is warmed with concd. (d., 1.4) nitric acid a clear yellow solution results. This solution, on the addition of water, deposits glistening yellow platelets, which on recrystallization from dil. alcohol melt at 112–113°. The melting point of the substance agrees with that given by Nef[10] for trimethyl-nitrobenzoquinone. The latter was prepared by nitrating pseudocumoquinone (trimethyl-quinone). Upon taking a mixed melting point, the mixture showed no lowering.

Summary

1. Sodium malonic ester has been added to duroquinone, giving as the primary products the hydroquinone and a red sodium derivative, which with acids, gives a yellow lactone-ester.

2. The reaction is complicated by oxidation, and the quinone is the oxidizing agent.

3. The yellow lactone-ester forms colorless acetyl and methyl derivatives, and a structure change of the *para*-keto-enol type is involved in these reactions. The colorless compounds are benzene derivatives, while the colored compounds are analogous to the oxyanthranols. The mechanism of the primary reaction has not yet been determined.

MINNEAPOLIS, MINNESOTA

[CONTRIBUTION FROM THE DIVISION OF BIOCHEMISTRY AND PHARMACOLOGY, UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL]

THE SEPARATION OF THE DICARBOXYLIC AMINO ACIDS FROM CERTAIN PROTEIN HYDROLYSATES BY ELECTRICAL TRANSPORT

BY G. L. FOSTER AND CARL L. A. SCHMIDT

RECEIVED MARCH 2, 1926 PUBLISHED JUNE 5, 1926

Some years ago Ikeda and Suzuki[1] patented a process for the separation of protein hydrolysates into three groups of amino acids by electrical transport. We became interested in this process during a survey of the methods for the preparation of amino acids in relatively large quantities, and we have described elsewhere the conditions under which the hexone bases may be separated from certain protein hydrolysates.[2] In the present paper experiments dealing with the transport of the predominantly acid amino acids are reported, and the conditions for their separation from certain protein hydrolysates are outlined. Data relative to the preparation of arginine and lysine by the method of electrical transport are also included.

---

[1] Ikeda and Suzuki, U. S. pat. 15,891, Jan. 30, 1912.

[2] Foster and Schmidt, *J. Biol. Chem.*, **56**, 545 (1923).