

THE REACTION OF 1,4-NAPHTHOQUINONE WITH MALONIC  
ESTER. PROOF OF STRUCTURE AND CHEMICAL  
CHARACTERIZATION OF THE PRODUCT

By

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...

Thesis submitted to the Faculty of the Graduate School  
of the University of Maryland in partial  
fulfillment of the requirements for the  
degree of Doctor of Philosophy

1948

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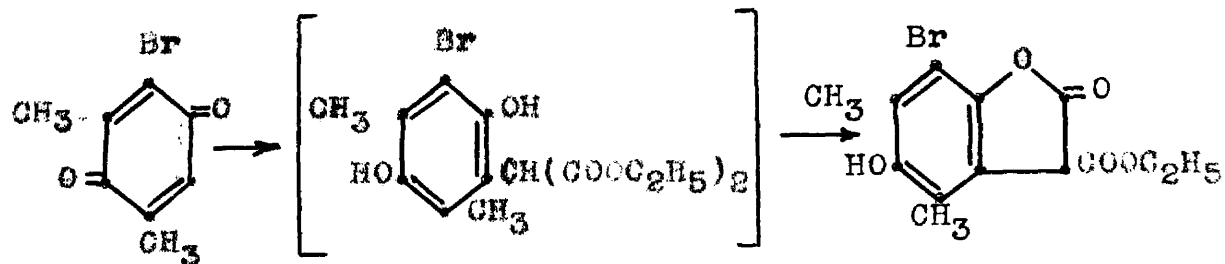
**HISTORICAL INTRODUCTION**

## HISTORICAL INTRODUCTION

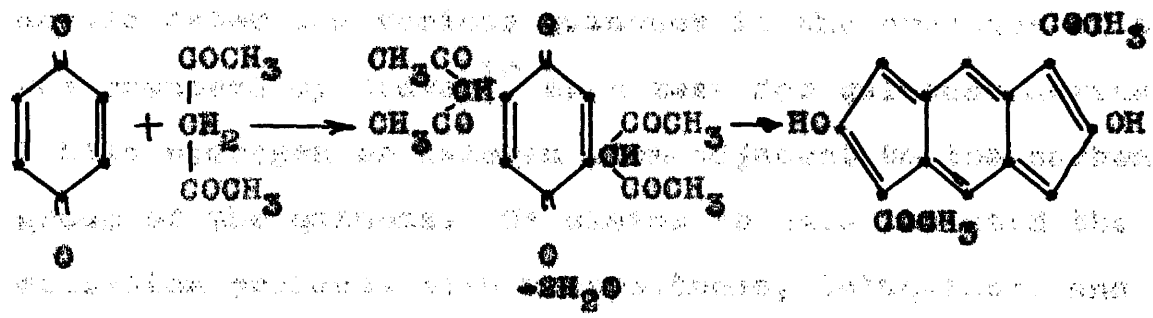
The object of this investigation was to determine the structure and chemical characteristics of the products formed by the condensation in the presence of a tertiary amine of 1,4-naphthoquinone with compounds containing a reactive methylene group. The active methylene compound used in most of the work reported here was malonic ester, but cyanoacetic ester was also investigated to a limited extent.

The products of these condensations are of potential importance because of their possible hemorrhagic or anti-hemorrhagic properties. They may also prove to be of aid in the correlation of structure with Vitamin K activity. The physiological properties of the quinones have been summarized recently by Rosenberg<sup>1</sup> and by Hofmann-Ostenhout.<sup>2</sup>

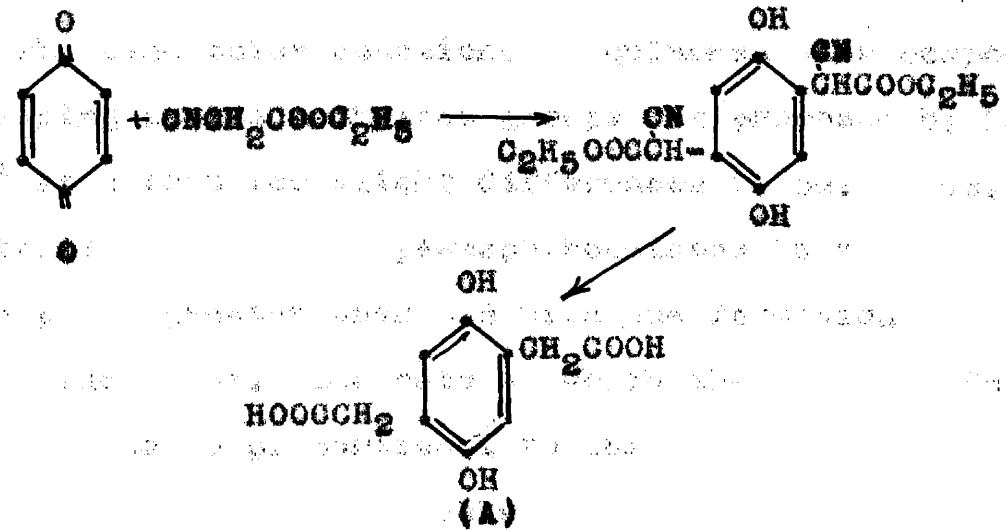
The reaction of substituted benzoquinones with compounds containing reactive methylene groups in the presence of sodium ethoxide has been the subject of an extended research project headed by Lee Irvin Smith.<sup>3</sup> When a brominated polymethylbenzoquinone such as bromo-*m*-xylequinone is treated with sodio-malonic ester, 1,4-addition takes place at the unsubstituted position of the ring and an isocoumaranone results:



Benzoquinone itself has been shown to condense with two moles of acetoacetic ester<sup>4</sup> in the presence of sodium ethoxide. The intermediate product then cyclizes to a difurobenzene derivative with the elimination of two moles of alcohol. When the reaction was carried out in acetone solution using a zinc chloride catalyst,<sup>5,6</sup> benzoquinone and acetoacetic ester condensed in one to one ratio with the formation of a benzofuran derivative in addition to a difurobenzene. The reaction of two moles of acetylacetone<sup>7,8</sup> with benzoquinone in pyridine solution was shown to result in an indacene derivative:



Here recently the preparation of 2,5-dihydroxyterephthalic acid has been described by Weid and coworkers:<sup>9</sup>



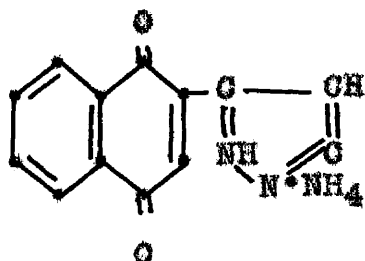


The reaction, which was carried out in alcohol in the presence of ammonium hydroxide, yielded a purplish-red precipitate to which the structure (A) above was ascribed. A mechanism, similar to one previously postulated by Ionescu,<sup>8</sup> but apparently overlooked by Wood and coworkers, was proposed. According to their mechanism, 1,4-addition of the active methylene compound to each eno-one system of benzoquinone occurred with the formation of an intermediate dihydroxycyclohexadiene, which was then oxidized by excess benzoquinone to a hydroquinone derivative.

The formation of an intense blue color from cyanoacetic ester and various quinones in the presence of ammonia was proposed by Craven<sup>10</sup> as a test for quinones having a labile hydrogen or halogen atom adjacent to the carbonyl group of the quinone. He claims to have isolated the condensation products with benzoquinone, toluquinone and chloranil, as well as with 1,4-naphthoquinone. Craven promised further work on the preparation and constitution of these compounds; however, no further work has appeared.

The same color reactions of quinones with compounds containing active methylene groups was proposed by Kesting<sup>11</sup> as a test for slight differences in pH. Thus, malonitrile reacts with 1,4-naphthoquinone in solutions whose pH is greater than 2.5 with the formation of an intense blue color. The rate at which the color is formed was shown to be proportional to the hydroxyl ion concentration. Kesting<sup>12</sup> was not able to isolate the blue compound

but claims to have obtained it in the form of an ammonium salt to which he at first ascribed the structure:

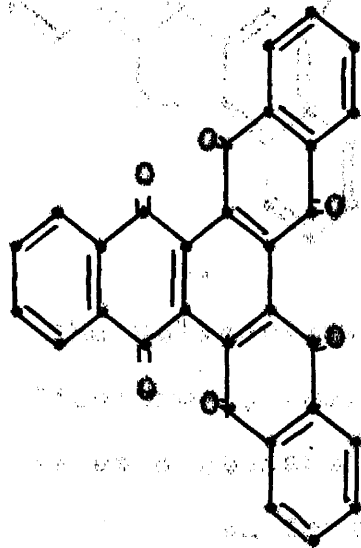


Because malonic ester<sup>13</sup> also gave the intense blue color with 1,4-naphthoquinone and with benzoquinone, Kesting<sup>14</sup> was forced to discard his previous theory and assumed a "heteropolar color-complex" or aci-salt such as:

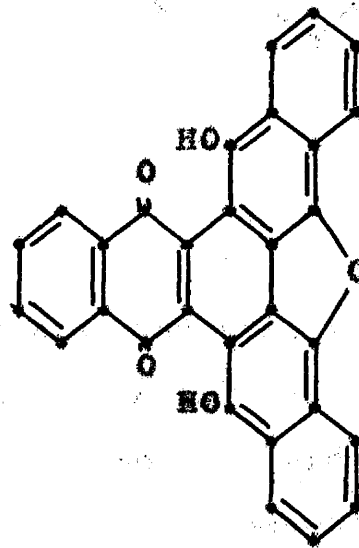


Since 1,4-naphthoquinone itself contains two active hydrogens, it is not unreasonable to suppose that polymerization would take place rather readily. This self-condensation appears to have been noted first by Villiger and von Krammichfeldt<sup>15</sup> during the purification of 1,4-naphthoquinone by steam distillation at 120°. A yellow, extremely insoluble, high-melting residue remained. Further investigation revealed that this material, which had the properties of a vat dye, could also be obtained by heating 1,4-naphthoquinone in phenol, alcohol, or pyridine.<sup>16,17</sup> When 1,4-naphthoquinone was distilled in steam at 150-170° a greenish condensation product was obtained which was reducible in alkaline medium while the yellow material could be reduced in acidic or neutral medium. The structures of the products

were established by Pummerer and coworkers<sup>16,17,18</sup> as tri-phthaloylbenzene (B) for the yellow polymer and as its anhydro-quinhydron (C) for the green polymer:



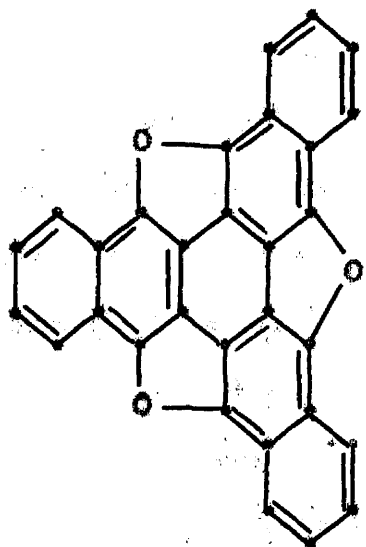
(B)



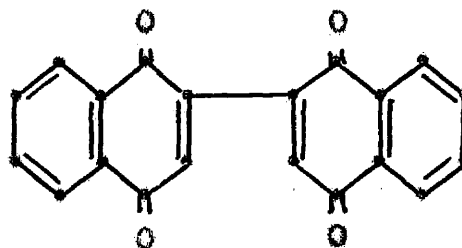
(C)

The action of sulfuric acid<sup>19</sup> on 1,4-naphthoquinone or of aluminum chloride<sup>20,21</sup> on 1,4-naphthoquinone and 1,4-naphthohydroquinone leads to the formation of the tri-ether trioxide-trinaphthalene. (D)

As one might anticipate, some dimeric product is also formed in the polymerisation to triphthaloylbenzene, and under controlled conditions, Pummerer and coworkers<sup>18</sup> were able to isolate the dimer (E) almost exclusively:

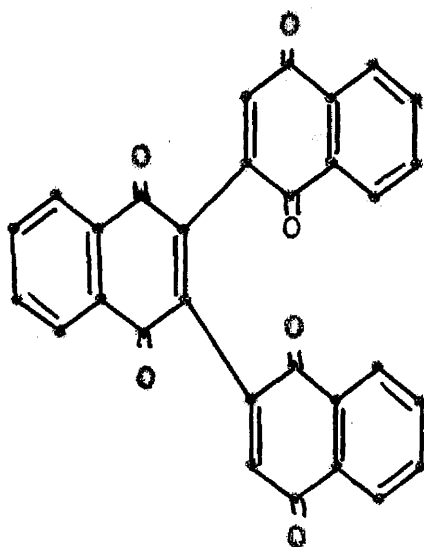


(D)



(E)

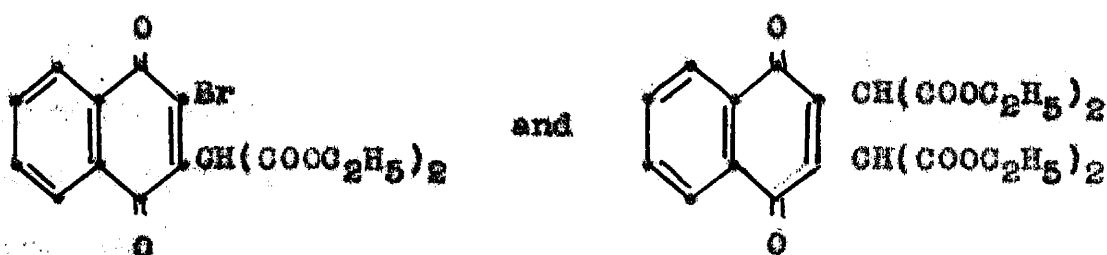
The polymerization process also has been applied to 2,3-dichloro-1,4-naphthoquinone by Schell<sup>22</sup> using copper powder as a condensing agent. He also referred to his compound, which formed a tetraacetate on reductive acetylation, as triphthaloylbenzene; however, Pummerer views the Schell compound as 2,3-bis-(1,4-naphthoquinonyl-2)-1,4-naphthoquinone:



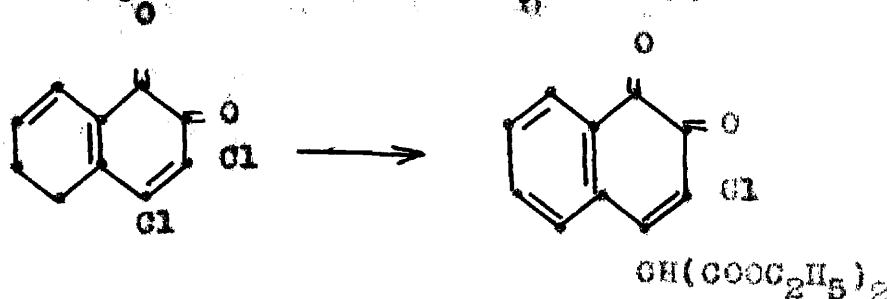
The condensation to trimers of 5- and 6- substituted

1,4-naphthoquinones has been studied by Fierz-David.<sup>23</sup>

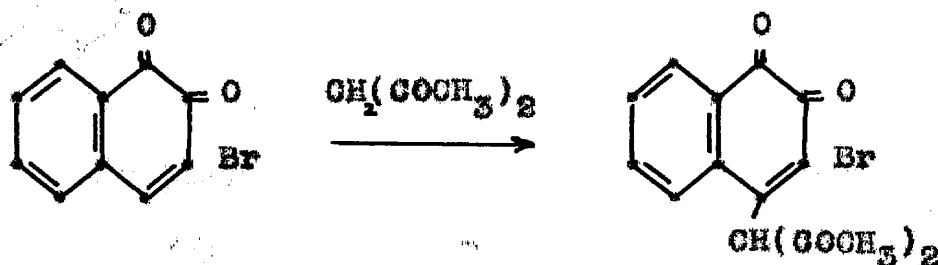
Liebermann<sup>24</sup> in 1898 obtained a transient blue-green color when 1,4-naphthoquinone was reacted with malonic ester in the presence of sodium ethoxide in alcoholic solution. He was able only to isolate a tan product which was not analysed; however, when 2,3-dihalo-1,4-naphthoquinones were condensed with the sodium derivatives of malonic,<sup>25,26</sup> cyanoacetic,<sup>27</sup> acetoacetic<sup>28,29</sup> and acetone dicarboxylic esters products of the following types were precipitated by acidification:



The reaction more recently has been extended to 2-mesityl-3-bromo-1,4-naphthoquinone by Yuan.<sup>30</sup> When treated with the sodium derivatives of malonic and cyanoacetic esters the halogen was split out as sodium bromide. This reaction is, however, not limited to halogenated 1,4-naphthoquinones. 3,4-Dihalo-1,2-naphthoquinones<sup>31</sup> have been found to condense with the sodium derivatives of compounds containing active methylene groups with replacement of the halogen atom in the 4- position.

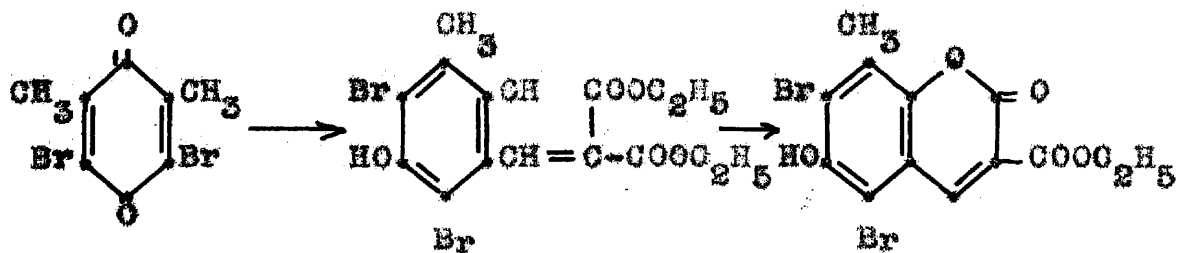


When a 3-halo-1,2-naphthoquinone<sup>31</sup> was treated with acetylacetone in the presence of oxygen and sodium ethoxide, replacement of the hydrogen atom in the 4- position occurred:

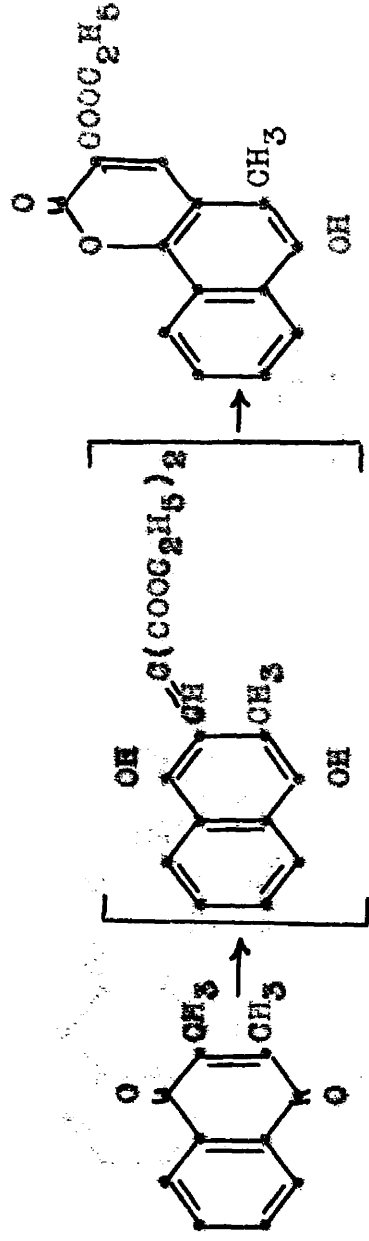


As a by-product, 3-bromo-4-ethoxy-1,2-naphthoquinone also was isolated.

When a brominated polymethylbenzoquinone containing no unsubstituted positions in the ring, such as dibromo-*m*-xyloquinone,<sup>32</sup> was treated with sodio-malonic ester, the halogen remained intact and addition of the enolate to a methyl group took place. This product cyclized by the loss of alcohol:



With 1,4-naphthoquinones containing methyl groups in the 2- position<sup>33</sup> the reaction took a similar course and the enolate added 1,4 to the methylquinone. On acidification of the deep purple intermediate a benzocoumarin derivative was isolated:

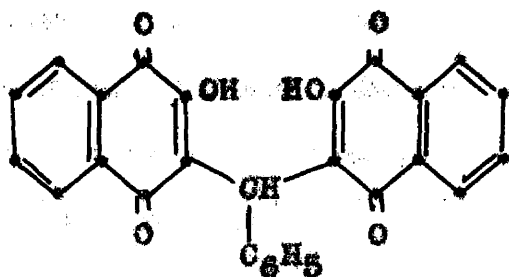


When polymethylbenzoquinones containing one or more unsubstituted positions were condensed with malonic ester in the presence of sodium ethoxide, 1,4- addition to the quinone ring took place. Thus trimethylbenzoquinone<sup>34</sup> and sodio-malonic ester yield 1,3,4-trimethyl-2,6-dihydroxyphenylmalonic ester which cyclizes to a benzofuran derivative.

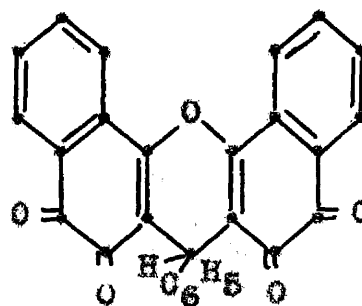
In order to obtain additional support for the proposed structures of the compounds obtained in this investigation by the condensation of 1,4-naphthoquinone with malonic ester it was advisable to consider alternative methods of synthesis. A few of the most promising of these methods will be considered. The compounds obtained by these methods are also of potential interest as type compounds for the comparison of ultraviolet absorption spectra.

Zincke and Thelan<sup>35</sup> appear to have been the first to investigate the condensation of 1,4-naphthoquinones with aldehydes. When 2-hydroxy-1,4-naphthoquinone and benzaldehyde were warmed in alcoholic solution the primary product isolated was a dinaphthoquinonylmethane derivative (F). In addition, a small amount of the cyclic dehydration pro-

duct (G) was obtained:



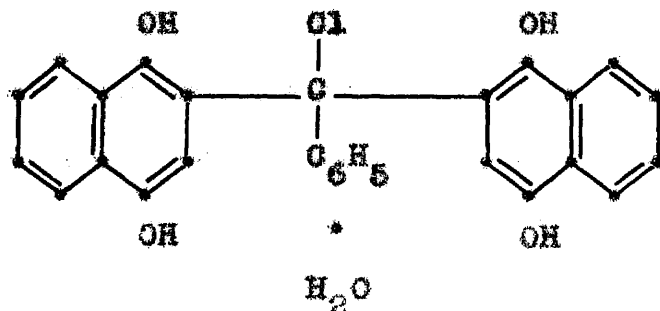
(F)



(G)

When the reaction was carried out in a mixture of acetic and hydrochloric acids the condensation between 2-hydroxy-1,4-naphthoquinone and an aliphatic aldehyde such as isovaleraldehyde led to the formation of 2-hydroxy-3-( $\Delta^1$ -3-methylbutenyl)-1,4-naphthoquinone (isolapachol).<sup>36</sup>

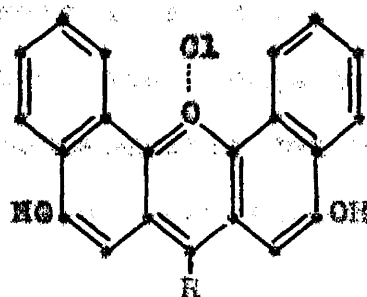
By condensing 1,4-naphthohydroquinone with benzaldehyde or benzotrichloride in the presence of a mixture of acetic and hydrochloric acid Wurgraft<sup>37</sup> obtained a red dyestuff whose analysis indicated the following structure:



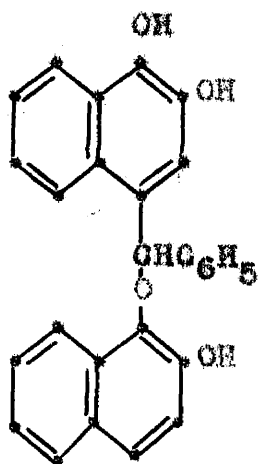
Raudnitz and Puluj<sup>38</sup> who repeated Wurgraft's work obtained a compound which they considered to be the anhydrous pigment. They found that other aromatic and aliphatic aldehydes condensed similarly with 1,4-naphthohydroquinone as well as with 1,4-naphthoquinone. The best yields (40-44%) were obtained when an equimolecular



mixture of quinone and hydroquinone was reacted with the aldehyde. In the presence of alkali the pigments dissolved with the formation of a deep blue color which faded on standing. Largely on the basis of anhydrous picrates which were prepared from the pigments, Fieser and Fieser<sup>39</sup> assigned an anthocyanidin structure to the condensation products;

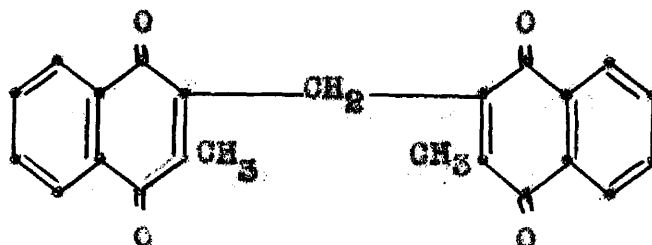


The reaction of aldehydes with naphthohydroquinones is not limited to the 1,4-isomers. Fieser and Hartwell<sup>40</sup> obtained 2-hydroxy-1,4-naphthofuchsone-1 (or its o-quinonoid isomer) as a product of the reaction between 1,2-naphthohydroquinone and benzophenone dichloride. With benzaldehyde and hydrogen chloride or with benzal chloride in benzene a colorless product was obtained to which Fieser and Fieser<sup>41</sup> assigned the following structure;



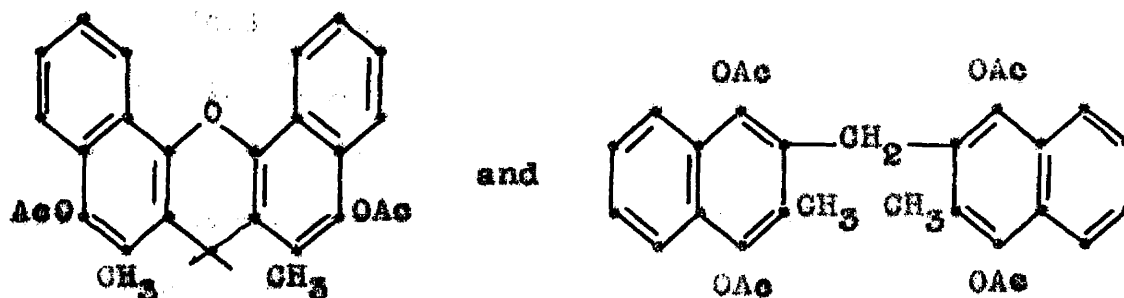
When 1,2-naphthohydroquinone was replaced by the 1,4-isomer no crystalline material could be isolated. The product from 1,2-naphthohydroquinone was cleaved to 2-hydroxy-4-benzal-1-naphthone and 1,2-naphthohydroquinone by the action of concentrated sulfuric acid.

When 1,4-naphthohydroquinone was reacted with formaldehyde in either acid or alkaline solution von Euler and Kispecky<sup>42</sup> were able to isolate only tars. 2-Methyl-1,4-naphthohydroquinone, however, yielded a bis-methyl-naphthoquinonylmethane when treated with formaldehyde in the presence of alkali and air:

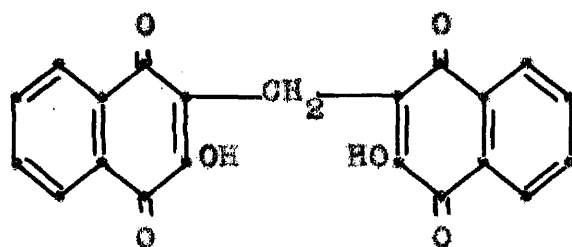


A closely related compound was obtained by Fieser and Seligman<sup>43</sup> who reacted 2,6-dimethyl-1,4-naphthoquinone with diazomethane. They believed their product to be bis-(3,7-dimethyl-1,4-naphthoquinonyl-2)-methane.

In the presence of an acidic catalyst 2-methyl-1,4-naphthoquinone and formaldehyde gave a mixture of phenolic products<sup>42</sup>, which on acetylation with acetic anhydride formed a diacetate and a tetraacetate:



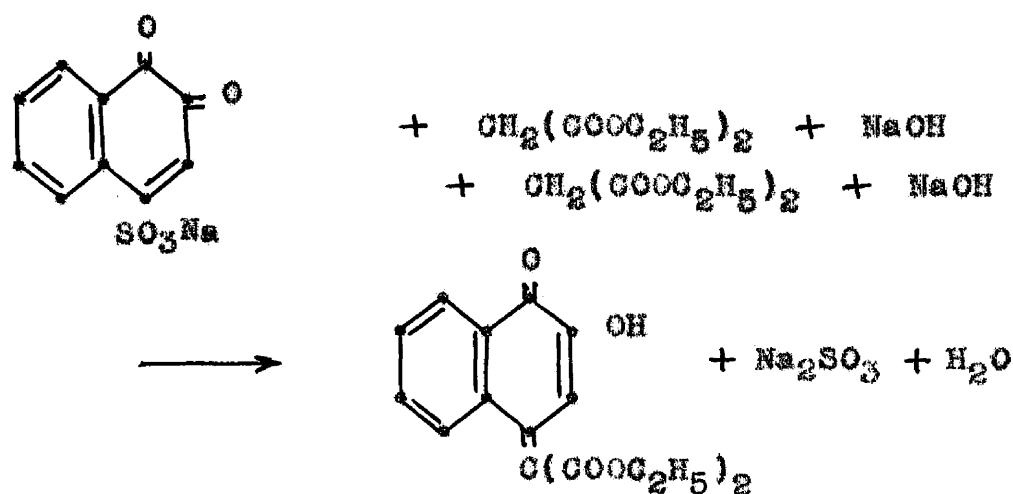
During their study of the relation between structure and anti-hemorrhagic activity, Meunier and coworkers<sup>44</sup> condensed 2-hydroxy-1,4-naphthoquinone with formaldehyde in the presence of alkali and obtained a greenish-yellow product of the following structure which they named Antivitamin K:



Both 1,4-naphthoquinones and 1,4-naphthohydroquinones react readily with allylic alcohols. Thus, Vitamin K<sub>1</sub> has been synthesized by heating 2-methyl-1,4-naphthoquinone with phytol<sup>45</sup>, by reacting 2-methyl-1,4-naphthohydroquinone with phytol in dioxane solution in the presence of oxalic acid<sup>46</sup>, trichloroacetic acid<sup>46</sup> or phosphoric acid<sup>47</sup>, followed by oxidation to the quinone. Another variation employs the monosodium salt of the hydroquinone and phytyl bromide.<sup>48,49</sup> Other beta-unsaturated alcohols<sup>50,51</sup> and olefins such as isoprene<sup>51</sup> react in the same manner.

The intense color reactions given by 1,2-naphthoqui-

none-4-sulfonic acid with amines and compounds containing active methylene groups appears to have been studied first by Ehrlich and Herter.<sup>52,53</sup> Further investigation of these reactions was carried out by Sachs and his students.<sup>54,55</sup> In the presence of sodium hydroxide, sodium or potassium 1,2-naphthoquinone-4-sulfonate reacted with malonic ester, benzylcyanide, malononitrile, etc., to form yellow crystalline compounds as a result of the replacement of the sulfonic acid group by an active methylene residus. The reaction was formulated as follows:



The reactions and tautomerization of the products have been investigated by Dean and Nierenstein<sup>56</sup> and by Fieser and coworkers.<sup>41,57</sup> The application of a modification of this synthesis proved to be very helpful in supporting the structure proposed for the product obtained by condensing 1,4-naphthoquinone with malonic ester in this investigation.

## DISCUSSION

## DISCUSSION

The first step in the proof of structure of the condensation product of 1,4-naphthoquinone and malonic ester was a study of the optimum conditions for its preparation. It was found that when 1,4-naphthoquinone and diethyl malonate were brought together in a basic medium an intense blue color appeared. The color was formed instantly from the components in alcoholic and aqueous alcoholic solutions when a trace of sodium ethoxide or sodium hydroxide was added. As the reaction continued, however, the color faded in a short time to a muddy brown and no trace of blue compound could be isolated.

Of all solvents tried, pyridine<sup>8,58</sup> was the most satisfactory, although the product which had separated at the end of twenty hours at room temperature was always a dirty greenish gray. Upon extraction of this crude material with benzene in a Soxhlet apparatus and concentration of the extract an intensely blue crystalline product was isolated.\* Many other solvents were investigated; in each case, however the blue compound was either very difficult to isolate because of greater solubility (quinoline, dimethylaniline)

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\*This compound and its oxidation product were first obtained, but not identified, by Dr. Yolanda T. Pratt in the laboratories of Prof. L. F. Fieser at Harvard University. The author wishes to thank them for deferring to his interest in this problem.

or none of the desired material was formed (benzene, di-oxane). Tertiary amines, with the exception of triethylamine, generally gave some indication that the blue material was formed, and in these cases careful acidification at low temperature precipitated a dark tar or an amorphous purple powder. Either of these could be extracted with benzene to yield a violet solution from which varying amounts of the desired blue compound were recovered by fractional crystallization. Isolation of further crops from the mother liquors yielded red hydrolysis products. At temperatures above  $50^{\circ}$  and below  $10^{\circ}$  the formation of the blue compound appeared to be inhibited entirely.

The best procedure for preparing the blue compound was to treat an approximately saturated solution of the quinone in pyridine at  $45^{\circ}$  with diethyl malonate and allow the mixture to stand overnight at room temperature. The rather viscous dark brown mother liquors were washed from the greenish-gray filter cake with ice-cold pyridine. Since the blue compound was appreciably soluble in pyridine, the volume of the wash-liquid had to be kept to a minimum. Other solvents such as cold benzene, alcohol, ether and ligroin were less effective in removing the brown mother liquors. The blue material was found to be soluble in most hot organic solvents, although alcohol or acetic acid brought about considerable decomposition with the formation of a red by-product. Benzene appeared to be the best solvent since the blue material was moderately soluble in

boiling benzene and crystallized rapidly upon cooling the solution. Numerous recrystallizations from benzene were necessary in order to obtain a pure product of constant melting point and correct analysis.

The blue compound was obtained in yields of 13-15% based upon equations (2), (3) and (4) below. Most of the succeeding reactions were carried out in much higher yields and frequently the yields were nearly quantitative. Considerable difficulty was encountered in the purification of this and subsequent compounds for analysis, due to their low solubilities, instability and high melting points. Up to nine recrystallizations were required in order to obtain pure products, and even then certain of the analytical results were not entirely satisfactory.

Analysis of the fine blue matted needles indicated that naphthoquinone, malonic ester and benzene had combined in the molecular ratio of 2:1:0.5. The benzene apparently was held firmly in a molecular complex which is not decomposed upon drying at 100° at one mm. pressure for one hour. Complexes from quinones and hydrocarbons have been discussed in the literature.<sup>59,60</sup>

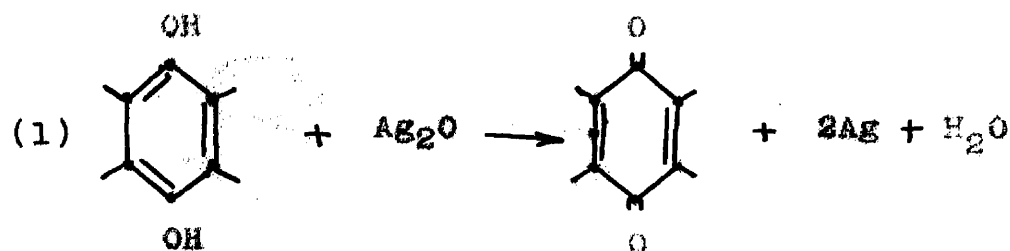
Extraction of the greenish-gray precipitate with acetone or repeated recrystallization of the benzene complex from acetone afforded the benzene-free blue compound, identical in physical appearance and melting point with the product obtained by crystallization from benzene. The analysis corresponded to  $C_{27}H_{22}O_8$ .



The dull yellow residue which remained in the Soxhlet thimble after extraction of the blue compound corresponded to 17-22% of the weight of 1,4-naphthoquinone employed. The self-condensation of this quinone to polymers in the presence of pyridine has been described in the Historical Introduction. The polymerization in pyridine was carried out by Pummerer<sup>16,17</sup> in 42% yield by refluxing for one hour, but in this investigation it was found to take place even at room temperature. The extraction residue was extremely insoluble in most organic solvents, but it could be recrystallized satisfactorily from boiling nitrobenzene. The resulting bright yellow needles darkened above 300° and did not melt below 400°. The reactions and elementary analysis of the compound correspond to those of triphthaloylbenzene.<sup>23</sup> After treatment with concentrated sulfuric acid and zinc dust, the characteristic green anhydro-quinhydrone<sup>23</sup> was precipitated when the mixture was diluted with water.

When the blue compound was oxidized with either silver oxide or chromic acid a greenish-yellow product resulted. Employing silver oxide with benzene as the solvent the greenish-yellow oxidation product was isolated in 98-99% yield as a benzene complex. The complex was not decomposed by drying at 100° at one mm. pressure for one hour. Its elementary analysis corresponded to the formula  $C_{27}H_{20}O_8 \cdot \frac{1}{2}C_6H_6$ .

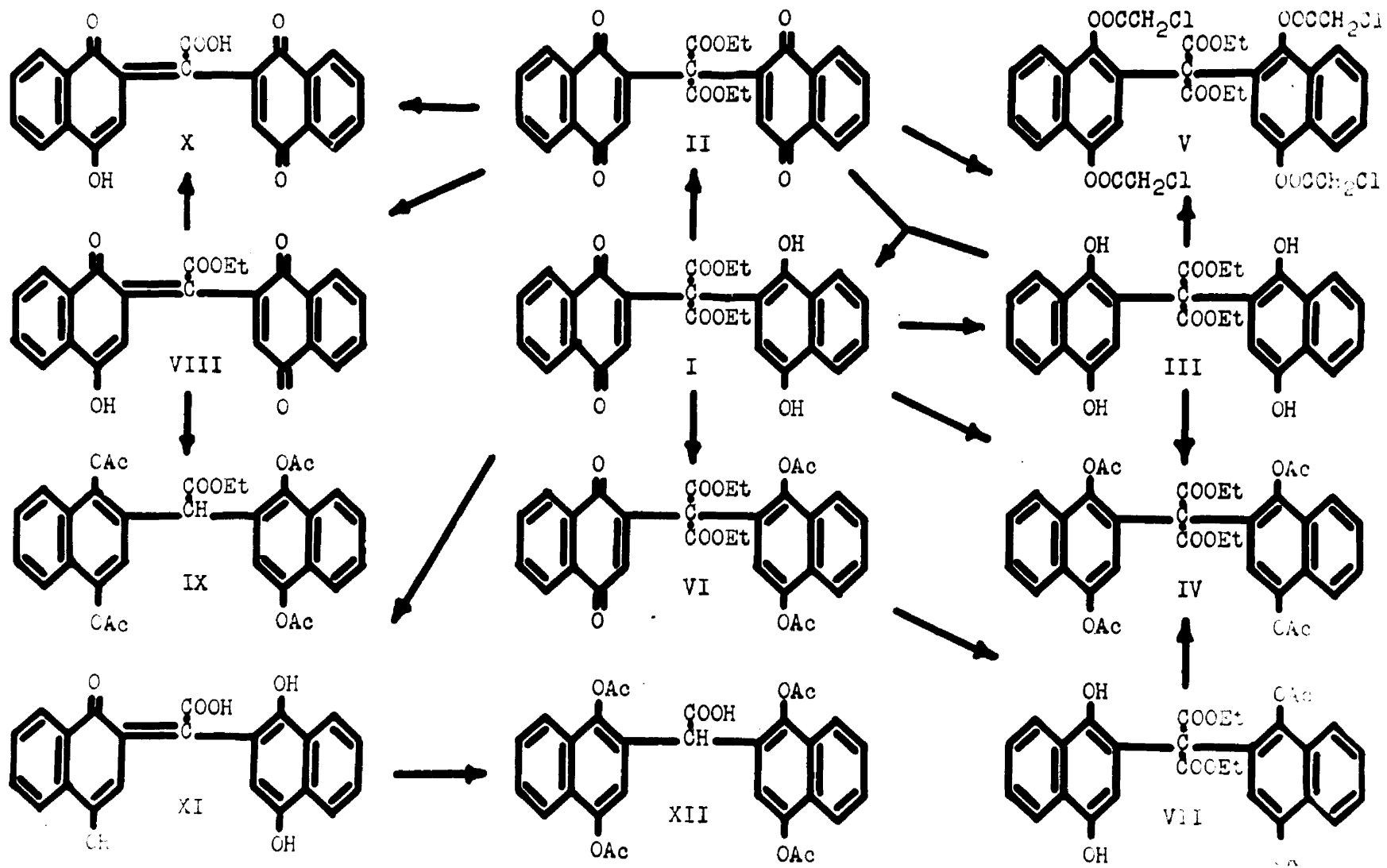
Assuming the following equation to be applicable:



the weight of metallic silver recovered provided a convenient determination of the equivalent weight of the blue compound(I). By this method an equivalent weight of 490 was found. From the ratio of 2:1:0.5 for 1,4-naphthoquinone, malonic ester and benzene as in structure (I) (see Chart I), an equivalent weight of 513.5 was calculated. This was of especial value because the deep blue color of the compound made it impossible to obtain molecular weights by the Rast method.

Oxidation of the blue compound with chromic acid in acetic acid solution followed by crystallization of the product from acetic acid gave a 60% yield of the solvent-free compound (II) identical in appearance and melting point with the benzene complex. This oxidation product was also obtained free from solvent of crystallization in 95% yield by silver oxide oxidation using acetone as the solvent. Elementary analysis gave the empirical formula  $\text{C}_{27}\text{H}_{20}\text{O}_3$ .

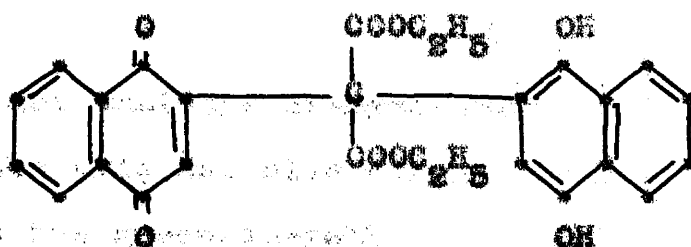
Both the blue and greenish-yellow compounds were readily reduced in quantitative yield by sodium dithionite to the same reduction product (III). The colorless dihydroquinone (III) was found to be extremely unstable, and rapidly took on a blue tinge within a few minutes when exposed to air. A sample which was stored for eighteen months



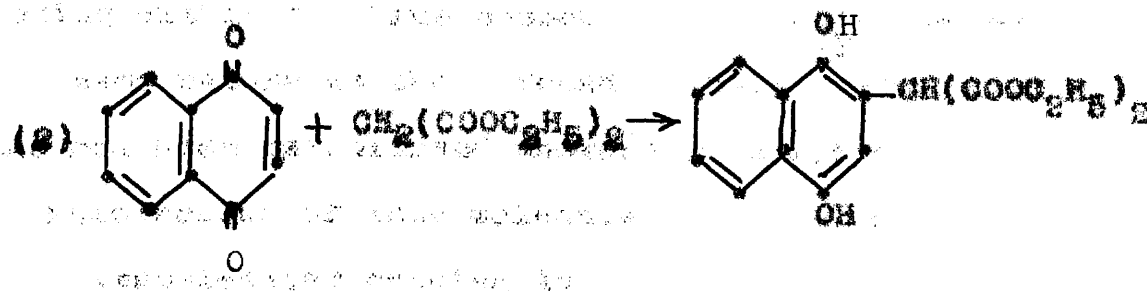
Scheme I

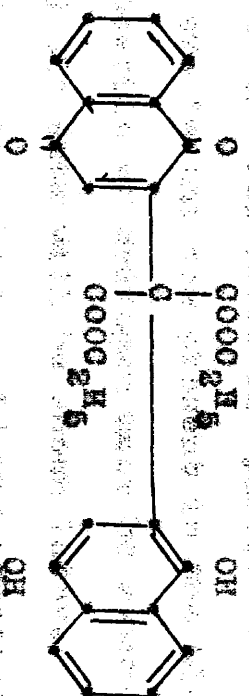
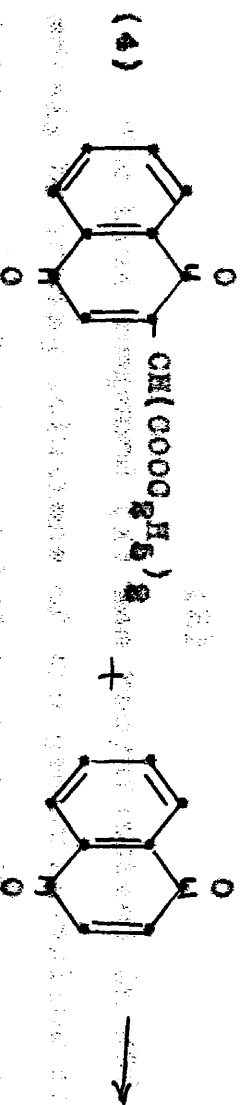
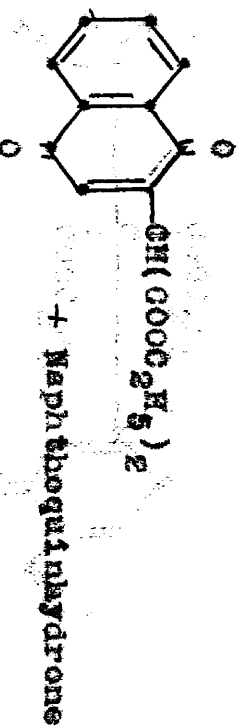
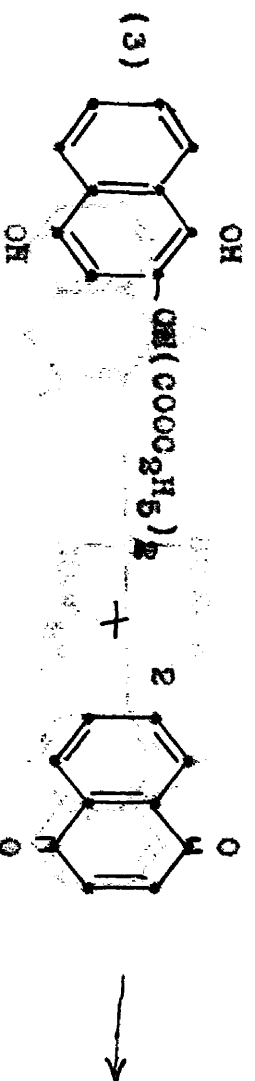
in a corked vial assumed the intense blue color of the original condensation product. The reduced material could be preserved conveniently in sealed, evacuated Pyrex ampoules. It decomposed rapidly when melted in open soft glass capillaries and a sharp melting point could be obtained only in an evacuated Pyrex capillary. When recrystallized from peroxide-free ether and ligroin under a nitrogen atmosphere the elementary analysis of the colorless needles corresponded to  $C_{27}H_{24}O_8$ .

It was noted that upon reduction the greenish-yellow oxidation product (II) passed through an intense blue intermediate stage, and on further reduction a colorless product was obtained. Assuming two naphthoquinone residues present in the blue compound, this observation suggested that one existed as the quinone and the other as a hydroquinone. A possible structure would be:

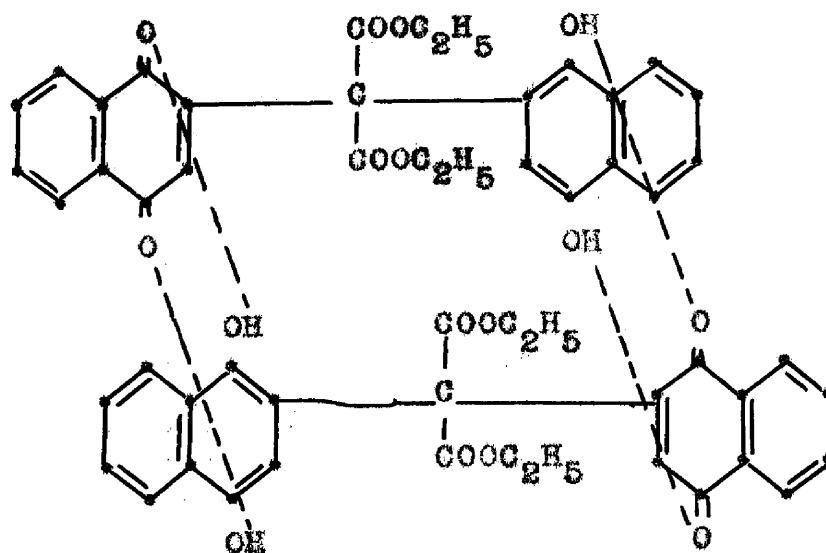


The following mechanism of formation is proposed:





The fact that the di-hydroquinone (III) gradually reverts to the original blue compound and apparently does not proceed to the greenish-yellow material (II) suggests that a strong stabilizing influence such as hydrogen bonding is acting within the blue compound. These forces may be of the same nature as those found in quinhydrone itself. It has not been established whether this hydrogen bonding is intramolecular or intermolecular. A possible structure for an intramolecular bonding is:

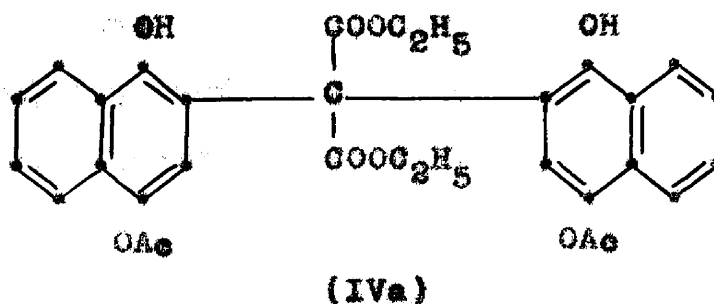


(H)

The blue compound (I) was resynthesized in 95% yield merely by mixing solutions of the greenish-yellow di-quinone (II) and the colorless di-hydroquinone (III). If structure (H) above is the one present in the blue compound a disproportionation of hydrogen must be assumed. That this is indeed the case will be shown later.

The tetraacetate (IV) was prepared from both the quinone-hydroquinone (I) by reductive acetylation (69% yield) and from the di-hydroquinone (III) by acetylation (89%). Elementary analysis and mixed melting point showed that the two tetraacetates were identical. In addition the tetrachloracetate (V) was prepared (65% yield) because the chlorine content would fix the number of acetyl groups more accurately than would the carbon and hydrogen analyses of the tetraacetate.

Mild reductive acetylation of the quinone-hydroquinone (I) produced a colorless diacetate in 93-96% yield, to which the following structure is assigned provisionally:



This compound is stable only when pure; the crude product decomposed readily with the formation of a red material which was very difficult to remove once it contaminated the diacetate. Further acetylation converted the diacetate (IVa) in quantitative yield to the same tetraacetate (IV) obtained from the quinone-hydroquinone (I) under more rigorous conditions.

Direct acetylation of the quinone-hydroquinone (I) without reduction gave the orange quinone-hydroquinone diacetate (VI) in 87% yield. That this compound still contained a quinonoid group was evidenced by the intense orange color and by the fact that a positive Craven<sup>10</sup> test was obtained. It also was reduced to a di-hydroquinone diacetate (VII) (85% yield). This diacetate was not identical with the di-hydroquinone diacetate (IVa) obtained by mild reductive acetylation of the quinone-hydroquinone (I) for they melted 15° apart and the mixed melting point showed a depression of 15° from the lower melting isomer. Mild oxidation carried out by boiling the diacetate (VII) in alcoholic solution in the presence of air brought about a partial reversion to an orange product which was probably the quinone-hydroquinone diacetate (VI), whereas when the

diacetate (IVa) was boiled in alcohol some decomposition to a red compound occurred. The diacetate (VII) was converted into the tetraacetate (IV) in 92% yield by further acetylation.

The fact that the blue compound could be converted to the orange diacetate (VI) is evidence that the structure of the quinone-hydroquinone (I) is that of an internal quinhydrone and probably not a molecular complex of the diquinone (II) and the di-hydroquinone (III). An alternate possibility would be a semi-quinone. Coryell<sup>61</sup> and Michaelis<sup>62</sup>, however, have measured the magnetic susceptibility of several p-quinhydrones and found them to be diamagnetic and hence to contain no semiquinone molecules which are paramagnetic due to the presence of an odd number of electrons.

Considerable difficulty was experienced in obtaining molecular weights of the compounds described. Potentiometric titration of the quinone-hydroquinone (I) with standard sodium dithionite solution failed because of the extreme insolubility of the blue compound in aqueous solutions. The molecular weight of the quinone-hydroquinone (I) determined by freezing point depression (Rast) was inconclusive due to the intense color of the campher solution which made it impossible to determine the melting point with accuracy. The Rast method applied to the greenish-yellow diquinone (II) was unsuccessful because of extensive decomposition to a brownish-red material. The colorless tetra-



acetate (IV) appeared to be the most stable compound for a molecular weight determination in camphor. Nine experiments utilizing this method gave a molecular weight of 574 with an average deviation of  $\pm 17$  from the mean value. The calculated molecular weight for the tetraacetate (IV) is 645. For the tetrachloracetate (V) the average value of four determinations was 915 with an average deviation of  $\pm 39$  from the mean value. The calculated value is 782. In molten camphor both the tetraacetate and the tetrachloracetate show some evidence of decomposition accompanied by a yellowing of the solution.

An attempt was made to obtain a saponification equivalent of the quinone-hydroquinone (I) by hydrolyzing with standard potassium hydroxide in diethylene glycol and back-titrating with standard hydrochloric acid, but the results were inconclusive. The insolubility of the yellow potassium salt and of the free red acid resulted in a drifting end-point. By acidification of the saponification mixture with hydrochloric acid a gelatinous brick-red precipitate (XI) was obtained in 93% yield. After four recrystallizations from chloroform and methanol the small red needles gave an elementary analysis corresponding to  $C_{22}H_{14}O_6$ . This corresponded to the usual saponification and decarboxylation of a malonic ester.

By saponifying the greenish-yellow di-quinone (II) a similar red acid (X) was obtained in 78% yield, which differed from (XI) only in its hydrogen content.

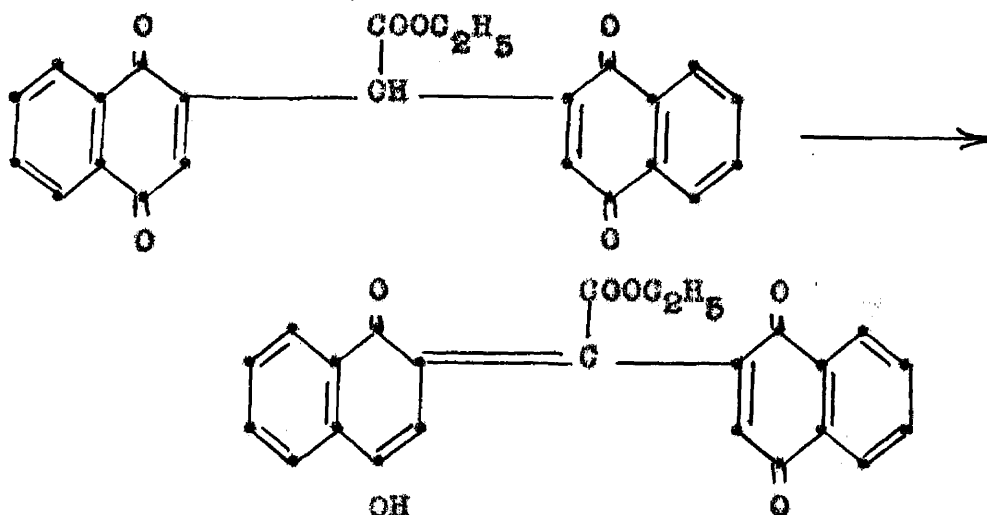
Compound (XI) was reductively acetylated in pyridine

with acetic anhydride to a tetraacetate (XII) in 93% yield. The product was hygroscopic and very difficult to purify because hydrolysis occurred readily. Nine recrystallizations from absolute alcohol yielded colorless crystals whose analysis corresponded to  $C_{30}H_{24}O_{10}$ .

In an attempt to develop characteristic color reactions for the quinone-hydroquinone (I) isolated in very low yields during various modifications of the pyridine condensation procedure and for the di-quinone (II), it was noted that both (I) and (II) dissolve in concentrated sulfuric acid with the evolution of a gas and the formation of an intense red color. Analysis of the gas evolved from (II) revealed the presence of carbon dioxide and traces of carbon monoxide, although no attempt was made to analyze the gas completely. The transformation from (II) to (VIII) may have been initiated by the small amount of water present in the sulfuric acid.

Upon pouring the red solution resulting from the reaction of sulfuric acid and the di-quinone (II) into water a flocculent red precipitate was obtained in quantitative yield. Six recrystallizations from chloroform and methanol yielded ruby prisms (VIII) whose analysis corresponded to  $C_{24}H_{16}O_6$ . Saponification of (VIII) gave the same red acid (X) (61%) as that obtained by saponification of the di-quinone (II). Reductive acetylation of (VIII) formed the colorless tetraacetate (IX) (yield 64%). The extreme change in color that occurred on saponification with alkali or

decarbethoxylation with concentrated sulfuric acid suggested that radical structural alterations had occurred. The red color also suggested that isomerization to an ortho-quinone had taken place:



In the enolic isomer the conjugation extends through both naphthalene rings and a greater absorption would be anticipated than for the di-quinone (II) in which two rings are insulated from each other by a disubstituted carbon bridge.

Ultraviolet absorption spectra were measured on a Beckman quartz spectrophotometer, model DU, with a hydrogen discharge lamp as the ultraviolet source, using 1 cm quartz cells. The solvent was 95% ethanol and concentrations of the compounds were approximately 10 mg. per liter ( $2 \times 10^{-5}$  molar). These concentrations gave instrument densities within the range of 0.5 and 1.4, values which have been shown by Vandenbelt and coworkers<sup>63</sup> to result in optimum extinction coefficients.

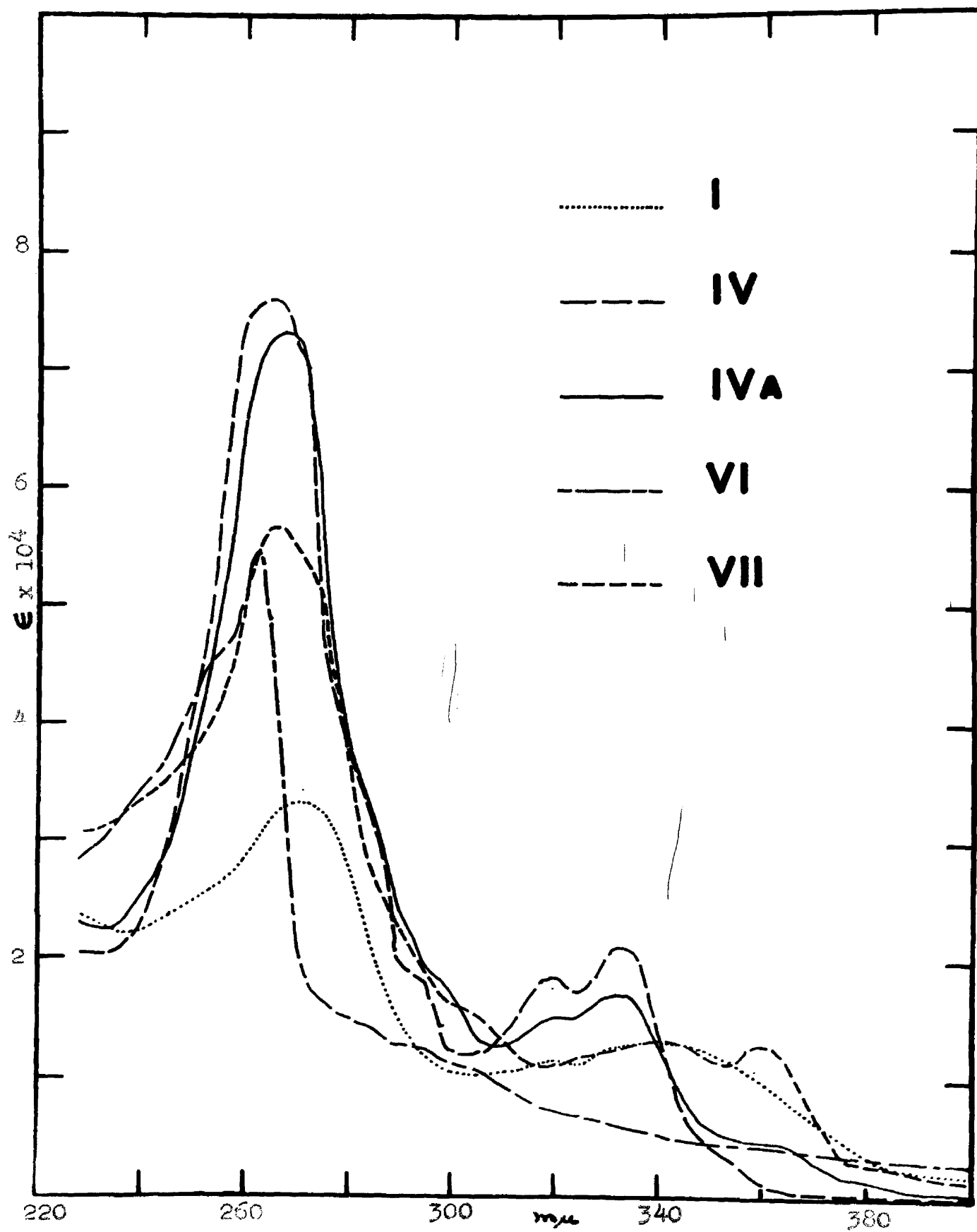


Figure A

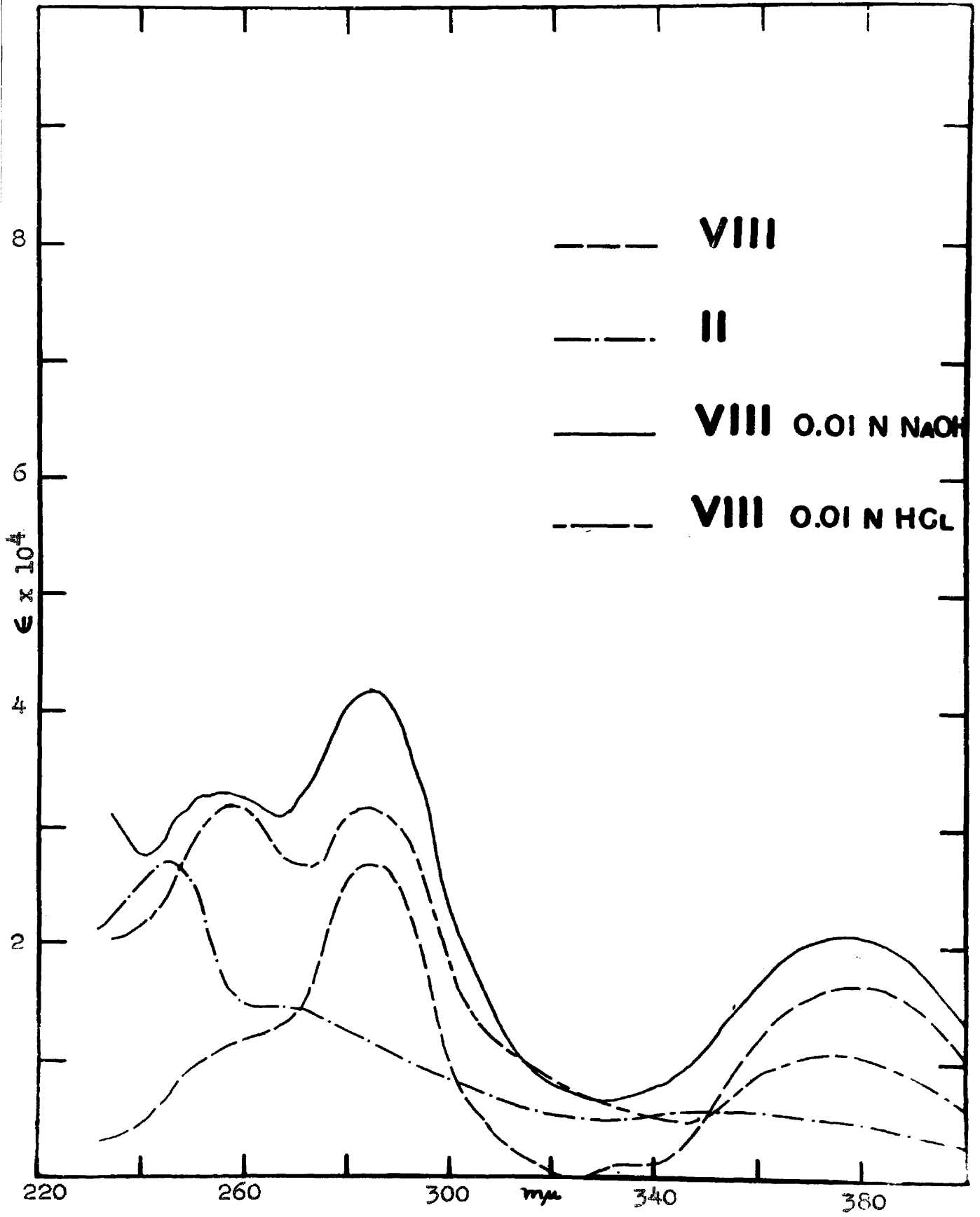


Figure B

Table 1.

## Absorption Spectra

Compound	Concn. $\times 10^{-5}$ M.	Solvent	$\lambda$ max. in $m\mu$	$\epsilon$	$\lambda$ max. in $m\mu$	$\epsilon$	$\lambda$ max. in $m\mu$	$\epsilon$
I	2.26	95% Ethanol	271	33300	342	13200		
II	2.29	"	244	26500	355	5630		
IV	1.94	"	265	76100	320	18400	333	21100
IV <sub>a</sub>	1.90	"	268	73600	320	15300	333	17400
VI	2.20	"	262	54900				
VII	2.00	"	265	56700	342	13200	362	12600
VIII	2.23	"			285	26600	378	16600
VIII	2.23	0.01 N HCl in 95% Ethanol	258	32000	283	31700	375	10500
VIII	2.23	0.01 N NaOH in 95% Ethanol	258	32900	283	41600	378	20700

The ultraviolet absorption curves for a number of the compounds are shown in Figures A and B. It is apparent from curves (IV), (IVa) and (VII) of Figure A that the general absorption of the tetraacetate and the two diacetates is similar as would be expected. It is also apparent, however, that in agreement with the conclusion previously arrived at, the two diacetates are not identical.

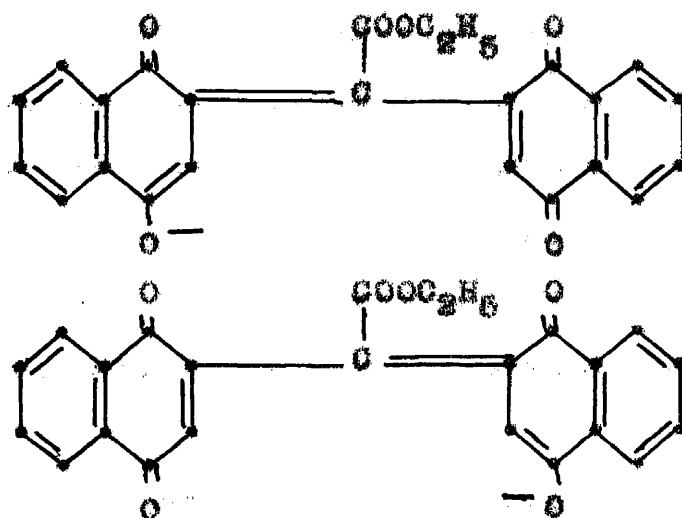
Curve (II) of Figure B shows that the absorption curve for the diquinonyl-maleonic ester (II) has a  $\lambda_{\text{max}}$  at 244  $m\mu$  ( $\epsilon = 26500$ ) in good agreement with the value of 250  $m\mu$  ( $\epsilon = 19500$ ) found for 2-methyl-1,4-naphthoquinone.<sup>64</sup> This wavelength also agrees satisfactorily with the value of  $239 \pm 5 m\mu$  shown by Woodward<sup>65</sup> to be characteristic of  $\alpha, \beta$ -disubstituted- $\alpha, \beta$ -unsaturated ketones. The inflection in the curve at about 265  $m\mu$  may be attributable to the fact that compound (II) is also an  $\alpha, \beta, \beta$ -trisubstituted- $\alpha, \beta$ -unsaturated ketone.<sup>65</sup> Since the carbethoxyl groups are not conjugated with the ring systems they would be expected to have little effect on the spectrum.<sup>65</sup>

The curves in Figure B contrast the absorption of compound (VIII) in acidic, neutral and basic media with that of the di-quinone(II). The absorption peak for compound (VIII) in acidic and neutral media at 258  $m\mu$  corresponds almost exactly with the maximum found by Bleut and coworkers<sup>67</sup> for the undissociated enolic tautomers of cyclic  $\beta$ -diketones in acidic and concentrated neutral solutions. In acidic solution the ionization of the enol would be repressed and, as

expected, the extinction coefficient at 258  $m\mu$  is greater in the acidic medium than in the neutral solution but the absorption of compound (VIII) at this point in alkaline solution is unexplained.

For cyclic  $\beta$ -diketones in either dilute neutral or alkaline solution the absorption peak has been reported at 284  $m\mu$ .<sup>67</sup> The maxima of compound (VIII) at 285  $m\mu$  in neutral solution and at 283  $m\mu$  in alkaline solution in Figure B can be ascribed to the presence of the enolate ion. As would be expected this absorption is greater in alkaline solution than in neutral or acidic media, but contrary to these results the acidic solution might be expected to show less absorption at this wavelength than the neutral solution.

In alkaline solution compound (VIII) probably exists as the resonance hybrid represented by the following structures:

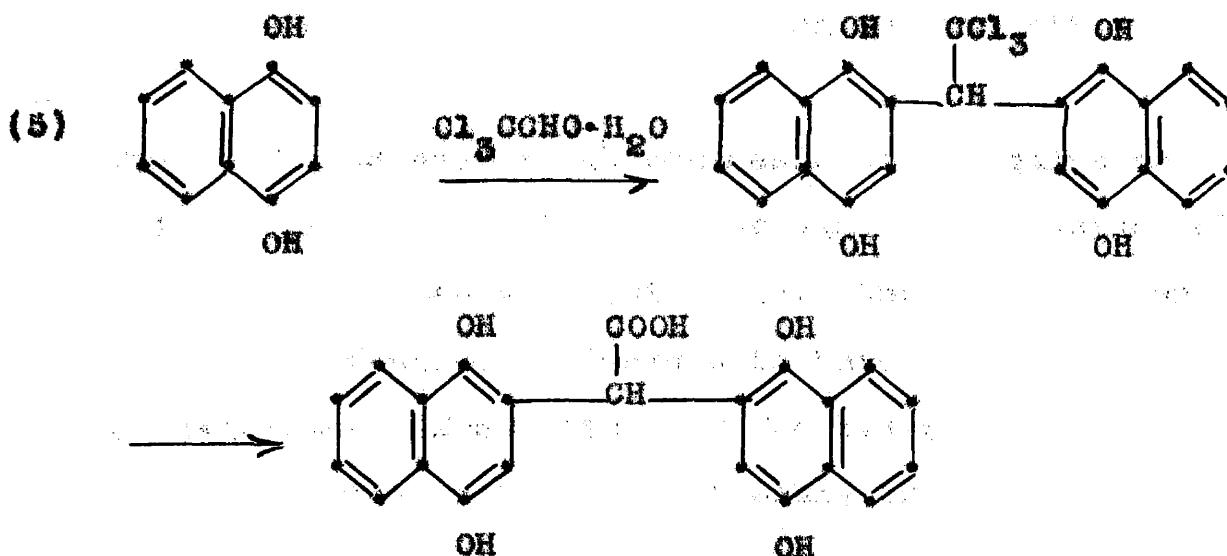


Various synthetic methods were considered for an alternate preparation of the quinone-hydroquinone (I) or one of its derivatives in order to corroborate the structure



proposed.

One unsuccessful method attempted was the condensation of 1,4-naphthoquinone or of 1,4-naphthohydroquinone with chloral followed by hydrolysis of the trichloromethyl group to compound (XI) or its reduction product:



When sulfuric acid or a mixture of acetic anhydride and acetic acid was used as a condensing agent only highly insoluble halogen-free amorphous products were obtained. When the reactants were refluxed in benzene using *p*-toluenesulfonic acid as a catalyst and azeotropically distilling off the water formed, none of the desired product could be obtained. Traces of an intensely red water-soluble product were isolated, which may have been an anthocyanidin derivative.<sup>39</sup>

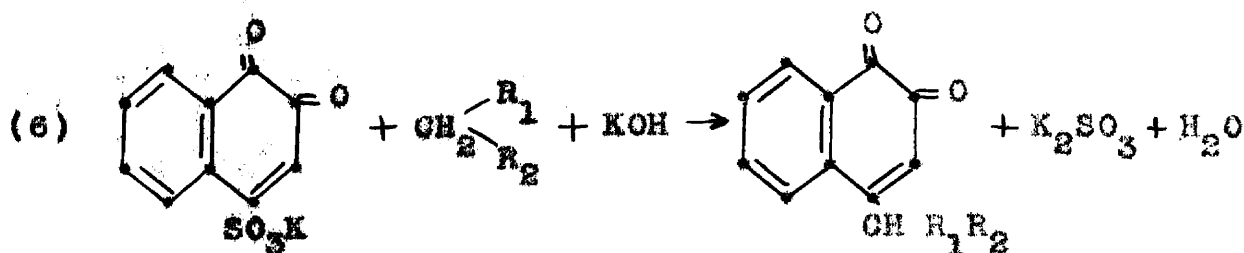
A second and as yet unsuccessful synthesis of compound (X) was the attempted oxidation of bis-(2-naphthyl)-acetic acid. 2-Acetylnaphthalene was oxidised to 2-naphthoic acid<sup>68</sup> which in turn was converted to 2-naphthol.<sup>69</sup> Rearrangement

with potassium ethoxide in ether gave 2-naphthilic acid<sup>70</sup> and this was reduced to bis-(2-naphthyl)-acetic acid.<sup>70</sup> Oxidation with chromic acid in acetic acid at 55° gave a low yield of a reddish-brown product which could not be purified further. The presence of p-quinone groups was shown, however, by a positive Craven test<sup>10</sup> on the oxidation product.

The third and successful synthesis of the quinone-hydroquinone (I) was carried out through the potassium salt of 1,4-naphthoquinone-2-sulfonic acid. The condensations of 1,8-naphthoquinone-4-sulfonic acid have been reviewed in the Historical Introduction but the 1,4-quinone does not appear to have been condensed previously in a similar manner.

Potassium 1,4-naphthoquinone-2-sulfonate<sup>71</sup> and malonic ester in the presence of sodium hydroxide solution gave a 40% yield of the quinone-hydroquinone (I) when allowed to stand at room temperature for one week. The conditions of the reaction were investigated and found to be quite critical. After varying conditions widely a satisfactory procedure was developed using an aqueous-alcoholic medium. This is the preferred method for the synthesis of the compound (I).

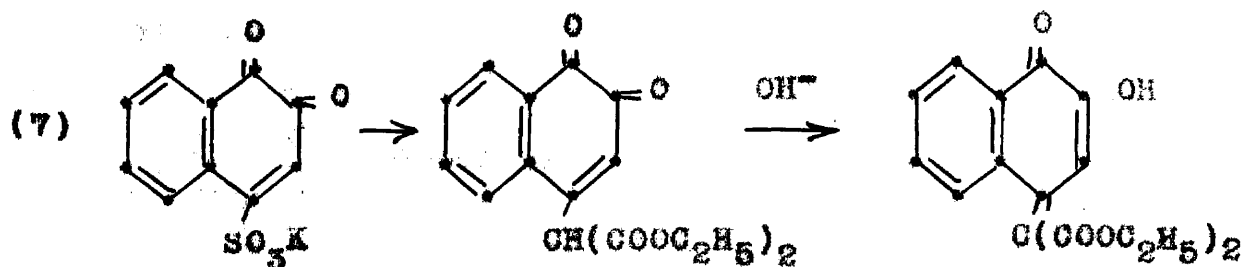
In the literature review it was shown that 1,2-naphthoquinone-4-sulfonic acid condenses with active methylene groups in the presence of alkali in one to one ratio:



The literature describes the condensation products variously as derivatives of 4-alkyl-1,2-naphthoquinone or of its enolic tautomer 2-hydroxy-1,4-naphthoquinone-4-methide. Fieser and Bradsher<sup>57</sup> have shown that the condensation product of potassium 1,2-naphthoquinone-4-sulfonate and malonic ester exists largely in the ortho-quinonoid form but that it is definitely able to act in the para-quinonoid form in alkaline solution. Since para-quinones are invariably more stable<sup>41</sup> than ortho-quinones this isomerization is to be anticipated.

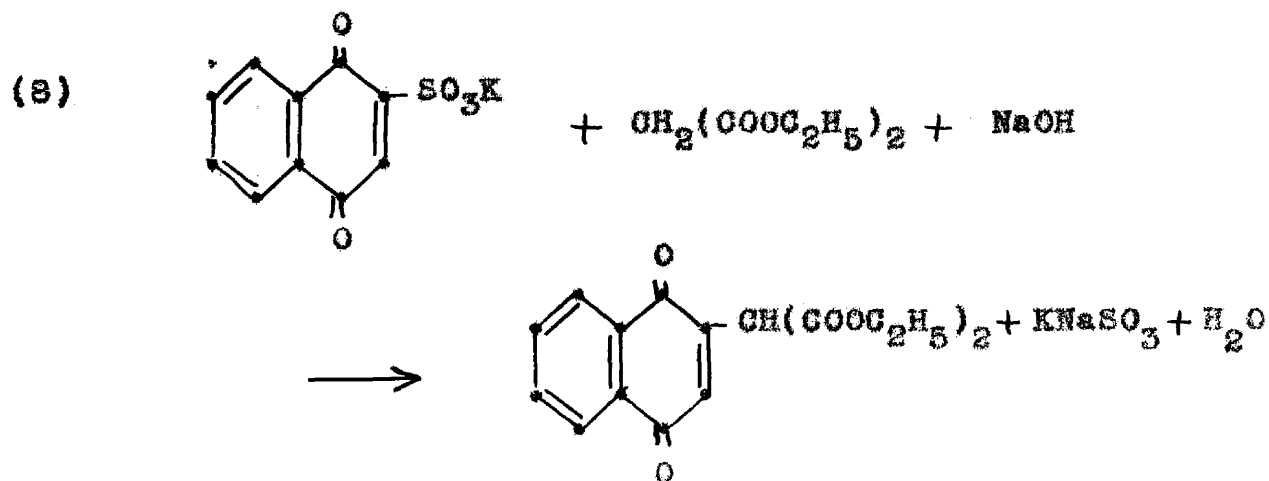
The condensation of potassium 1,4-naphthoquinone-2-sulfonate with malonic ester probably gives 1,4-naphthoquinonyl-2-malonic ester as the first product of the reaction. The reaction, as evidenced by the formation of an intense blue color, does not take place until a trace of sodium hydroxide is added.

This observation makes it readily understandable why potassium 1,2-naphthoquinone-4-sulfonate reacts with but one mole of malonic ester while potassium 1,4-naphthoquinone-2-sulfonate reacts with two moles of this ester.



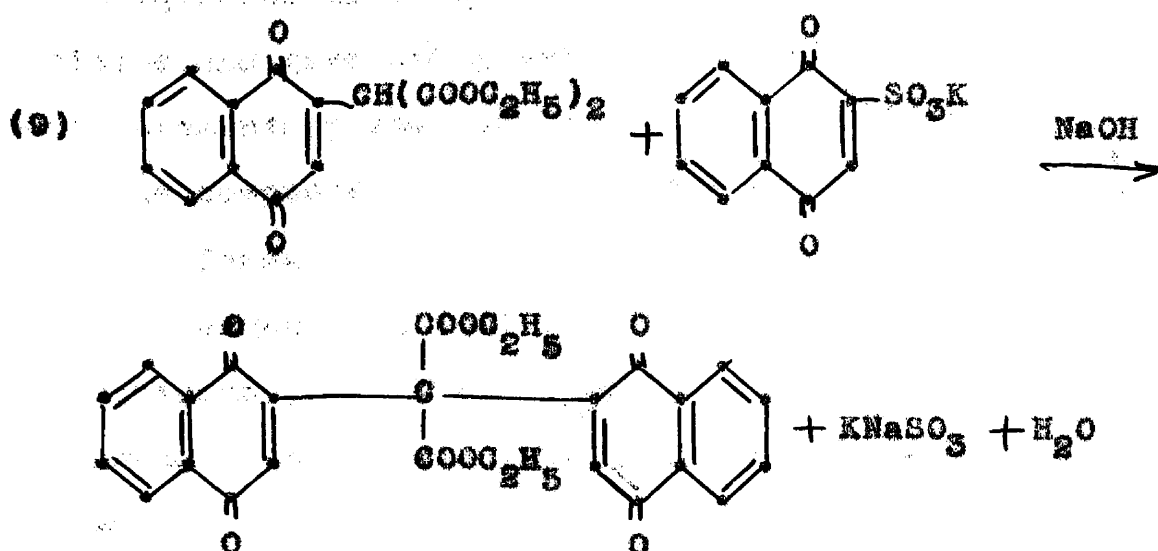
In the presence of alkali 1,2-naphthoquinonyl-4-malonic ester tautomerizes to 2-hydroxy-1,4-naphthoquinone-4-dicarbethoxymethide. This tautomer, no longer containing an active hydrogen atom on the methide carbon, cannot condense with a second mole of the sulfonic acid derivative.

On the other hand, potassium-1,4-naphthoquinone-2-sulfonate and malonic ester probably give a p-quinonoid condensation product directly:



Since the intermediate 1,4-naphthoquinonyl-2-malonic ester is already in the more stable para-quinonoid form it is not isomerized by alkali and still retains a reactive hydrogen atom. Further reaction with a second mole of the sulfonic acid then results in replacement of this last active hydrogen with the formation of a derivative of bis-(1,4-naphtho-

quinonyl-malonic ester:

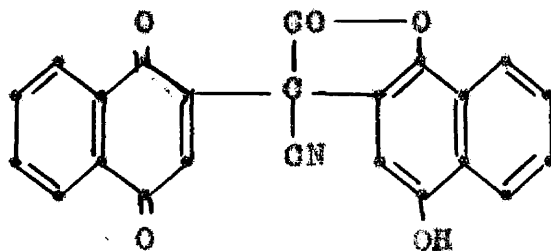


The fact that none of the di-quinone (II) was isolated may be attributed to the reducing action of the sulfite<sup>40</sup> ion which partially reduces (II) to the more stable quinone-hydroquinone (I). This explanation may be applied equally well to the condensation of ortho- and para-quinone sulfonic acids as well as to the free quinones, which was the original preparation of the blue compound. As pointed out in the Historical Introduction, 1,2-naphthoquinone reacts with sodio-malonic ester to form 1,2-naphthoquinonyl-4-malonic ester.

It was thought to be of interest to apply this reaction to other compounds containing active methylene groups. With ethyl cyanoacetate in pyridine 1,4-naphthoquinone condensed rapidly with the evolution of considerable heat. An orange-yellow product was precipitated within twenty minutes which was much less soluble and very much more difficult to purify than the condensation product obtained from diethyl malonate.

The crude product, amounting to one fourth the weight of the naphthoquinone used, was recrystallized several times from pyridine and gave orange-yellow needles (m.p. 310° dec.) whose elementary analysis corresponded roughly to  $C_{26}H_{14}N_2O_4$ .

The compound dissolved in concentrated sulfuric acid with the formation of a deep magenta color. Its solubility in this reagent was much less than that of the quinone-hydroquinone (I). When warmed to 50°, however, the compound was brought completely into solution. The addition of water caused a flocculent red precipitate to deposit. This product, too, was much less soluble in chloroform than the compound (VIII) obtained by treating the di-quinone (II) with sulfuric acid, but it could be recrystallized satisfactorily from ethylene dichloride. Bright ruby needles were obtained whose elementary analysis corresponded to a quinone-hydroquinone cyanoacetic acid lactone,  $C_{23}H_{11}O_5N$ :



It is planned to carry out further work on this and other products from the condensation of active methylene compounds with 1,4-naphthoquinone in these laboratories.

## EXPERIMENTAL

EXPERIMENTAL<sup>\*,\*\*</sup>

Diethyl (1,4-dioxo-1,4-dihydronaphthyl-2)-(1,4-dihydroxy-naphthyl-2)-malonate (I).

1,4-Naphthoquinone<sup>72</sup> (6.32 g.) was dissolved in 16 ml. of pyridine at 45°. Diethyl malonate (6.40 g.) was added and the solution was allowed to stand for twenty hours at room temperature. The dark-brown mixture was chilled in the refrigerator for several hours, filtered, and washed with several small portions of ice-cold pyridine. The product, a greenish-gray powder (1.94 g.), was extracted with benzene in a Soxhlet apparatus and the blue benzene solution chilled in the refrigerator overnight. Yield, 0.68 g. (13-15% based on equations (2), (3) and (4) of the Discussion) of fine, matted, dark blue needles melting with decomposition at 259-260°. For analysis a sample was recrystallized six times from benzene and dried at 100° at one mm. pressure for one hour; m.p. 265.5-268° (dec., evacuated capillary).

ANAL. Calcd. for  $C_{27}H_{22}O_8 \cdot \frac{1}{2}C_6H_6$ : C, 70.17; H, 4.91.

Found: C, 70.13; H, 4.41; H, 4.40, 4.47.

When the greenish-gray material was extracted with

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\* All melting points are corrected.

\*\* Analyses by Miss Eleanor Werble and Mrs. Mary Aldridge.



acetone the solvent-free quinone-hydroquinone was obtained in 12% yield upon crystallization. Four recrystallizations from boiling acetone (recovery 51%) gave fine, dark blue, matted needles which melted in an evacuated capillary at 265-267° with decomposition.

Anal. Calcd. for  $C_{27}H_{22}O_8$ : C, 68.35; H, 4.68.

Found: C, 68.24, 68.65; H, 4.64, 4.62.

### Triphthaloylbenezene

The dull yellow amorphous powder (1.1-1.4 g., 17-22%) which remained in the thimble after extraction with acetone or benzene was recrystallized eight times from boiling nitrobenzene. The bright yellow prisms of triphthaloylbenezene did not melt below 380°.

Anal. Calcd. for  $C_{39}H_{12}O_6$ : C, 76.92; H, 2.58.

Found: C, 76.65, 76.66; H, 2.82, 2.82.

### Diethyl bis-(1,4-dioxo-1,4-dihydronaphthyl-2)-malonate (II) from the quinone-hydroquinone (I).

Two grams of the quinone-hydroquinone (I) (crystallized once from benzene) was suspended in 250 ml. of benzene. Two grams of freshly prepared silver oxide was added and the mixture was stirred for one hour. The color of the supernatant solution changed from pale blue at the start of the reaction to a light greenish-yellow. The mixture was then heated to boiling, the solid filtered off, and the filter-cake extracted with several small portions of boiling benzene. The combined filtrates were concentrated to a small

Volume and chilled overnight in the refrigerator. The product which crystallized out was filtered off and washed with 5 ml. of cold benzene. The yield of bright greenish-yellow needles of the di-quinone benzene complex was 1.95-1.98 g. (98-99%); m.p. 209-210° (dec.). For analysis the product was recrystallized four times from benzene and dried at 100° at one mm. pressure for one hour. Yield, 1.40 g. (70%); m.p. 197-199° (dec.).

Anal. Calcd. for  $C_{27}H_{20}O_8 \cdot \frac{1}{2}C_6H_6$ : C, 70.44; H, 4.53.

Found: C, 70.20, 70.44; H, 4.27, 4.37.

The black filter-cake from the oxidation consisting of silver and silver oxide was washed thoroughly with hot benzene and it was then repeatedly extracted with hot dilute ammonium hydroxide until all organic matter and silver oxide were removed. The residue of silver was dried to constant weight at 100°. Weight, 0.880 g.

Equivalent Weight. Calcd: 513.5.

Found: 490.

The di-quinone (II) was obtained free from solvent of crystallization by oxidation in acetic acid solution with chromic acid. Seven hundred milligrams of the quinone-hydroquinone (crystallized once from benzene) was added to 1000 ml. of acetic acid at 40°. During a period of one-half hour a solution of 0.150 g. of chromic acid in 50 ml. of acetic acid was added slowly with constant stirring. The color gradually changed from blue to greenish-yellow and all of the solid dissolved. After distilling off the acetic

acid in vacuo at 40-45° the greenish-yellow residue was washed with 5% aqueous sodium bicarbonate to remove a small amount of reddish decomposition product and then with ether to extract a trace of unoxidized blue material. The residue weighed 0.38 g. (60%); m.p. 206-210° (dec.). For analysis a sample was recrystallized four times by dissolving in hot acetic acid, adding hot water to incipient precipitation and then chilling rapidly in an ice-bath. The greenish-yellow needles of the di-quinone (II) were dried at 100° at one mm. pressure for one hour; m.p. 197-199° (dec., evacuated capillary).

Anal. Calcd. for  $C_{27}H_{20}O_8$ : C, 68.64; H, 4.27.

Found: C, 68.59, 68.58; H, 3.95, 4.05.

The same solvent-free di-quinone was obtained in 95% yield by oxidation of the quinone-hydroquinone (I) (crystallized from acetic acid) with silver oxide using acetone as a solvent. After recrystallization from acetone the greenish-yellow di-quinone (80%) was dried at 100° at one mm. pressure for one hour; m.p. 197.5-199° (dec., evacuated capillary).

Anal. Calcd. for  $C_{27}H_{20}O_8$ : C, 68.64; H, 4.27.

Found: C, 68.78, 68.50; H, 4.11, 4.36.

Diethyl bis-(1,4-dihydroxynaphthyl-2)-malonate (III) from the quinone-hydroquinone (I).

One gram of the finely powdered recrystallized benzene complex of the quinone-hydroquinone (I) was suspended in 25 ml. of ether and the suspension was shaken for twenty

minutes with a solution of 2 g. of sodium dithionite in 20 ml. of water. The blue color disappeared during this period. The aqueous phase was then separated and discarded. The ethereal layer was filtered through anhydrous magnesium sulfate under an atmosphere of nitrogen to avoid reoxidation to the quinone-hydroquinone by air. The colorless solution was concentrated under nitrogen to a volume of 15 ml. and ligroin (30-60°) was added to incipient precipitation. After chilling overnight in the refrigerator to complete the crystallization a quantitative yield of the di-hydroquinone (III) was obtained as transparent colorless needles which became opaque on drying under reduced pressure; m.p. 213-220° (dec., evacuated capillary). The product which rapidly turned blue when exposed to air was recrystallized five times for analysis by dissolving in boiling dry peroxide-free ether<sup>73</sup>, adding ligroin (30-60°) to incipient precipitation, and chilling overnight in the refrigerator. The crystals were dried at 100° at one mm. pressure for one hour. Yield, 0.24 g. (24%); m.p. 229.5-230.5° (dec., evacuated capillary).

Anal. Calcd. for  $C_{27}H_{24}O_8$ : C, 68.04; H, 5.08.

Found: C, 68.10, 67.81; H, 4.84, 4.82.

Diethyl bis-(1,4-dihydroxynaphthyl-2)-malonate (III) from the di-quinone (II).

Utilizing the procedure described for the reduction of the quinone-hydroquinone (I) with sodium dithionite, 0.100 g. of once crystallized di-quinone (II) was converted in

quantitative yield to the di-hydroquinone; m.p. 228.5-230° (dec., evacuated capillary). The original greenish-yellow solution passed through a blue intermediate reduction stage and the color was completely discharged after shaking for fifteen minutes. Three recrystallizations from a mixture of dry peroxide-free ether and ligroin (30-60°) gave 0.08 g. (86%) of colorless needles of the di-hydroquinone; m.p. 229.5-231° (dec., evacuated capillary). Analyses are given for the preparation above.

Resynthesis of the quinone-hydroquinone (I) from the di-quinone (II) and the di-hydroquinone (III).

A solution of 50 mg. of the pure di-quinone (II) in 30 ml. of warm 95% alcohol was mixed with a solution of 50 mg. of the pure di-hydroquinone (III) in 10 ml. of alcohol. The mixture immediately turned deep blue and upon stirring for a few minutes a flocculent blue precipitate settled out. The yield was 95 mg. (95%); m.p. 261.5-262.5° (dec.). One recrystallization from benzene gave 75 mg. (70%) of fine, matted, dark blue needles of the benzene complex; m.p. 264-266° (dec.). A mixture of this product and the quinone-hydroquinone benzene complex obtained from 1,4-naphthoquinone and malonic ester showed no depression in the melting point.

Anal. Calcd. for  $C_{27}H_{22}O_8 \cdot \frac{1}{2}C_6H_6$ : C, 70.17; H, 4.91.

Found: C, 70.25, 69.98; H, 4.70, 4.93.

Diethyl bis-(1,4-diacetoxynaphthyl-2)-malonate (IV) from the di-hydroquinone (III).

Fifty milligrams of the crude di-hydroquinone (III) was mixed with one ml. of pure dry pyridine, and 0.3 ml. of acetic anhydride was added to the greenish-amber suspension. After stirring for ten minutes at room temperature all of the solid dissolved and the clear amber solution was allowed to drip very slowly with vigorous stirring onto 10 g. of crushed ice. One hour later the yellowish precipitate was filtered off, washed with water and dried in the air. Yield, 60 mg. (89%); m.p. 235-240° (dec.). For analysis the crude product was recrystallized six times from absolute alcohol. The yield of colorless plates was 27 mg. (40%); m.p. 258-260° (dec.).

Anal. Calcd. for  $C_{35}H_{32}O_{12}$ : C, 65.21; H, 5.01.

Found: C, 65.05, 65.27; H, 4.98, 5.03.

Diethyl bis-(1,4-diacetoxynaphthyl-2)-malonate (IV) from the quinone-hydroquinone (I).

One-half gram of the quinone-hydroquinone (I) (crystallized once from benzene) was suspended in a mixture of 10 ml. of pyridine and 10 ml. of acetic anhydride. The mixture was refluxed in an oil-bath for one-half hour, while adding 1 g. of zinc dust in approximately 0.01 g. portions. The resulting amber solution was filtered, cooled to room temperature, and poured slowly with stirring into 200 ml. of ice-water. Stirring was continued for one-half hour longer to coagulate

the precipitate. The pale yellow solid was filtered off and recrystallized from absolute alcohol. Yield, 0.45-0.47 g. (66%-69%); m.p. 256.5-259° (dec.). Recrystallization from absolute alcohol gave 0.40 g. (59%) of ivory-colored plates, melting with decomposition at 257.5-260°. A mixture of this product and the di-hydroquinone tetraacetate (IV) obtained by acetylation of the di-hydroquinone showed no depression in the melting point.

Diethyl bis-[1,4-di-(chloroacetoxy)-naphthyl-2]-malonate (V)  
from the di-hydroquinone (III).

One-half gram of the crude di-hydroquinone (III) was suspended in 5 ml. of dry pyridine and 4 g. of redistilled chloroacetic anhydride was added to the greenish solution. The color became dark brown. Within one minute all of the solid dissolved and the resulting amber solution was poured slowly onto 100 g. of crushed ice with stirring. A glistening gum precipitated which crystallized to a granular yellow powder after scratching and stirring for two hours. One crystallization from 1000 ml. of absolute alcohol gave 0.530 g. (65%) of tan plates; m.p. 234.5-237.5° (dec.). For analysis the product was recrystallized by dissolving it in the minimum amount of boiling acetone. A ten-fold volume of methanol was then added and the solution was filtered. Crystallization of the ivory-colored plates was complete after cooling in the refrigerator overnight. Four recrystallizations gave an overall yield of 0.22 g. (27%);

m.p. 238.5-240° (dec.).

Anal. Calcd. for  $C_{55}H_{88}O_{12}Cl_4$ : C, 53.73; H, 3.61; Cl, 18.13.

Found: C, 54.19, 54.20; H, 3.67, 3.62; Cl, 18.21, 18.01.

Diethyl bis-(1-hydroxy-4-acetoxynaphthyl-2)-malonate (IVa)  
from the quinone-hydroquinone (I).

One hundred milligrams of the finely powdered quinone-hydroquinone (I) (crystallized once from benzene) was suspended in 2 ml. of acetic anhydride. One hundred milligrams of zinc dust and a drop of triethylamine were added. The mixture was warmed gently for a few minutes until the blue color was discharged and then was filtered. The filter-cake was washed with 5 ml. of hot acetic acid and 0.2 ml. of water was added to the combined filtrates. The solution was heated to the boiling point to hydrolyze the excess acetic anhydride; hot water was then added to incipient precipitation. When the solution was chilled rapidly with stirring in an ice-bath 0.102-0.105 g. (93-96%) of salmon-pink crystals separated; m.p. 234.5-235.5° (dec.). The crude product was recrystallized twice from dilute alcohol, once from acetone and twice from absolute alcohol. The yield of small colorless needles was 52 mg. (48%); m.p. 239-240.5° (dec.).

Anal. Calcd. for  $C_{31}H_{29}O_{10}$ : C, 66.42; H, 5.04.

Found: C, 66.89, 66.96; H, 5.24, 5.44.



Diethyl bis-(1,4-diacetoxynaphthyl-2)-malonate (IV) from the di-hydroquinone diacetate (IVa).

Three hundred and fifty milligrams of once-crystallized di-hydroquinone diacetate (IVa) was suspended in a solution of 3.5 ml. of pyridine and 2 ml. of acetic anhydride. All of the solid dissolved upon stirring at room temperature for one hour. The amber solution was allowed to drip slowly with stirring into 50 ml. of ice-water. A quantitative yield of yellowish, flocculent precipitate was obtained which was recrystallized from 200 ml. of absolute alcohol. Yield, 0.28 g. (69%); m.p. 234-237° (dec.). For analysis the product was recrystallized six times from absolute alcohol. The yield of ivory-colored plates weighed 0.16 g. (40%); m.p. 258.5-260° (dec.). A mixture of this product with the di-hydroquinone tetraacetate (IV) obtained by acetylation of the di-hydroquinone showed no depression of the melting point.

Anal. Calcd. for  $C_{35}H_{32}O_{12}$ : C, 65.21; H, 5.01.

Found: C, 65.49, 65.52; H, 5.08, 5.16.

Diethyl (1,4-dioxo-1,4-dihydronaphthyl-2)-(1,4-diacetoxynaphthyl-2)-malonate (VI) from the quinone-hydroquinone (I).

Two hundred milligrams of the quinone-hydroquinone (I) (crystallized once from benzene) was suspended in a solution of 5 ml. of acetic anhydride and 10 ml. of pyridine. When the suspension was heated on the steam bath for ten minutes the color changed from blue through black, green, and yellow

to a deep amber. After cooling the mixture to room temperature the excess acetic anhydride was hydrolyzed by the addition of a little water and the solution was then poured slowly with stirring into 75 ml. of ice-water. The mustard-yellow, flocculent precipitate which separated was recrystallized from 40 ml. of absolute alcohol. Yield, 0.19 g. (87%); m.p. 210-213° (dec.). For analysis the product was recrystallized three times from absolute alcohol. The bright orange prisms weighed 91 mg. (42%); m.p. 215.5-216.5° (dec.).

Anal. Calcd. for  $C_{31}H_{26}O_{10}$ : C, 66.66; H, 4.69.

Found: C, 66.81, 67.05; H, 4.45, 4.44.

Diethyl (1,4-dihydroxynaphthyl-2)-(1,4-diacetoxynaphthyl-2)-malonate (VII) from the quinone-hydroquinone diacetate (VI).

Two hundred milligrams of the crude quinone-hydroquinone diacetate (VI) was suspended in 30 ml. of ether and the suspension was shaken for twenty minutes with a solution of 1 g. of sodium dithionite in 20 ml. of water. The aqueous phase was separated and discarded. The colorless ether layer was filtered through anhydrous magnesium sulfate and concentrated to 20 ml. After adding 100 ml. of ligroin (30-60°) to the solution the product was allowed to crystallize overnight in the refrigerator. The yield of ivory-colored plates was 0.17 g. (85%); m.p. 222-224° (dec., evacuated capillary). Two recrystallizations from a mixture of dry peroxide-free ether and ligroin gave 0.14 g. (70%) of colorless plates; m.p. 223-226° (dec., evacuated capillary). A mixture of this product and the di-hydroquinone diacetate (IVa)

(m.p. 239-240.5°) melted at 208-213° (dec.).

Anal. Calcd. for  $C_{31}H_{28}O_{10}$ : C, 66.42; H, 5.04.

Found: C, 66.76, 66.92; H, 4.82, 4.82.

Diethyl bis-(1,4-diacetoxynaphthyl-2)-malonate (IV) from the di-hydroquinone diacetate (VII).

Eighty milligrams of the crude di-hydroquinone diacetate (VII) was dissolved in a mixture of 1 ml. of pyridine and 1 ml. of acetic anhydride. After standing at room temperature for one hour the clear amber solution was heated on the steam bath for a few minutes to complete the reaction and a little water was added to hydrolyze the excess acetic anhydride. The cooled solution was then poured slowly with stirring into 50 ml. of ice-water. After standing for one-half hour the light yellow precipitate was filtered off. Yield, 55 mg. (92%). One recrystallization from 40 ml. of absolute alcohol gave 55 mg. (60%) of ivory-colored plates; m.p. 258.5-260° (dec.). A mixture of this product and the di-hydroquinone tetraacetate (IV) obtained by acetylation of the di-hydroquinone (III) showed no depression in the melting point.

Ethyl (1-oxo-4-hydroxy-1,2-dihydronaphthylidene-2)-(1,4-dioxo-1,4-dihydronaphthyl-2)-acetate (VIII) from the di-quinone (II).

Seventy-five milligrams of the di-quinone (II) (crystallized once from benzene) was added to 2 ml. of concentrated sulfuric acid at room temperature. The di-quinone

dissolved with the formation of an intense red color and a gas was evolved. After five minutes the solution was poured into 20 ml. of ice-water. The flocculent bright red precipitate which separated was filtered off, washed with water until the washings were neutral, and dried in the air. Yield, 59 mg. (100%). For analysis the product was recrystallized by dissolving in boiling chloroform, adding hot methanol to incipient precipitation, and chilling in an ice-bath for several hours. After six recrystallizations 30 mg. (51%) of brilliant ruby prisms were isolated; m.p. 305° (dec.).

Anal. Calcd. for  $C_{24}H_{16}O_6$ : C, 71.99; H, 4.01.

Found: C, 72.07, 72.08; H, 3.89, 3.73.

Ethyl bis-(1,4-diacetoxynaphthyl-8)-acetate (IX) from the decarboethoxylated di-quinone (VIII).

Twenty-five milligrams of the crude decarboethoxylated di-quinone (VIII) was suspended in 3 ml. of acetic anhydride; 50 mg. of zinc dust and one drop of triethylamine were added. After stirring for five minutes the color had disappeared almost entirely leaving a faintly pink solution. One-half hour later 5 g. of ice was added to decompose the excess anhydride. The solution was heated nearly to the boiling point, hot water was added to incipient precipitation, and the solution was chilled rapidly in an ice-bath. The pale pink crystals weighed 23 mg. (64%). The tetraacetate dissolved slowly in boiling alcohol and solution was accompanied by considerable decomposition. For purification the

crude product was dissolved in a small volume of boiling acetone and several volumes of absolute alcohol were added. Most of the acetone was then removed by distilling off about one-half of the solvent. The solution was then chilled in an ice-bath. Three such recrystallizations gave 11 mg. (31%) of small colorless needles; m.p. 270-273° (dec.).

Anal. Calcd. for  $C_{32}H_{28}O_{10}$ : C, 67.12; H, 4.95.

Found: C, 67.18, 67.31; H, 4.88, 4.81.

(1-Oxo-4-hydroxy-1,2-dihydronaphthylidene-2)-(1,4-dioxo-1,4-dihydronaphthyl-2)-acetic acid (X) from the decarbethoxylated di-quinone (VIII).

One hundred milligrams of the crude decarbethoxylated di-quinone (VIII) was added to 6 ml. of 1 N potassium hydroxide in diethylene glycol. Upon heating the mixture at 175° for three minutes with stirring all of the solid dissolved. When the cooled solution was poured into 50 ml. of water a yellow opalescent colloid resulted and upon acidification with hydrochloric acid a red gelatinous precipitate separated. The mixture was shaken with 25 ml. of chloroform at 50° which quantitatively extracted the red product. After filtration the chloroform extract was concentrated to 10 ml. and 35 ml. of hot methanol was added. Crystallization began in a few minutes and after chilling overnight in the refrigerator the product was collected. Yield, 57 mg. (61%). For analysis the product was recrystallized four times from chloroform and methanol. Yield, 35 mg. (38%). The small red prisms melted with decomposi-

tion at approximately  $315^{\circ}$  when introduced into the copper block just below this temperature.

Anal. Calcd. for  $C_{22}H_{12}O_6$ : C, 70.97; H, 3.25.

Found: C, 70.64, 70.64; H, 3.53, 3.54.

(1-Oxo-4-hydroxy-1,2-dihydronaphthylidene-2)-(1,4-dioxo-1,4-dihydronaphthyl-2)-acetic acid (X) from the di-quinone

(II). Two hundred milligrams of the di-quinone (II) (crys-

Two hundred milligrams of the di-quinone (II) (crystallized once from benzene) and 5 ml. of 1 N potassium hydroxide in diethylene glycol were heated with stirring at  $130^{\circ}$  for three minutes. The yellowish solution was cooled to room temperature and poured into 25 ml. of water. After acidification with hydrochloric acid and extraction with chloroform the red product was crystallized with the aid of methanol. Yield, 110 mg. (76%). The product was recrystallized three times in the same manner. Yield, 80 mg. (55%). The small ruby prisms melted with decomposition at approximately  $315^{\circ}$  when introduced into the copper block near this temperature. Analysis of this compound is given above.

(1-Oxo-4-hydroxy-1,2-dihydronaphthylidene-2)-(1,4-dihydroxynaphthyl-2)-acetic acid (XI) from the quinone-hydroquinone (I).

One gram of the purified quinone-hydroquinone (I) benzene complex was heated at  $130^{\circ}$  for three minutes with 35 ml. of 1 N potassium hydroxide in diethylene glycol. The cooled yellow solution was poured into 200 ml. of water and the

mixture was acidified with hydrochloric acid. The brick-red precipitate was extracted with chloroform at about 50°.

The extract after concentration to 50 ml. and addition of 250 ml. of methanol gave 0.68 g. (93%) of small red needles. For purification the product was recrystallized four times from chloroform and methanol. A yield of 0.48 g. (66%) of small red needles was obtained which melted with decomposition at approximately 330° when introduced into the copper block just below this temperature.

Anal. Calcd. for  $C_{22}H_{14}O_6$ : C, 70.59; H, 3.77.

Found: C, 70.90, 71.05; H, 3.87, 4.06.

Di-(1,4-diacetoxynaphthyl-2)-acetic acid (XII) from the saponified quinone-hydroquinone (XI).

Five hundred and fifty milligrams of the saponified quinone-hydroquinone (XI) (once recrystallized from chloroform and methanol) was suspended in 5 ml. of pyridine and 15 ml. of acetic anhydride. The mixture was refluxed for one-half hour. During this time 1 g. of zinc dust was added in approximately 0.01 g. portions. The amber solution was cooled and allowed to drip slowly into 100 ml. of ice water. The yellow-brown gum crystallized to a granular, tan solid after stirring for one hour. Yield, 0.74 g. (93%). For analysis the product was recrystallized nine times from absolute alcohol. The small colorless crystals were dried for three hours at 100° at one mm. pressure. Yield, 0.14 g. (18%); m.p. 264.5-266° (dec.).

Anal. Calcd. for  $C_{30}H_{24}O_{10}$ : C, 66.17; H, 4.44.

Found: C, 65.59; H, 4.77.

Synthesis of diethyl (1,4-dioxo-1,4-dihydronaphthyl-2)-  
(1,4-dihydrosynaphthyl-2)-malonate (I).

Potassium 1,4-naphthoquinone-2-sulfonate monohydrate<sup>71</sup> (1.45 g.) was dissolved in 40 ml. of water at 35°. This solution was added during three minutes to a mixture of 0.6 g. of diethyl malonate and 1.5 ml. of 10% aqueous sodium hydroxide in 8 ml. of alcohol. The transient blue color faded to a deep amber and within a few minutes deposited a dark blue flocculent precipitate. The filtrate (pH=6) was allowed to stand at room temperature for one week. Each day 40-90 mg. of blue precipitate was collected. At the end of seven days a total of 463 mg. (40%) had been isolated; m.p. 264.5-267° (dec.). One recrystallization from benzene gave 375 mg. (30%) of fine dark blue, matted needles of the benzene complex; m.p. 261-263° (dec.). For analysis the product was recrystallized four times from benzene. Yield, 195 mg. (17%); m.p. 264-266° (dec.). A mixture of this product and the benzene complex of the quinone-hydroquinone (I) obtained from 1,4-naphthoquinone and malonic ester showed no depression in melting point.

Anal. Calcd. for  $C_{27}H_{22}O_8 \cdot \frac{1}{2}C_6H_6$ : C, 70.17; H, 4.91.

Found: C, 70.24, 70.28; H, 4.62, 4.56.

This compound was converted to the tetraacetate in 66% yield by reductive acetylation as previously described. A



mixture of this product with the di-hydroquinone tetra-acetate (IV) prepared from the di-hydroquinone (III) showed no depression in melting point.

Attempted synthesis of (1-oxo-4-hydroxy-1,2-dihydronaphthylidene-2)-(1,4-dioxo-1,4-dihydronaphthyl-2)-acetic acid (X).

Di-(2-naphthyl)-acetic acid<sup>69</sup> (3.12 g.) was dissolved in 100 ml. of hot acetic acid and cooled to 55°. At this temperature a solution of 10 g. of chromic oxide in 14 ml. of 1:1 aqueous acetic acid was allowed to drip in with stirring during one-half hour. The temperature of the reaction mixture was maintained at 55° by occasional cooling in an ice bath. Ten minutes later the temperature began to fall spontaneously and after standing for one hour the solution was poured into 500 ml. water. The gelatinous precipitate which separated was filtered off, washed with water and dried on a porous plate. Yield, 1.40 g. of light brown lumps. The crude product was extracted with boiling ethylene dichloride. The reddish-amber extract which gave a strongly positive Craven<sup>10</sup> test was evaporated to a small volume and two volumes of hot methanol were added. A dark reddish-brown precipitate (150 mg.) separated which became chocolate brown on drying and could not be purified further.

Condensation of 1,4-naphthoquinone with cyanoacetic ester.

One and six tenths grams of 1,4-naphthoquinone was dissolved in 4 ml. of pyridine at 45°. When 1.1 g. of ethyl cyanoacetate was added an exothermic reaction took place and

yellow-orange crystals began to deposit after about twenty minutes. Crystallization was completed by chilling overnight in the refrigerator. Yield, 0.39 g. Two recrystallizations from pyridine gave 0.15 g. (38% recovery); m.p. approximately  $310^{\circ}$  (dec.).

Anal. Calcd. for  $C_{26}H_{14}N_2O_4$ : C, 74.64; H, 3.37; N, 6.85.

Found: C, 75.20, 75.11; H, 3.37, 3.45; N, 6.84, 6.62.

One hundred milligrams of the purified condensation product was added to 5 ml. of concentrated sulfuric acid at room temperature. The mixture immediately assumed a deep magenta color with partial solution of the compound. When the mixture was warmed to  $50^{\circ}$  for five minutes with stirring all of the solid dissolved. After pouring into 20 ml. of ice-water, the reddish-orange precipitate was filtered off, washed neutral with water, and dried in air. Yield, 90 mg. of brick-red powder. The product was recrystallized from ethylene dichloride. Yield, 28 mg. of small intensely red prisms which did not melt when introduced into the copper block at  $360^{\circ}$ .

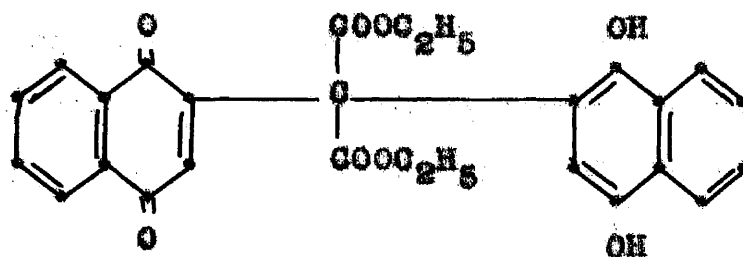
Anal. Calcd. for  $C_{23}H_{11}O_5N$ : C, 72.44; H, 2.91; N, 3.67.

Found: C, 72.61; H, 2.96; N, 4.12.

## SUMMARY

## SUMMARY

1,4-Naphthoquinone has been condensed with malonic ester in the presence of a base such as pyridine to form a deep-blue product whose structure has been shown to be:



(I)

Compound (I) was oxidized with silver oxide or chromic acid to the greenish-yellow di-quinone (II). Both (I) and (II) were reduced with sodium dithionite to the colorless di-hydroquinone (III). Compound (I) was resynthesized in nearly quantitative yield by mixing solutions of equimolecular amounts of (II) and (III).

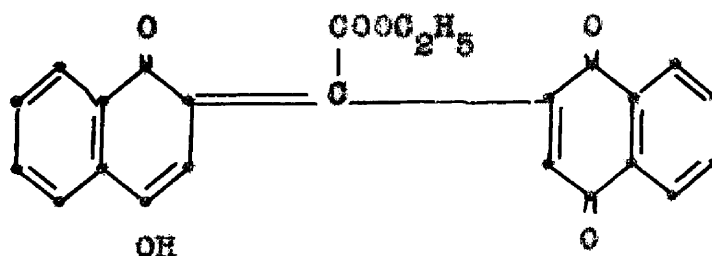
Reductive acetylation of (I) with zinc and acetic anhydride in the presence of triethylamine gave a di-hydroquinone diacetate (IVa) which on further acetylation formed the tetraacetate (IV).

Vigorous reductive acetylation of (I) in the presence of pyridine yielded the same tetraacetate (IV). By acylation of the di-hydroquinone (III) both the tetraacetate (IV) and the tetrachloroacetate (V) were prepared. The results of molecular weight determinations on compounds (IV) and (V) agreed satisfactorily with the calculated

values.

A quinone-hydroquinone structure is assigned to the blue compound rather than that of a quinhydrone type of complex composed of equimolecular amounts of the di-quinone (II) and the di-hydroquinone (III) on the basis of acylation experiments. Acetylation of (I) gave an orange quinone-hydroquinone diacetate (VI) which was reduced by sodium dithionite to the di-hydroquinone diacetate (VII). Compound (VII), which was proven to be different from (IVa), also yielded the tetraacetate (IV) on further acetylation.

When the greenish-yellow di-quinone (II) was treated with concentrated sulfuric acid an interesting reaction occurred with the loss of the elements of carbon dioxide and ethylene and the formation of the bright red compound (VIII):



(VIII)

This enolic structure was supported by ultraviolet absorption spectra studies. The contrast between the absorption spectrum of (VIII) and that of the di-quinone (II) was marked as would be predicted, since in (II) the two ring systems are not conjugated with each other as they are in (VIII). It is reasonable to assume that under al-

alkaline conditions the enolate ion of compound (VIII) exists as a resonance hybrid with the corresponding structure in which the ortho-quinonoid bonds are in the alternate half of the molecule. Ultraviolet absorption studies indicate this assumption to be correct.

Compound (VIII) was reductively acetylated to the tetraacetate (IX) and hydrolyzed to the free acid (X). Compound (X) was also obtained by hydrolysis of the di-quinone (II). When the alkaline hydrolysis product of the blue quinone-hydroquinone (I) was acidified, decarboxylation occurred and the enolic form of the quinone-hydroquinone acetic acid (XI) was obtained. Upon reductive acetylation this gave the bis-(diacetoxy-naphthyl)-acetic acid (XII).

Although the quinone-hydroquinone (I) was obtained in only 13-15% yields, most of the other transformations described proceed in nearly quantitative yields.

Further support of structure (I) was obtained by a different synthesis. It was found that potassium 1,4-naphthoquinone-2-sulfonate condenses with malonic ester in the presence of alkali to give (I) in 40% yield. This would be the preferred method of preparation.

Evidence is presented which indicates that cyanoacetic ester condenses with 1,4-naphthoquinone in a fashion similar to but not identical with that of malonic ester.

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