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2,5-Dihydroxy-*p*-benzenediacetic Acid and Related Compounds from *p*-Benzoquinone[1]

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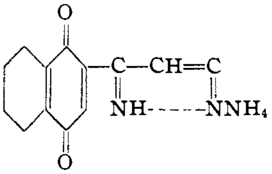
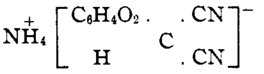
In connection with some proposed work, it became necessary to synthesize diethyl α,α'-dicyano-2,5-dihydroxy-*p*-benzenediacetate (I). The addition of ethyl cyanoacetate to *p*-benzoquinone was chosen as a possible reaction which would eventually lead to the desired compound.

While the chemistry of the addition of sodium enolates to substituted *p*-benzoquinones has been studied extensively by L. I. Smith[4] and his co-workers, the reaction between *p*-benzoquinone itself and active methylene compounds has not been conclusively investigated. Craven[5] reported the formation of a deep blue color by the action of ethyl cyanoacetate with *p*-benzoquinone in the presence of ammonium hydroxide; the structures of the compounds formed were not elucidated. Prior to Craven's work, Kesting[6,7] had reported the formation of deeply colored compounds from *p*-benzoquinone and α-naphthoquinone by the action of malononitrile in the presence of dry ammonia in ether solution. The structures of these compounds were first reported as salt types (VI) and later as heteropolar complexes (VII) in which one or both of the methylene hydrogens was replaced by a quinone molecule. Other enolates were reported as acting similarly.



VI



$$\overset{+}{NH_4}\left[\begin{matrix}C_6H_4O_2\,. & & .\,CN\\ & C & \\ H & & .\,CN\end{matrix}\right]^-$$

VII

The addition of sodium enolates to quinones which have one or two unsubstituted positions has been found by Smith[8,9] and his co-workers to give, in two cases studied, the hydroquinone that might be expected from a 1,4-addition to the ene-one system present. The hydroquinones were not isolated as such, however, but rather the coumarin and the isocoumaranone which would result from a ring closure effected by loss of water or alcohol.

Ikuta[10] has studied the reaction between acetoacetic ester and quinone and has isolated two products which were reported by him as being a difurobenzene derivative and a 5-hydroxybenzofuran derivative.

Thus, from the literature, it could be surmised that *p*-benzoquinone would react with ethyl cyanoacetate in the presence of bases to give a variety of products and we have found this to be the case. In the work herein reported, the addition of ethyl cyanoacetate to *p*-benzoquinone was carried out in the presence of ammonia in aqueous alcohol solution and was accompanied by a series of color changes of the solution from blue through green to brown. Also, a purplish-red, crystalline compound gradually separated which was insoluble in cold dilute acids or bases, and sparingly soluble in hot alcohol or acetic acid. Other enolates containing an alpha cyano group (malononitrile and cyanoacetamide) reacted in a similar way to give high melting, sparingly soluble compounds. When the additions were carried out in the presence of ammonia in dry ether, highly colored unstable compounds similar to those described by Kesting[6,7] were isolated. Efforts are now being made to relate these to the compounds we have obtained.

Analyses for carbon, hydrogen and nitrogen upon the purplish-red compound obtained by the addition of ethyl cyanoacetate to *p*-benzoquinone showed that two moles of the ester had added and that ring closure involving the elimination of water or alcohol had not occurred. Acid hydrolyses in air of this adduct gave up to 90% yields of a colorless acid whose structure was proved to be 2,5-dihydroxy-*p*-benzenediacetic acid (II). The structure of this acid was established by oxidation, after methylation of the phenolic groups, to the known dimethoxyterephthalic acid and also by several chemical tests such as phenol tests with ferric chloride, formation of a quinone (III) by oxidation, and formation of the cyclic ester (IV) suggested by the proposed structure. The colored compounds obtained by the addition of cyanoacetamide or malononitrile to *p*-benzoquinone likewise underwent acid hydrolysis to give (II).

The formation of II in high yields under what normally are not reducing conditions makes it appear that the structure of the purplish-red compound is correctly represented as the desired hydroquinone (I). In further support of this structure, compounds which analyzed for the mono- and di-acetyl derivatives of I resulted when the purplish-red compound was acetylated in the usual way. These derivatives yielded II by acid hydrolysis.

The formation of the hydroquinone (I) is readily accounted for on the basis of a 1,4-addition of

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(4) Dr. Smith has published some eighteen papers on the addition of enolates to methyl and bromo substituted *p*-benzoquinones, the most recent being: Smith, Arnold and Nichols, This Journal, **65**, 2131 (1943).

(5) Craven, *J. Chem. Soc.*, 1605 (1931).

(6) Kesting, *Z. angew. Chem.*, **41**, 358, 745 (1928).

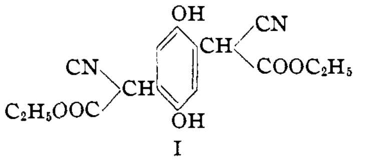
(7) Kesting, *J. prakt. Chem.*, **138**, 215 (1933).

(8) Smith and MacMullen, This Journal, **58**, 629 (1936).

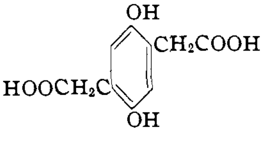
(9) Smith and Nichols, *ibid.*, **65**, 1742 (1943).

(10) Ikuta, *J. prakt. Chem.*, [2] **45**, 65 (1892).

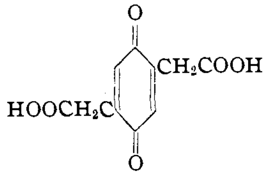
the enolate to each ene-one system of *p*-benzoquinone to form an intermediate cyclohexadiene (V) which was then oxidized by excess *p*-benzoquinone to an aromatic type. In support of this, the theoretical quantity of hydroquinone was isolated from the reaction mixture.



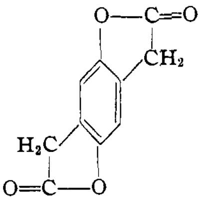
I



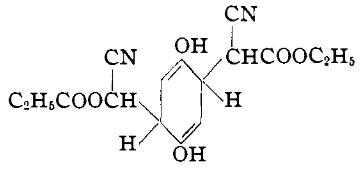
II



III



IV



V

Obviously, a hydroquinone formulation does not account for the color, the loss of color when hydrolyzed or acetylated and the insolubility in sodium hydroxide of the addition product. Repeated crystallizations of the purplish-red compound from acetic acid did not remove the color; rather, two color modifications resulted depending on the rate of crystal growth—small purplish needles and blue-black triclinic crystals. Hydrochloric acid brought about a color change to blue. On the other hand, the color was removed momentarily by repeated treatment with carbon in hot acetic acid; recrystallization of the colorless product from acetic acid gave rise to blue crystals. Desorbing the carbon by solvent action gave blue and red compounds, the weight of which was about 50% of the original weight. These colorless and colored products gave II on hydrolysis.

Depending on conditions, mild oxidation of the purplish-red compound gave one of four compounds as the chief product: a blue, a red, a violet-blue, or a yellow compound. These compounds, as well as other phases of the problem connected with the color of the adducts, are being further studied.

Experimental Part

Addition of Ethyl Cyanoacetate to *p*-Benzoquinone.—A solution of 60 g. of *p*-benzoquinone in 900 ml. of ethyl alcohol at 45° was added slowly with stirring to a mixture containing 63 ml. of ethyl cyanoacetate, 150 ml. of concd. ammonium hydroxide and 250 ml. of ethyl alcohol. After standing for three hours, the purplish-red precipitate that had formed was removed and washed with alcohol on a suction filter. Further purification was not necessary for most purposes; yield 28 g. Recrystallization from hot glacial acetic acid (sparingly soluble) gave purplish-black triclinic crystals; m. p. 278–278.5° (cor.), insoluble in water, alcohol and benzene. Rapid cooling of the acetic acid solution often gave small purplish-red crystals.

Anal. Calcd. for $C_{16}H_{16}O_6N_2$: C, 57.8; H, 4.9; N, 8.4. Found: C, 57.3; H, 4.9; N, 8.7.

Addition of Malononitrile to *p*-Benzoquinone.—A solution of 22 g. of quinone in 300 ml. of ethyl alcohol at 40° was added slowly with stirring to a solution containing 27 g. of malononitrile, 60 ml. of concd. ammonium hydroxide and 150 ml. of ethyl alcohol. The reaction mixture stood for thirty minutes, after which the light tan precipitate was removed and washed with hot acetic acid and then ethyl alcohol; yield 15.1 g., m. p. above 350°.

Anal. Calcd. for $C_{12}H_6O_2N_4$: N, 23.5. Found: N, 23.5.

Addition of Cyanoacetamide to *p*-Benzoquinone.—A solution of 20 g. of quinone in 150 ml. of alcohol at 45° was added slowly with stirring to a solution of 20 g. of cyanoacetamide in 25 ml. of concd. ammonium hydroxide and 150 ml. of alcohol. After standing an hour the solution was filtered and the precipitate washed with alcohol; yield 8 g. Crystallization of a small quantity from hot acetic acid gave glistening black needles, m. p. above 350°.

Hydrolysis of the Addition Products.—Each of the aforementioned addition products was hydrolyzed in strong acid solution to give the same acid, 2,5-dihydroxy-*p*-benzenediacetic acid (II). The procedure is illustrated as follows: 5 g. of the adduct from ethyl cyanoacetate and *p*-benzoquinone was refluxed with 150 ml. of concd. hydrochloric acid until solution was complete (about twenty hours). Upon cooling, the acid separated as tan needles. Decolorization with carbon and recrystallization from hot water gave white needles, m. p. 233°. Heating for a short time at the melting point formed the lactone.

Anal. Calcd. for $C_{10}H_{10}O_6$: C, 53.1; H, 4.4. Found: C, 53.2; H, 4.5.

Diethyl 2,5-Dihydroxy-*p*-benzenediacetate.—To 0.5 g. of finely powdered II was added 50 ml. of absolute ethyl alcohol. The mixture was shaken until most of the acid was dissolved. Dry hydrogen chloride was then bubbled through for several minutes whereupon the temperature rose to 65°. The temperature was maintained at 65–70° for two hours after which the solvent was removed by distillation at reduced pressure. Crystallization from an alcohol–water mixture gave 0.58 g. of white plates, m. p. 151–151.5° (cor.).

Anal. Calcd. for $C_{14}H_{18}O_6$: C, 59.6; H, 6.4. Found: C, 59.6; H, 6.5.

Di-γ-lactone of 2,5-Dihydroxy-*p*-benzenediacetic Acid (IV).—A mixture containing 0.1 g. of II, 1 ml. of acetic anhydride and 30 ml. of benzene was heated at 80° until all of II went into solution. After removing benzene by evaporation on a water-bath, the product was recrystallized from alcohol. White needles, m. p. 281–282°, resulted.

Anal. Calcd. for $C_{10}H_6O_4$: C, 63.2; H, 3.3. Found: C, 63.5; H, 3.2.

3,6-Diketo-1,4-cyclohexadiene-1,4-diacetic Acid (III).—A 2.0-g. sample of II was dissolved in 225 ml. of water and the solution was cooled to 17° and 0.8 ml. of sulfuric acid was then added. A water solution containing 1.3 g. of potassium dichromate was added slowly with stirring to the above solution while the temperature was maintained at 17°; 1.7 g. of bright-yellow, crystalline material separated. Recrystallization from alcohol gave yellow plates, m. p. 185°. Alcoholic solutions of the quinone upon standing turned red and to obtain the pure product, it was necessary immediately to cool the solution to 10 or 15°. Heating in water gave dark brown solutions. The quinone was reduced to II in the usual way in water solution by sodium hydrosulfite.

Anal. Calcd. for $C_{10}H_8O_6$: C, 53.6; H, 3.6. Found: C, 53.4; H, 3.9.

2,5-Dimethoxy-*p*-benzenediacetic Acid.—Seven ml. of dimethyl sulfate was added to a solution of 4.0 g. of II in

35 ml. of 10% sodium hydroxide with vigorous stirring. The temperature of the mixture was then maintained at 50° and the mixture stirred until the dimethyl sulfate layer had disappeared. Then 10 ml. more of sodium hydroxide and 3.8 ml. of dimethyl sulfate were added and the mixture stirred until solution was complete. This step was repeated three more times. The solution was cooled and then acidified with hydrochloric acid. Filtration yielded a tan material. In order to saponify any ester that was formed, this was refluxed in 25 ml. of 20% sodium hydroxide for 45 minutes. Cooling, acidification, and filtration yielded 3.2 g. of tan product. Recrystallization from water accompanied by decolorization with carbon gave white crystals, m. p. 242–243°.

Alkaline oxidation of the methoxy compound with potassium permanganate gave the known 2,5-dimethoxyterephthalic acid. The identity of this compound was verified by melting point, fluorescence, and also by conversion into the diethyl ester whose physical properties checked those given in the literature.

Summary

Ethyl cyanoacetate, cyanoacetamide, and malononitrile react with *p*-benzoquinone in the presence of ammonium hydroxide to give highly colored, crystalline compounds.

Each of the colored compounds upon hydrolysis gave the colorless acid, 2,5-dihydroxy-*p*-benzenediacetic acid. Several derivatives of this new acid are reported.

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

The Arylbutadiene–Maleic Anhydride Reaction

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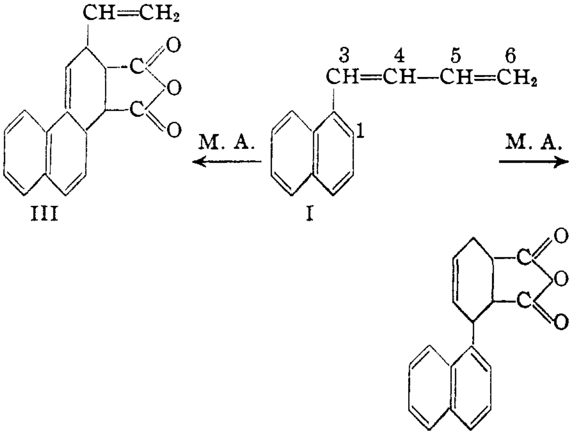
It has now been well established that certain aromatic double bonds will in conjunction with a vinyl group form a diene system which is reactive toward the common dienophiles (maleic anhydride, etc.). With one exception[2] (1,1-diphenylethylene), the examples thus far reported have the vinyl (or substituted vinyl) group attached to the α-[3] or β-[4]positions in naphthalene, the 9-position[5] in phenanthrene, or the para position to one of the oxygen atoms in the veratrole or methylenedioxybenzene[6] systems.

That the success of this reaction must depend upon the importance of certain necessary resonance contributing structures has already been pointed out.[6]

If the vinyl group in the above-mentioned molecules is replaced by a butadienyl substituent, it becomes apparent that two competitive diene systems are present within a single molecule. Thus, for example, 1-α-naphthylbutadiene (I) can react with maleic anhydride (M. A.) to give two different isomeric adducts II and III depending upon whether the 3,6 or 1,4 diene system is involved.

A qualitative consideration of the relative importance of the resonance contributing structures in I leads to the supposition that II rather than III should be the predominant product formed. The experimental results reported in this paper show that adducts of the type II are produced perhaps exclusively.

Maleic anhydride has been allowed to react with three arylbutadienes each of which has two active diene groups. The aryl substituent consisted of 1-naphthyl-3,4-dimethoxyphenyl, and 3,4-methylenedioxyphenyl. Structures of the adducts formed in the first two cases were established with certainty but all attempts to elucidate the carbon skeleton in the third case, although it is undoubtedly analogous to the other two, failed.



III I II

Unfortunately, the pure dienes polymerized so rapidly that they could not be isolated as such; consequently, the diene in each case was formed during the course of the reaction by dehydration (with maleic anhydride) of the appropriate alcohol.

The formula for compound IV follows from its conversion into dimethyl 3-α-naphthylphthalate (V) which was synthesized independently by means of an Ullmann reaction. Hydrogenation and cyclization of IV to give the hydrobenzanthronecarboxylic acid VI strongly indicates (as shown by models) the *cis* configuration for the α-naphthyl group in IV with respect to the adjacent carbonyl linkage.

[1] Abstracted from the Ph.D. thesis of Eugene C. Coyner submitted to the Graduate Faculty of the University of Minnesota, April, 1944.

[2] Wagner-Jauregg, *Ann.*, **491**, 1 (1931).

[3] Cohen, *Nature*, **136**, 869 (1935).

[4] Cohen and Warren, *J. Chem. Soc.*, 1315 (1937).

[5] Bergmann and Bergmann, THIS JOURNAL, **59**, 1443 (1937).

[6] Hudson and Robinson, *J. Chem. Soc.*, 715 (1941).