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

Reduction of 1,4-Di-(2-hydroxy-3,4,6-trimethylphenyl)-butane-1,4-dione: The Two Stereoisomeric Diols[1,2]

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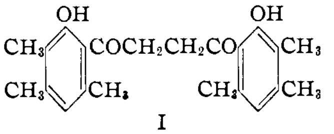
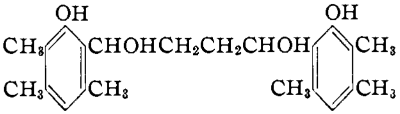
The bis-phenolic-1,4-diketone I has been catalytically reduced to the bis-phenolic-1,4-diol II, which was obtained in the two stereoisomeric forms. One of the diols, m.p. 254–255°, was readily dehydrated to the acetate of the phenolic diene V by action for ten minutes of boiling acetic anhydride in pyridine. The other diol, m.p. 208–210°, underwent no dehydration, but was converted into a tetraacetate, even when boiled for two hours with acetic anhydride in pyridine. Both diols were converted into the diene-diacetate V by action of boiling acetic anhydride alone. The significance of these facts is discussed in relation to the configurations of the diols. The phenolic diene IV was obtained by hydrolysis of the acetate V; attempts to convert IV into a bis-quinone were not successful. Reduction of the diacetate of the diketone I by action of sodium and isopropyl alcohol led to a substance insoluble in Claisen alkali, and derived from the diacetate by loss of an acetyl group and the elements of water. This substance, formulated as a chromone, is probably derived from the diacetate by an initial rearrangement of the type studied by Baker and Venkataraman.

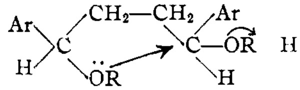
The preparation of 1,4-di-(2-hydroxy-3,4,6-trimethylphenyl)-butane-1,4-dione (I) by Fries rearrangement of the succinate of 2,3,5-trimethylphenol, has been described in the previous paper[3] together with certain reactions of the 1,4-diketone. In this paper, there is described the reduction of the diketone I and the chemistry of the resulting diols II.



I



IIa, m.p. 254–255°
IIb, m.p. 208–210°

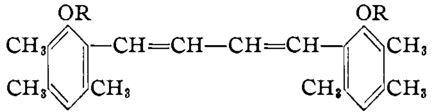


IIc, Ar-Ar *trans* (R = H or Ac)
IId, Ar-Ar *cis* (R = H or Ac)

Hydrogenation of I was erratic unless the sample was pretreated with Raney nickel to remove an unknown impurity. After pretreatment, hydrogenation proceeded quantitatively to give approximately equal amounts of the two diols IIa and IIb. The best results were obtained by hydrogenating under 500 lb. pressure, in ethanol, using Adams platinum oxide catalyst. Action of lithium aluminum hydride failed to reduce I.

The mixture of diols—one *meso* and one *dl*—was separated into IIa and IIb by extraction with a mixture of ethanol and acetone; the insoluble portion (IIa) melted at 254–255° with decomposition, whereas the soluble portion (IIb) melted at 208–210° with decomposition.

That the two diols were stereoisomers followed from these facts: they were isomeric and were the only reduction products of I; the diols, when acetylated under mild conditions, gave isomeric tetraacetates (IIIa and IIIb); both diols could be dehydrated to the same diene diacetate (V); and finally, the infrared spectra of the pair of diols (II) and of the pair of tetraacetates (III) were so similar that structural isomerism was excluded.[4] The spectra of the diols II show a band at 3200–3600 cm.$^{-1}$, characteristic of the free hydroxyl group; this band is also present in the spectrum of the phenolic diene IV. This band is absent in the spectrum of the diketone I, showing the powerful chelating effect of the ortho carbonyl groups in I. The spectra of the tetraacetates III and the diacetate V all show the band at 1750 cm.$^{-1}$ characteristic of the acetate carbonyl group, together with a series of strong bands at about 1200 cm.$^{-1}$. The band in the spectra of the tetraacetates III at 1750 cm.$^{-1}$ is a doublet, indicating the presence of two different kinds of acetate group—one phenolic, the other alcoholic.



IV, R = H
V, R = Ac

The behavior of the two diols toward a boiling mixture of acetic anhydride and pyridine was striking. When the low melting diol IIb was boiled with this mixture, the only product was the tetraacetate IIIb, but when the high melting diol IIa was boiled with this reagent for *ten minutes*, it was converted into the diene diacetate V. Although the low melting diol IIb was not affected by the boiling mixture of acetic anhydride and pyridine, it was transformed into the diene-diacetate V by action of boiling acetic anhydride containing sulfuric acid. The tetraacetate IIIb of the low melting diol was recovered in 60% yield after its solution in quinoline was boiled for three hours.

It is not known which of the diols II is *meso* and which is *dl*, but assuming that the conversion of these or their acetates II into the diene V involves an initial attack of a proton at one of the alcoholic hydroxyl (acetoxyl) groups, and further involves a cyclic transition state—IIc or IId—with participation of the "neighboring" oxygen atom in the 5-posi-

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[1] Abstracted from a thesis by Richard Remsen Holmes, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, July, 1950. American Chemical Society Predoctoral Fellow, 1946–1950.

[2] The authors acknowledge with thanks a grant from the Fluid Research Funds of the Graduate School of the University of Minnesota which made it possible to complete certain parts of this work.

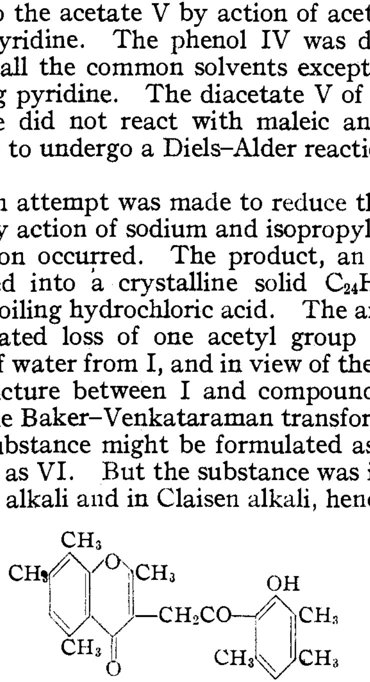
[3] L. I. Smith and R. R. Holmes, THIS JOURNAL, **73**, 3847 (1951).

[4] We wish to express our thanks to Mr. John Lancaster, Mr. Bertram Zaslow and to Dr. Bryce L. Crawford, Jr., of this Laboratory, for the determination of the absorption spectra discussed in this paper, and for aid in the interpretation of the curves. The complete curves may be found in the Ph.D. thesis of R. R. Holmes, ref. 1.

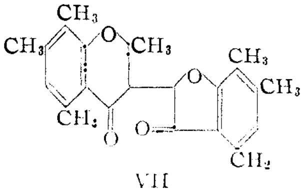
tion[5] then formation of a cyclic transition state would be much less affected by steric hindrance when the two aryl groups are *trans* to each other in this transition state (IIc). Such a cyclic "intermediate," with the aryl groups in the *trans* position, can be derived from the *meso* form of II or III, but not from the *dl* form. It is therefore likely that the diol which dehydrates readily—IIa—is the *meso* form, whereas the one which dehydrates with some difficulty—IIb—is the *dl* form. This applies only to elimination of the first molecule of water; elimination of the second molecule of water most likely proceeds *via* an ordinary Krafft reaction.[6] Such a difference in the chemical behavior of a pair of stereoisomers is not confined to a *meso–dl* pair, for diastereomeric pairs also occasionally show these differences.[7]

Hydrolysis of the acetate V to the phenolic diene IV by action of aqueous acid was slow, but was readily accomplished by action of potassium hydroxide in aqueous methanol. Action of *p*-toluenesulfonyl chloride upon IIa in boiling pyridine also produced IV. The phenol IV was readily converted into the acetate V by action of acetic anhydride in pyridine. The phenol IV was difficultly soluble in all the common solvents except acetone and boiling pyridine. The diacetate V of the phenolic diene did not react with maleic anhydride; this failure to undergo a Diels–Alder reaction is not surprising.

When an attempt was made to reduce the diacetate of I by action of sodium and isopropyl alcohol, no reduction occurred. The product, an oil, was transformed into a crystalline solid $C_{24}H_{26}O_4$ by action of boiling hydrochloric acid. The analytical data indicated loss of one acetyl group and one molecule of water from I, and in view of the similarity in structure between I and compounds which undergo the Baker–Venkataraman transformation,[8] the new substance might be formulated as a chromone such as VI. But the substance was insoluble in aqueous alkali and in Claisen alkali, hence it was improbable that any phenolic hydroxyl group was present. A structure such as VII would satisfy the requirements, but the compound was not investigated further.



VI



VII

It was originally hoped that the phenolic diene IV could be converted into a diene bis-quinone, but the phenol IV could not be coupled with diazotized sulfanilic acid. This was surprising, in view of the ready reaction between the related furan bis-phenol and diazotized sulfanilic acid,[3] and it may be because of the extreme insolubility of IV in alkali. Nitration and nitrosation of IV gave poorly defined products.

Experimental Part[9]

1,4-Di-(2-hydroxy-3,4,6-trimethylphenyl)-butane-1,4-diol (II). A.—A platinum oxide catalyst (3 g.) was suspended in dry ethanol (120 cc.) and reduced at atmospheric pressure in the conventional apparatus; hydrogen (685 cc.) was absorbed rapidly. The diketone I (3.5 g., 0.1 mole, m.p., 209–210°) was added, hydrogen was admitted under atmospheric pressure, and shaking was begun. After nine hours, when the theoretical amount of hydrogen was absorbed (490 cc., 0.2 mole), the mixture was removed. Dry ethanol (200 cc.) and acetone (200 cc.) were added, the mixture was heated to the boiling point, and the suspension was filtered while hot. The solid was extracted with aqueous alcoholic alkali (5%) and the extracts were filtered to remove the catalyst. The alkaline filtrate was acidified with hydrochloric acid (10%), the solid was removed and crystallized from pyridine, when it weighed 1.1 g. and melted at 254–255° (dec.).

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.34; H, 8.27.

The filtrates remaining after isolation of IIa were evaporated to dryness and the residue of white solid (2 g.) was crystallized from isopropyl alcohol (200 cc.). The tiny white needles of IIb (0.9 g.) melted at 208–210° (dec.).

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.88; H, 8.56.

A mixture of IIb and I melted at 188–197°. Many variants of the above procedure were tried, but none were successful. These included: a lower ratio of catalyst to diketone (little or no reduction); acetic acid as solvent (no reduction); W-6 Raney nickel catalyst (little or no reduction); action of lithium aluminum hydride (poor reduction); action of sodium and isopropyl alcohol (poor reduction). Attempts were made to reduce the diacetate of I, using as catalysts platinum oxide or copper chromite in ethyl acetate, isopropyl alcohol or acetic acid, but little or no reduction occurred. The above hydrogenation of I, although very slow, produced the diols in good yield provided enough time was allowed for complete reduction. Thus, the diketone I (14 g.) in dry ethanol (120 cc.) was reduced under 30 lb. pressure of hydrogen in the presence of 3 g. of platinum oxide catalyst. Complete reduction required six days; the product was 7 g. of IIa, m.p. 250–254°, and 6.3 g. of IIb, m.p. 206–207°.

B.—The diketone I (110 g.) was dissolved in boiling pyridine (700 cc.). Raney nickel catalyst (5 g., W-3) was added, the mixture was boiled for two hours, the catalyst was removed, and the filtrate was cooled. The solid (103 g., m.p., 208–210°) was removed, washed on the filter with several portions of methanol, and dried. Meanwhile the bomb was "cleaned" by subjecting it for six hours to 500 lb. pressure of hydrogen at 80° in the presence of ethanol (300 cc.) and the W-3 catalyst (5 g.), and then discarding the contents. The above diketone (100 g.) in ethanol (800 cc.) was then reduced in the bomb at 80° under 800 lb. pressure of hydrogen for 12 hours in the presence of platinum oxide catalyst (1 g.). A portion (10 g.) of the product was separated into Ia (5.3 g.) and IIb (4.1 g.). Both diols were insoluble in water, and only slightly soluble in most organic solvents. The higher melting diol IIa was considerably less soluble than the lower melting isomer. Both diols were

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(5) (a) S. Winstein, E. Grunwald, R. E. Buckles and C. Hanson, THIS JOURNAL, **70**, 816 (1948); (b) S. Winstein and R. Adams, *ibid.*, **70**, 838 (1948).

(6) E. R. Alexander and A. Mudrak, *ibid.*, **72**, 1810 (1950).

(7) (a) P. I. Pollak and D. Y. Curtin, *ibid.*, **72**, 961 (1950); (b) V. Bruckner, G. Fodor, J. Kiss and J. Kovács, *J. Chem. Soc.*, **885** (1948); (c) G. Fodor, V. Bruckner, J. Kiss and G. Óhegyi, *J. Org. Chem.*, **14**, 337 (1949).

(8) (a) W. Baker, *J. Chem. Soc.*, 1381 (1933); 1953 (1934); (b) D. C. Bhalla, H. S. Mahal and K. Venkataraman, *ibid.*, 868 (1935); (c) V. V. Virkar and T. S. Wheeler, *ibid.*, 1679 (1939); (d) T. A. Geissman, THIS JOURNAL, **71**, 1498 (1949).

(9) Microanalyses by R. Amidon, J. Buckley, W. Cummings, W. Hunter, R. Kelly, F. Robinson and H. Turner. All melting points are uncorrected.

readily soluble in aqueous alcoholic alkali (5%), and were recovered unchanged when the alkaline solutions were acidified.

1,4-Diacetoxy-1,4-di-(2-acetoxy-3,4,6-trimethylphenyl)-butane (III). A.—The diol IIb (3 g.) was boiled for ten minutes with pyridine (300 cc.) containing acetic anhydride (100 cc.), and the cooled solution was poured into water (1 l.). The solid was removed and crystallized from a mixture of ethyl acetate and petroleum ether (b.p., 30–60°) and then from a mixture of benzene and petroleum ether. It then weighed 2.1 g. (48%) and melted at 142–144°.

Anal. Calcd. for $C_{30}H_{38}O_8$: C, 68.42; H, 7.27. Found: C, 68.22; H, 7.35.

This tetraacetate IIIb was recovered substantially unchanged when its solution in pyridine and acetic anhydride was boiled for two hours. When a solution of IIIb in quinoline was refluxed for three hours, over 60% of IIIb was recovered unchanged; the rest of the material was an uncrystallizable gum.

B.—The diol IIa (4.5 g.) was suspended in a mixture of acetic anhydride (100 cc.) and pyridine (200 cc.), and the mixture was warmed gently on the steam-bath for 30 minutes. The clear solution was poured into ice-water (1 l.) and allowed to stand overnight. The solid (IIIa) was removed and crystallized three times from ethanol, when it weighed 4.2 g. and melted at 158–160°. A mixture of IIIa and IIIb melted at 127–136°; a mixture of IIIa and the diacetate of I (m.p. 155–156°) melted at 135–144°.

Anal. Calcd. for $C_{30}H_{38}O_8$: C, 68.42; H, 7.27. Found: C, 68.26; H, 7.46.

1,4-Di-(2-acetoxy-3,4,6-trimethylphenyl)-1,3-butadiene (V). A.—The high melting diol IIa (0.5 g.) was boiled for ten minutes in pyridine (50 cc.) containing acetic anhydride (15 cc.) and the cooled solution was poured into water (200 cc.). The solid was removed and crystallized from ethanol; it then weighed 0.3 g. (53%) and melted at 171–174°. The analytical sample, crystallized from a mixture of ethyl acetate and petroleum ether (b.p. 30–60°) formed fine white needles melting at 174–176°.

Anal. Calcd. for $C_{26}H_{30}O_4$: C, 76.81; H, 7.44. Found: C, 76.54; H, 7.68.

B.—The low melting diol IIb (25 g.) was boiled for three hours in acetic anhydride (1 l.) containing sulfuric acid (1.5 cc.). The product, isolated and crystallized as described above, weighed 16.1 g. (57%) and melted at 175–176°, alone or when mixed with the product from A above.

1,4-Di-(2-hydroxy-3,4,6-trimethylphenyl)-1,3-butadiene (IV). A.—The high melting diol IIa (1 g.) was boiled for two hours in pyridine (40 cc.) containing *p*-toluenesulfonyl chloride (8 g.). The cooled solution was poured into aqueous sodium bicarbonate (5%, 500 cc.), the mixture was stirred and warmed on a steam-bath for an hour, and the solid (1 g.) was removed and crystallized successively from benzene, ethyl acetate and benzene, when it then melted at 226–229° with sintering at 210–220°.

Anal. Calcd. for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.70; H, 8.17.

B.—The diacetate V (4.7 g.) was boiled for 40 minutes in methanol (200 cc.) containing water (100 cc.) and potassium hydroxide (10 g.). The solution was poured into aqueous acetic acid (20%, 1 l.), the solid (4.4 g.) was removed and crystallized twice from pyridine. It was white and melted at 225–230°.

Although insoluble in aqueous alkali, IV was soluble in Claisen alkali in the cold, giving a bright yellow solution; IV was recovered when this solution was diluted with water and acidified, although it then melted somewhat low (209-212°, alone or when mixed with pure IV). Acetylation of IV by action of acetic anhydride in pyridine produced the diacetate V, m.p. and mixed m.p. 175–176°.

For preparative purposes, it was not necessary to separate the diols before converting them into V, but the mixture of crude diols (80 g.) was boiled for three hours in acetic anhydride (700 cc.) containing sulfuric acid (3 cc.). The product, V, weighed 59 g. (67%). This, when hydrolyzed by boiling it for four hours with water (200 cc.), methanol (400 cc.) and potassium hydroxide (30 g.), gave IV (38 g., 78%).

The diacetate V (1 g.) and maleic anhydride (2 g.) were fused together over a low flame and the melt was kept at 100° for an hour. The orange melt deposited a solid at 60°; the cooled mixture was triturated with benzene and filtered. The solid weighed 0.85 g., and melted at 172–175°, alone or when mixed with V.

An attempt to couple IV with the diazonium salt of sulfanilic acid under the conditions successfully used with I[3] resulted in recovery of 73% of IV unchanged. This experiment also showed that IV was stable toward the action of a boiling, strongly acid solution of stannous or ferric chloride.

A cold (0°) solution of sodium nitrate (2 moles) in sulfuric acid (50 cc.) was added dropwise to a cold (ice-salt-bath) solution of the phenol IV (5.2 g.) in sulfuric acid (30 cc.). The solution was kept in the cooling bath for 30 minutes, and then poured into water. The resulting solid was apparently a polymer—it was infusible, and nothing crystalline could be obtained from it.

Powdered sodium nitrite (10 g.) was added to a suspension of the phenol IV (10 g.) in acetic acid (300 cc.). The mixture was allowed to stand for 12 hours at room temperature, with occasional shaking; more sodium nitrite (10 g.) was added and the mixture was allowed to stand for a further 12 hours and then poured into water. The yellow solid (9.1 g.) was removed and dried. It was readily soluble in most organic solvents; its solution in hot aqueous acetic acid (50%), on cooling, deposited a yellow solid melting at 110–116° with decomposition to a dark red liquid. The material could not be purified further, but an attempt was made to reduce it by boiling its solution in aqueous methanol with sodium hydrosulfite. Although the color faded considerably, the pale yellow solid obtained by pouring the solution into water could not be purified—all attempts to crystallize it led only to a dark red tar.

Chromone VII.—The diacetate of the diketone I (5 g.) was dissolved in boiling isopropyl alcohol (250 cc.), and sodium (5 g.) was added rapidly (20 minutes) portionwise. The solution was boiled until all the sodium dissolved (20 minutes) and then was poured into aqueous acetic acid (5%, 2 l.). The orange oil was removed and boiled for 18 hours with aqueous hydrochloric acid (1:1, 150 cc.). The solid (3.4 g., 80%) was removed and crystallized successively from benzene–petroleum ether, ethyl acetate and acetone, when it formed white needles melting at 215–218°.

Anal. Calcd. for $C_{24}H_{26}O_4$: C, 76.16; H, 6.93. Found: C, 75.97; H, 7.27.

The substance was insoluble in petroleum ether, slightly soluble in acetone, moderately soluble in ethyl acetate and benzene, and very soluble in chloroform. It was insoluble in hot aqueous alkali (5%) and in hot Claisen alkali.

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