The Aromatization of Cyclic Ketones. II. Novel Synthesis of Substituted Dihydroxybenzenes[1]

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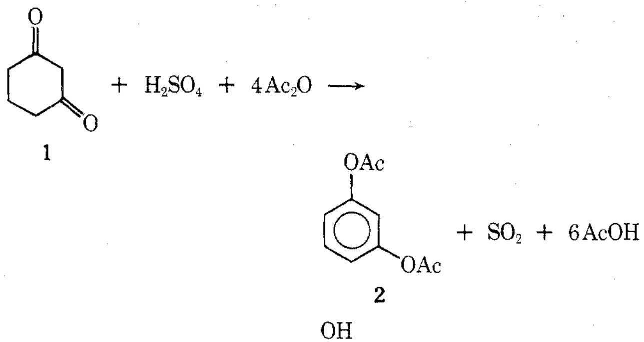
Dihydroxybenzenes are obtained in high yields when the corresponding cyclohexanediones are refluxed with concentrated sulfuric acid in acetic anhydride–acetic acid solvent followed by hydrolysis. 5,5-Dimethyl- and 2-methyl-1,3-cyclohexanediones are aromatized to 4,5-dimethyl- and 2-methyl-1,3-dihydroxybenzenes, respectively. Acetoxycyclohexenonesulfonic acids are believed to be the intermediates in the above aromatization reactions.

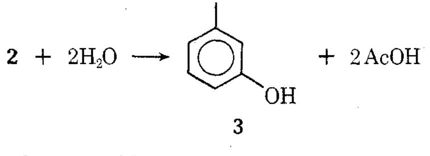
To date the syntheses of substituted dihydroxybenzenes from the corresponding cyclohexanediones involve two-step processes. Treatment of 5,5-dimethyl-1,3-cyclohexanedione with 30% oleum gives 5,5-dimethyl-1,3-cyclohexanedione-2-sulfonic acid. Refluxing the sulfonate with acetic anhydride followed by steam distillation gives about 18% yield[2] of 4,5-dimethyl-1,3-dihydroxybenzene. Catalytic dehydrogenation of 5-methyl-1,3-cyclohexanedione is unsuccessful.[3] Bromination of the sodium salts of 4-carboxyethyl-5-alkyl-1,3-cyclohexanediones in 1,2-dimethoxyethane followed by refluxing in DMF gives about a 75% yield of alkyl-1,3-dihydroxybenzenes.[4] Chlorination of 2-alkyl-1,3-cyclohexanediones followed by heating with a 25% solution of dry hydrogen chloride in DMF gives 50–70% yield of the alkyl dihydroxybenzene.[5]

This paper deals with a one-step aromatization of cyclohexanediones to the corresponding diacetoxybenzenes in high yields using acetic anhydride–sulfuric acid reagent.

Results and Discussion

Resorcinol diacetate (1,3-diacetoxybenzene) (**2**) was isolated when 1,3-cyclohexanedione (**1**) was heated in acetic anhydride solvent with concentrated sulfuric acid. Hydrolysis of the diacetate afforded resorcinol (1,3-dihydroxybenzene) (**3**) in 95% yield based on **1**. Sulfur dioxide was isolated as a by-product. The best results were obtained when 1 mol of H_2SO_4 was added, preferably at room temperature, to a solution of 1 mol of **1** in Ac_2O–AcOH with at least 4 mol of Ac_2O in a dry nitrogen atmosphere. The yields dropped appreciably (20–30%) when oxygen was bubbled through the reaction mixture during aromatization.

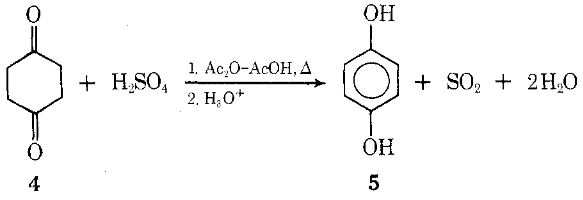


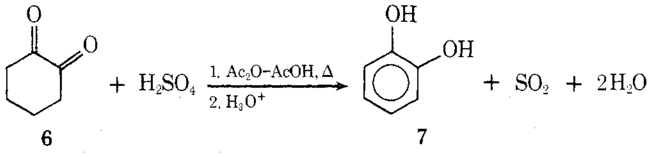


No aromatization occurred when sodium bisulfate, *p*-toluenesulfonic acid, or sulfoacetic acid was substituted for H_2SO_4, or when phthalic or succinic anhyride replaced Ac_2O.

The progress of the reaction was measured by the amount of SO_2 liberated. A quantitative measure of SO_2 gas formed during a typical run showed it to amount to 90% of the theoretical value. At all stages of the reaction, the amount of SO_2 formed corresponded to the amount of dione aromatized.

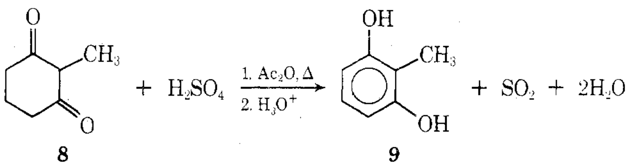
The aromatization of 1,4- (**4**) and 1,2-cyclohexanediones (**6**) with H_2SO_4 in Ac_2O–AcOH solvent gave after hydrolysis 1,4-dihydroxybenzene (**5**) and 1,2-dihydroxybenzene (**7**), respectively, in over 90% yields. When the aromatization was done in acetic anhydride only, in the absence of acetic acid, **4** gave only **5** while **6** gave **7** in about 60% yield and a minor product (20% yield) identified as a polyhydroxybenzene (more than two hydroxyl groups in the molecule). (Reactions of this type have been observed when α-substituted cyclohexanones are aromatized with H_2SO_4–Ac_2O. Such aromatizations will be fully discussed in a separate paper.)

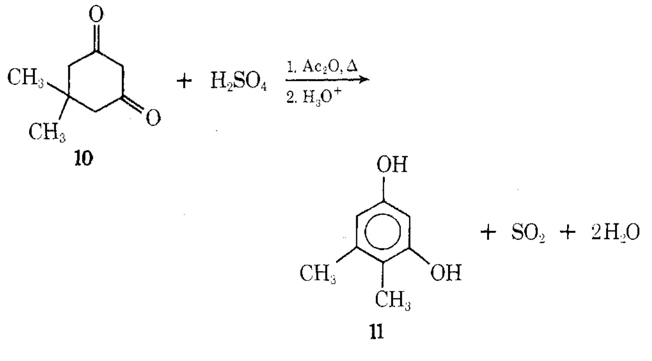




$$6 + H_2SO_4 \xrightarrow[2.\ H_3O^+]{1.\ Ac_2O,\ \Delta} 7\ (60\%) + \text{polyhydroxybenzene}\ (20\%)$$

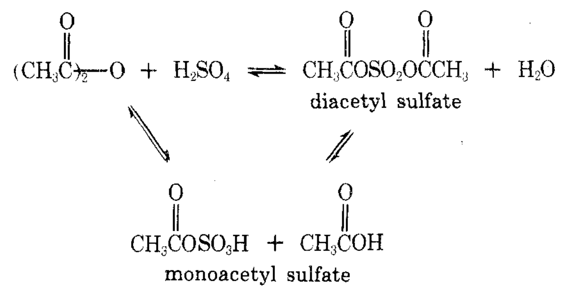
2-Methyl-1,3-cyclohexanedione (**8**) and dimedone (5,5-dimethylcyclohexane-1,3-dione) (**10**) gave 2-methyl-1,3-





dihydroxybenzene (**9**) and 4,5-dimethyl-1,3-dihydroxybenzene (**11**), respectively, when treated with H_2SO_4–Ac_2O. In the latter case, a 1,2-methyl shift occurred during aromatization.

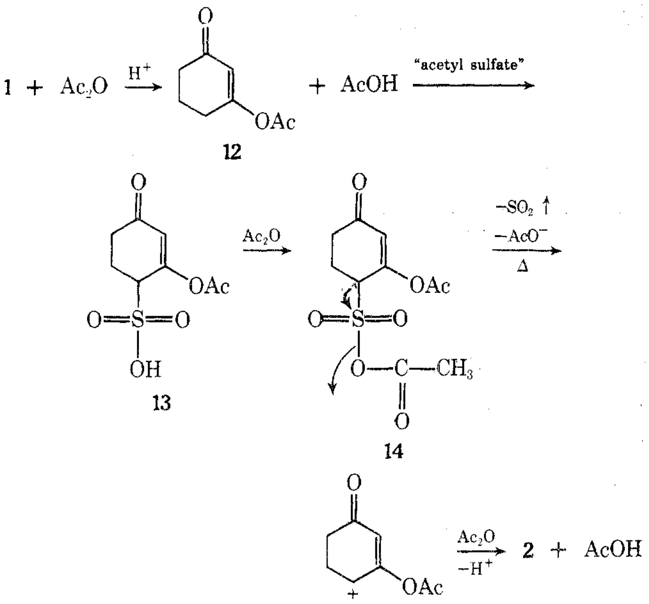
Acetic anhydride and sulfuric acid react at low temperatures to form a sulfonating species believed to be the mono- or the diacetyl sulfate, or both,[6] as shown below. For convenience it will be referred to as "acetyl sulfate." [Prolonged heating of acetyl sulfate affords[7] sulfoacetic acid [$HOSO_2CH_2C(=O)OH$], which could not be the intermediate since sulfoacetic acid did not aromatize diones.] It is believed that acetyl sulfate is the aromatizing species. This is done by sulfonating the dione or an intermediate which decomposes in the presence of Ac_2O to the aromatized product as shown in Scheme I.



$$(CH_3CO)_2O + H_2SO_4 \rightleftharpoons CH_3COSO_2OCCH_3 + H_2O$$

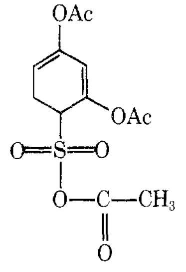
$$CH_3COSO_3H + CH_3COH$$

Scheme I



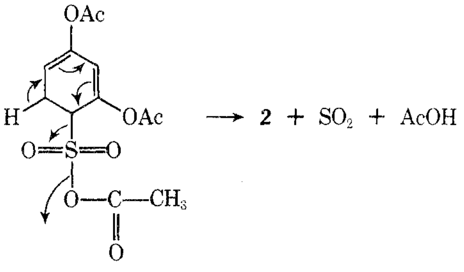
The first step in the aromatization of **1** is the formation of the monoenol acetate **12**. This is based on **12** being the only product isolated when **1** was treated with Ac_2O and catalytic amounts of H_2SO_4. Also **12** was isolated during the aromatization when the reaction mixture was quenched at reflux, prior to the 1-hr heating. Sulfonation of **12** would afford the 4-sulfonic acid **13**, since sulfonation of α,β-unsaturated ketones with acetyl sulfate occurs[8] on a carbon atom separated from the keto group by the vinyl moiety.

Sulfonates similar to **13** prepared[2] from 3,3,5-trimethylcyclohexenone aromatize to 3,4,5- and 2,3,5-trimethylphenols when refluxed in Ac_2O. Some sulfonates are isolated[9] during the aromatization of 3,3,5-trimethylcyclohexenone with Ac_2O–H_2SO_4, as in the aromatization of **1**, when the reaction mixture is quenched at 100° in anhydrous ethyl ether. The same ratio of 3,4,5- and 2,3,5-trimethylphenols is obtained when the sulfonate intermediates are refluxed in Ac_2O or when 3,3,5-trimethylcyclohexenone is aromatized[9] with Ac_2O–H_2SO_4. Furthermore, 3-phenyl-5,5-dimethylcyclohexenone-4-sulfonic acid, similar to **13**, is aromatized[10] to 3-phenyl-4,5-dimethylphenol when heated in Ac_2O. In all the above cases Ac_2O is essential to the aromatization. The reaction of the sulfonates, such as **13**, with Ac_2O would give the mixed anhydride (**14**). [Acetylation of the keto group in **13** could occur at this stage to give the intermediate **14a**. Decomposition of **14a**, as in the case of **14**, would give **2**.] The anhydride probably weakens the sulfur–hydroxyl bond of the sulfonic acid thus promoting the decomposition of the anhydride to AcO^-, SO_2, and a carbonium ion. Loss of a proton and subsequent acetylation of the keto group gives **2**. Such decomposition is believed to be initiated by heating.



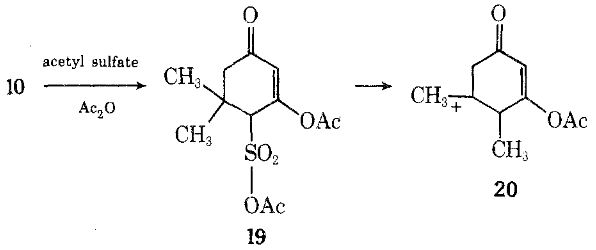
14a

A concerted one-step mechanism is also postulated. This is shown in the decomposition of the intermediate **14a**.



14a

In the aromatization of **10**, decomposition of the mixed anhydride **19** would be followed by methyl migration to form the tertiary carbonium ion **20**.



Experimental Section

The ir spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer; the nmr spectra were obtained on a Varian Associates Model V-4311 spectrometer operating at 60 MHz. All glc analyses were run on a SE-30 column programmed from 100 to 250°.

Aromatization of Cyclohexanedione. Into a 300-ml, three-neck flask equipped with a magnetic stirrer, a gas sparger, a condenser, and a thermometer were charged 3.0 g (0.027 mol) of 1,3-cyclohexanedione (**1**) (crystallized twice before use), 50 ml of Ac_2O, and 50 ml of AcOH. Concentrated sulfuric acid (2.65 g, 0.027 mol) was slowly added at room temperature to the mixture. The reaction mixture was then heated to reflux for 1 hr under nitrogen. The work-up of the reaction mixture was completed by quenching in 150 ml of ice–water and stirring for 30 min to decompose all the Ac_2O, followed by extraction with ether (4 × 50 ml). The combined ether extracts were washed once with 50 ml of saturated $NaHCO_3$ solution and once with 50 ml of saturated NaCl solution, dried, and stripped to give a residue (5.2 g) whose glc analysis indicated the presence of only one compound. Upon distillation of the residue [105° (25 mm)], 5.0 g (95% yield) of 1,3-diacetoxybenzene (**2**) was isolated. The product was identified by comparison of its ir and nmr spectra with authentic sample prepared by acetylation of **3** with Ac_2O.

1,4-Cyclohexanedione (5.0 g, 0.045 mol) was aromatized as in the above case with concentrated H_2SO_4 (4.27 g, 0.045 mol) in 50 mol of Ac_2O and 50 ml of AcOH. After work-up and distillation of the residue, 8.1 g (93% yield) of 1,4-diacetyoxybenzene was isolated.

Aromatization of 1,2-cyclohexanedione (5.0 g, 0.045 mol) with 4.27 g (0.045 mol) of H_2SO_4 in Ac_2O–AcOH solvent afforded after distillation 7.8 g (90% yield) of 1,2-diacetoxybenzene.

Isolation of Intermediates in the Aromatization of 1,3-Cyclohexanedione. The aromatization was done as before except that only 0.13 g (1.3 mmol) of concentrated H_2SO_4 were used. After work-up, a glc analysis indicated the presence of only one compound. It was identified as the monoenol acetate of 1,3-cyclohexanedione (**12**): ir (neat) 5.65 (–OAc), 6.1 (C═C), 5.95 μ (C═O); nmr ($CDCl_3$) δ 5.59 (s, 1 H, >C═CH–), 2.21 [s, 3 H, CH_3-C(═O)O].

When the aromatization was done as in the previous example except that the reaction mixture was quenched at reflux, about 10–15% of **2** was isolated along with 85–90% of **12**.

Aromatization of 1,2-Cyclohexanedione in Ac_2O. The aromatization of the title compound was done as before except that 100 ml of Ac_2O was used as solvnet instead of Ac_2O–AcOH. After work-up, a glc analysis indicated the presence of two compounds. The first (70%) was identified as 1,2-dihydroxybenzene diacetate by comparison of its ir and nmr spectra with an authentic sample prepared by acetylation of catechol with Ac_2O. The second compound (25%) is tentatively identified as 1,2,3-trihydroxybenzene triacetate. Further identification of this material and the type of aromatization will be fully discussed in a separate paper.

Aromatization of 5,5-Dimethyl-1,3-cyclohexanedione. The title compound (9.0 g, 0.065 mol) was aromatized with 7.0 g (0.072 mol) of concentrated H_2SO_4 in 100 ml of Ac_2O as in the above example. After work-up and distillation of the residue [115–125° (0.3 mm)], 11.4 g (80% yield) of 4,5-dimethyl-1,3-diacetoxybenzene was isolated. Hydrolysis of the product afforded **11** as identified by ir and nmr and comparison with known material.[2]

Sublimation and recrystallization from benzene gave pure **11**, mp 135–135.5° (reported 135.5–136°[2] and 133–134.5°, 134–135°[11]).

Preparation and Aromatization of 2-Methylcyclohexane-1,3-dione. Into a 1-l. flask equipped with a condenser, drying tube, dropping funnel, and thermometer were charged 300 ml of absolute methanol and 21.6 g (0.94 mol) of sodium metal in small pieces, followed by 112.0 g (1.0 mol) of **1**. The solution was then cooled to 15°, and 162.0 g (1.14 mol) of methyl iodide in 50 ml of methanol was added slowly through the dropping funnel over a period of 0.5 hr. The solution was then refluxed for 3.5 hr followed by evaporation of the solvent. Water (400 ml) was then added and the residue and solids thus formed were filtered (62.0 g, 50% yield), mp 199–204°. Recrystallization from benzene gave pure **8**, mp 205–206° (reported[12] 205–207°).

Aromatization of **8** (3.0 g, 0.024 mol) with 2.34 g (0.024 mol) of concentrated H_2SO_4 in 50 ml of Ac_2O, as in the previous cases, afforded after hydrolysis 2.5 g (85% yield) of **9**, mp 97–98°, 106–107.5° when molten compound was seeded with authentic sample (reported[4a] 96–97°, 106–108°, and 106–108°[13]).

Registry No.—**1**, 504-02-9; **2**, 108-58-7; **4**, 637-88-7; **6**, 765-87-7; **8**, 1193-55-1; **10**, 126-81-8; **11**, 527-55-9; **11** diacetate, 35236-36-3; **12**, 50557-37-4.

References and Notes

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Carbon-13 Nuclear Magnetic Resonance Characteristics of 3-Methylcyclohexane-1,2-diols

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The proton nmr parameters which establish the stereochemistry and conformation of the diols **1–4** are described. The relation between the ^{13}C chemical shifts of the carbon atoms and the stereochemistry of the diols is analyzed with regard to substituent effects and vicinal interactions.

In a recent investigation of the metabolism of toluene[1] we had occasion to prepare a series of 3-methylcyclohexane-1,2-diols to confirm the stereochemistry assigned to a reduction product of the metabolite encountered. We describe here the proton nmr spectra which establish the configuration of these materials, and an investigation of the relation of the ^{13}C chemical shifts of the series to the configurations.

Klein and Dunkelblum[2] have recently described the preparation and characterization of three 3-methylcyclohexane-1,2-diols. The all-trans equatorial configuration **1** was assigned to the diol obtained by the hydroboration of 3-methyl-2-cyclohexenone. The assignment was anticipated from the mode of preparation and supported by the appearance of H-2 as a triplet at 2.80 ppm, $J = 9$ Hz. The trans,cis diol, configuration **2**, was obtained from the reaction of 3-methylcyclohexene with hydrogen peroxide and formic acid. The nmr spectrum defied analysis, but the authors inferred from its complexity that the isomer exists in rapid equilibrium between the conformations **2a** and **2b**. The cis,trans isomer **4** was obtained from the reaction of 3-methylcyclohexene with either potassium permanganate or