[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF SCHERING CORPORATION]

REDUCTIONS WITH NICKEL-ALUMINUM ALLOY AND AQUEOUS ALKALI.¹ PART V. RUPTURE OF THE METHYLENEDIOXYL BRIDGE

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It was shown in a recent publication (1b) that alkoxyl and methylthiol groups are hydrogenolyzed from the benzene ring by the action of nickel-aluminum alloy and aqueous alkali. The ease with which these reactions occurred raised the question as to whether this remarkable fission by hydrogen would also take place if the ether linkage forms part of a heterocyclic ring system.

The first compounds of this type to be studied were methylenedioxybenzene and its derivatives. Normal rupture of the methylenedioxyl bridge to dihydroxyl compounds has been brought about by numerous reagents. However, several isolated instances of anomalous rupture of this ring have been reported in compounds such as β -piperonylacrylic acid (I) and its derivatives (2) and isomyristicin (II) (3). In the sodium amalgam reduction of I and II, the principal reaction was the normal hydrogenation of the side chain yielding 3,4-methylenedioxyhydrocinnamic acid and 3,4-methylenedioxy-5-methoxy-*n*-propylbenzene.



However, in addition to the normal reaction products, there was also isolated from I small amounts of *m*-hyrdoxyhydrocinnamic acid and from II, 3-*n*-propyl-5-methoxyphenol. The two latter phenolic compounds result from the rupture of the *para* oxygen from the benzene ring followed by the conversion of the methylenedioxyl complex into a hydroxyl group. Myristicin (III), however, in which the double bond in the side chain is not conjugated to the benzene ring, gives only the normal reduction product, 3,4-methylenedioxy-5-methoxy-*n*propylbenzene.

When subjected to reduction with nickel-aluminum alloy and aqueous alkali, methylenedioxybenzene and its derivatives undergo a ring rupture similar to that described for compounds I and II. However, instead of being formed in only minute amounts, the *m*-hydroxyl compounds are obtained as the main reaction products. Thus, by using the readily accessible and cheap piperonal

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as a starting material, this reduction procedure affords a convenient method for the preparation of many *m*-hydroxyl compounds which otherwise are not readily available.

Methylenedioxybenzene, the parent compound (IV R = H) of this series, gave phenol, whereas *m*-cresol was obtained from piperonyl alcohol (IV $R = CH_2OH$) and piperonal (IV R = CHO). It is believed that the heterocyclic ring opens as indicated in formula IV, and the intermediate compound V is hydrogenolyzed into methyl alcohol and the corresponding phenol (VI). This mechanism is supported by our previously reported findings (1b). If the rupture of the methylenedioxyl bridge had occurred as indicated in Formula VII, then the parent compound (IV R = H) should have yielded guaiacol and

REDUCTION PRODUCT	YIELD, %
Phenol	65
m-Cresol ^b	40
m-Cresol	75
m-Cresol	60
m-Hydroxybenzoic acid	80
m-Hydroxyphenylacetic acid	75
m-Hydroxyhydrocinnamic acid	80
1. β -Piperonylpropionic acid	20-25
2. m-Hydroxyhydrocinnamic acid	65-70
	REDUCTION PRODUCT Phenol m-Cresol ^b m-Cresol m-Hydroxybenzoic acid m-Hydroxyphenylacetic acid m-Hydroxyhydrocinnamic acid 1. β-Piperonylpropionic acid 2. m-Hydroxyhydrocinnamic acid

TABLE I METHYLENEDIOXYBENZENE AND ITS DERIVATIVES

^e 25 cc. of alcohol used as solvent. ^b 40% of the 3,4-methylenedioxytoluene recovered unchanged. ^c This reduction was carried out at $25^{\circ} \pm 5^{\circ}$.

not phenol, since guaiacol has been shown to be unaltered by this reduction procedure (1b).



 $R = H, CH_3, CH_2OH, CHO, COOH, CH=CH-COOH$

Under the conditions of this reduction method, the rupture of the methylenedioxyl bridge is independent of the type of substituent present. This rupture is, however, inhibited by lowering the reaction temperture. When β -piperonylacrylic acid is hydrogenated at 25°, it is possible to isolate approximately 20–25% of the β -piperonylpropionic acid. Even under such mild conditions, rupture of the methylenedioxyl bridge occurs, since the reaction mixture yields 65–70% of *m*-hydroxyhydrocinnamic acid, the sole reduction product at elevated temperatures. In Table I are listed the compounds containing the methylenedioxyl bridge which have been studied.

EXPERIMENTAL

General procedure. Compounds 1-4, inclusive, in Table I were reduced as previously described (1a), the yields being based on the reduction of 10 g. of substance. All melting and boiling points are corrected. During the addition of the alloy to the alkaline solution, it is desirable to add the alloy directly in the vortex of the solution in order to avoid the development of hydrogen on the surface of the liquid.

Reduction of piperonylic acid. Eighty-three grams (0.5 m.) of piperonylic acid (4) was dissolved in 1200 cc. of water containing 150 g. of sodium hydroxide. The reaction mixture was heated to about 50° and 100 g. of Raney's nickel-aluminum alloy was gradually added in the course of $3\frac{1}{2}$ to 4 hours, with stirring, the temperature being maintained at $65-75^{\circ}$ during the addition of the alloy. Excessive foaming was controlled by the use of octyl alcohol. The reaction mixture was then stirred for 2 hours, maintaining the temperature at 90-95°, and the original volume of the solution was maintained by the addition of water. The hot solution was filtered from the suspended nickel and washed with two 50-cc. portions of hot 2% sodium hydroxide. The filtrate and washings were acidified to Congo paper with concentrated hydrochloric acid. After thoroughly chilling, the precipitated *m*-hydroxybenzoic acid was filtered; yield, 50-52 g., m.p. $201-202^{\circ}$. An additional 6-8 gm. of *m*-hydroxybenzoic acid may be obtained by extraction of the filtrate with ether.

Reduction of 3,4-methylenedioxyphenylacetic acid. Eighteen grams (0.1 m.) of 3,4-methylenedioxyphenylacetic acid (5) was dissolved in 300 cc. of 10% NaOH and 20 g. of alloy added. The reduction was carried out as usual, and the crude product was recrystallized from benzene-petroleum ether; yield, 11 g. The *m*-hydroxyphenylacetic acid softened at 110° and was completely melted at 121°. Previously reported m.p. 127–128° (6). Numerous attempts to raise the melting point by recrystallization were futile. Calculated for C₈H₈O₃; C 63.16%, H 5.26%; Found C 62.86%, H 5.48%. Neutralization Equivalent, 152; Found 152.5. The 2,4,6-tribromo-3-hydroxyphenylacetic acid melted at 235–236°; literature m.p. 236–237° (6).

Reduction of β -piperonylacrylic acid. Ninety-six grams (0.5 m.) of β -piperonylacrylic acid (7) was reduced as described for piperonylic acid. Recrystallized from benzene, the *m*-hydroxyhydrocinnamic acid was obtained in a yield of 64-68 g., m.p. 99-100°. Previously reported m.p. 110° (8). Calculated for C₈H₁₀O₈; C 65.06%, H 6.07%; Found C 65.47%, H 6.05%. Neutralization Equivalent, 166; Found 166.2.

Cold reduction of β -piperonylacrylic acid. The above reduction was repeated using 9.6 g. (0.05 m.) of β -piperonylacrylic acid, 200 cc. of 10% sodium hydroxide and 15 g. of Raney's alloy. The temperature throughout the reaction was kept at $25^{\circ} \pm 5^{\circ}$. After filtration from the nickel residue, the alkaline solution was acidified to Congo red paper with concentrated HCl and cooled. Long, fine, white needles separated which were filtered; yield, 1.9 g., m.p. 81-85^{\circ}. Recrystallized from benzene-petroleum ether, m.p. 86.5-87.5°. Previously reported for β -piperonylpropionic acid, m.p. 84° (9); 87-88° (10). Neutralization Equivalent, 194; Found 194.3. The filtrate was extracted with ether and after removal of the ether, the residue was recrystallized from benzene, yield 5.5 g., m.p. 99-100°; mixed melting point with *m*-hydroxyhydrocinnamic acid, 99-100°.

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SUMMARY

1. Methylenedioxybenzene and several of its derivatives substituted in the 4-position, on reduction with Raney's alloy and aqueous alkali, have been converted to the m-hydroxyl compounds in good yields.

2. It has been found possible by controlling the temperature of this reduction method to hydrogenate selectively a carbon-to-carbon double bond in the presence of the methylenedioxyl bridge.

3. The rupture of the methylenedioxyl bridge by this reduction method has been found to be independent of the type of substituent present.

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