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NORMAN, OKLAHOMA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, HARVARD UNIVERSITY]

Diene Addition between *trans*-Piperylene and Citraconic Anhydride

BY WEI-YUAN HUANG,[1] H. L. HOLMES[2] AND LOUIS F. FIESER

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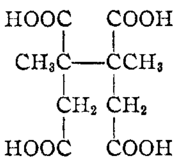
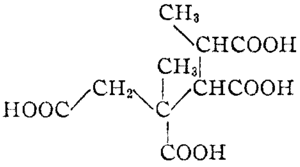
Diels–Alder reaction between *trans*-piperylene and citraconic anhydride yielded 82% of Δ^4-2,3-dimethylcyclohexene-1,2-dicarboxylic acid anhydride (VI); the structure of the adduct was proved by dehydrogenation. Oxidative cleavage of the adduct gave α,β-dimethyl-β,β'-dicarboxyadipic acid (VIII).

An optically active hexanetetracarboxylic acid, $C_{10}H_{14}O_8$, has been obtained by chromic acid oxidation of the two veratrum alkaloids, cevine[3] and germine[4]; and was shown[5] to be different from synthetic β,β'-dimethyl-β,β'-dicarboxyadipic acid (I). Fieser and Fieser[6] proposed an alternative structure, namely, α,β'-dimethyl-β,β'-dicarboxyadipic acid (II), and the present investigation was an attempt to synthesize this acid.

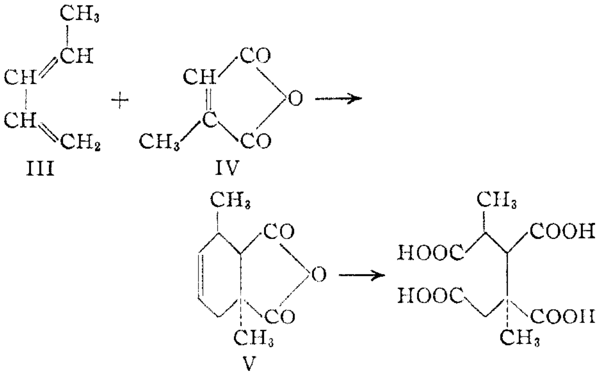


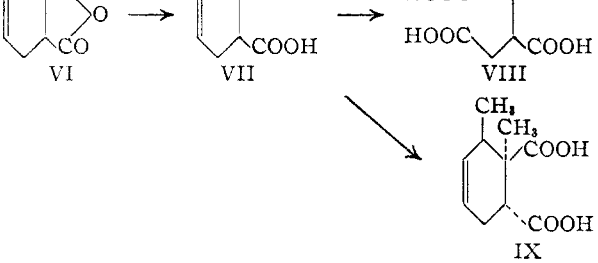
I



II

The particular scheme consists of a Diels–Alder addition between *trans*-piperylene (III) and citraconic anhydride (IV) followed by oxidative cleavage of the double bond of the adduct. The assumption was that the diene addition would follow the steric course illustrated. However, palladium dehydrogenation of the dihydro derivative of the dicarboxylic acid resulting from the hydrolysis of the adduct gave *o*-xylene and an acid, probably 2,3-dimethylbenzoic acid; the former was characterized by infrared spectrum as well as by permanganate oxidation to *o*-phthalic acid, identified as phthalanil. These results indicate that the isomeric adduct, Δ^4-2,3-dimethylcyclohexene-1,2-dicarboxylic acid anhydride[7] (VI), was formed in spite of the apparent steric hindrance of the two neighboring methyl groups. Consequently the synthetic tetracarboxylic ester, which was obtained by ozonolysis of the dimethyl ester of the diacid, Δ^4-2,3-dimethylcyclohexene-1,2-dicarboxylic acid (VII), followed by further oxidation with alkaline silver oxide and re-esterification, is the tetramethyl ester of α,β-dimethyl β,β'-dicarboxyadipic acid (VIII). Alkaline isomerization of the *cis*-diacid (VII) afforded a high melting acid, presumably the *trans*-diacid IX.





Experimental

Δ^4-2,3-Dimethylcyclohexene-1,2-dicarboxylic Acid Anhydride (VI).—Citraconic anhydride was prepared from citric acid in the usual way[8]; and *trans*-piperylene was obtained by dehydration of 3-pentene-2-ol[9] over alumina at 420 to 470° under 40 mm. pressure.[10]

The Diels–Alder addition was carried out as follows. A mixture of 150 g. of freshly distilled citraconic anhydride and 97 g. of *trans*-piperylene and 50 cc. of sodium-wire dried toluene was sealed in five Pyrex Carius tubes and allowed to stand at 25° for 24 hours and then heated in a steel bomb for 24 hours at 100°. After cooling to room temperature, the pale yellow viscous product was fractionated under reduced pressure and the main fraction (221 g.) distilled from 140 to 210° at 17–18 mm. Refractionation under reduced pressure gave 197 g. (82%) of the adduct, Δ^4-2,3-dimethylcyclohexene-1,2-dicarboxylic acid anhydride, b.p. 137° at 10 mm., n^{20}D 1.4870, sp. gr. 28°/28° 1.158, λ^{chf} 5.46, 5.63 μ.

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[1] National Institutes of Health predoctoral fellow, 1950–1952.

[2] Research Fellow, 1949–1951.

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[4] L. C. Craig and W. A. Jaobs, *ibid.*, **148**, 57 (1943).

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[8] R. L. Shriner, S. G. Ford and L. J. Roll in "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 140, 368.

[9] E. R. Coburn, *Org. Syntheses*, **27**, 65 (1947).

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Anal. Calcd. for $C_{10}H_{12}O_3$ (180.20): C, 66.64; H, 6.72. Found: C, 66.81; H, 6.93.

From the earlier fractions, 13.7 g. (9.1%) of citraconic anhydride was recovered.

The adduct formed an **acid anilide**, presumably Δ^4-2,3-dimethylcyclohexene-1,2-dicarboxylic acid-1-anilide, which was crystallized from dioxane, m.p. 210° dec.

Anal. Calcd. for $C_{16}H_{19}O_3N$ (273.32): N, 5.13. Found: N, 5.17.

The anil was prepared by heating *trans*-piperylene with citraconic anil at 100° for 24 hr. in a sealed tube. The solidified product was recrystallized from water, m.p. 62–63°, λ^{chf} 5.45, 5.63, 5.89 μ.

Anal. Calcd. for $C_{16}H_{17}O_2N$ (255.30): N, 5.49. Found: N, 5.66.

Δ^4-2,3-Dimethylcyclohexene-1,2-dicarboxylic Acid (VII).—A mixture of 20 cc. of the anhydride (VI) and 100 cc. of water was refluxed for half an hour. The resulting solution was concentrated until the crystalline acid began to separate. The mixture was then thoroughly chilled with ice-water and the product collected on a büchner funnel and dried at 80°; yield 22.4 g. (88%), m.p. 171–173° dec.; recrystallized twice from hot water, m.p. 187–188° dec.

Anal. Calcd. for $C_{10}H_{14}O_4$ (198.21): C, 60.59; H, 7.12; neut. equiv., 99.11. Found: C, 60.66; H, 7.11; neut. equiv., 99.5.

The dimethyl ester was prepared by treating an ethereal suspension of the diacid with excess diazomethane and recrystallizing from ether, m.p. 65–66°.

Anal. Calcd. for $C_{12}H_{18}O_4$ (226.26): C, 63.70; H, 8.02. Found: C, 63.60; H, 8.21.

A high melting **trans-dicarboxylic acid** (IX) was obtained as follows: Two grams of sodium was dissolved in 50 cc. of methanol and the resulting solution was refluxed with 2 g. of Δ-2,3-dimethylcyclohexene-1,2-dicarboxylic acid anhydride for 3 hours. The methanol was then removed by distillation and the residue was again refluxed with 20 cc. of water for 2 hours. The solution was cooled to room temperature and acidified, then extracted with ether. The ethereal solution was evaporated and the residue thus obtained recrystallized from alcohol–water; yield 0.5 g. (23%) of the *trans*-dicarboxylic acid, m.p. 225–227°.

Anal. Calcd. for $C_{10}H_{14}O_4$ (198.21): C, 60.59; H, 7.12; neut. equiv., 99.11. Found: C, 60.83; H, 7.09; neut. equiv., 101.

The dimethyl ester of the *trans*-dicarboxylic acid was crystallized from ether, m.p. 38–40°.

Anal. Calcd. for $C_{12}H_{18}O_4$ (226.26): C, 63.70; H, 8.02. Found: C, 63.38; H, 7.76.

2,3-Dimethylcyclohexane-1,2-dicarboxylic Acid.—A mixture of 5 g. of Δ^4-2,3-dimethylcyclohexene-1,2-dicarboxylic acid, 450 mg. of platinum oxide in 50 cc. of acetic acid was hydrogenated in a Hershberg hydrogenator. The hydrogenation was completed in about half an hour. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to a sirup which on treatment with hot water gave 4.8 g. of crude product, m.p. 175–180° dec.; recrystallized from acetone–water, m.p. 198–200° dec.

Anal. Calcd. for $C_{10}H_{16}O_4$ (200.23): C, 59.98; H, 8.06. Found: C, 60.25; H, 8.34.

Dehydrogenation of 2,3-Dimethylcyclohexane-1,2-dicarboxylic Acid.—A mixture of 0.8 g. of 2,3-dimethylcyclohexane-1,2-dicarboxylic acid, 0.8 g. of 10% palladium-charcoal and 8 cc. of acetone was heated in a sealed tube at 320° for 16 hours.[11] The catalyst was filtered and washed thoroughly with ether, the filtrate and washings were combined and washed with sodium carbonate solution. The aqueous solution on acidification afforded a crude acid, m.p. 120°; recrystallization from aqueous alcohol gave an acid, presumably 2,3-dimethylbenzoic acid,[12] m.p. 143–144°, λ^{chf} 2.95 (broad; CH band extending to 3.85), 5.9, 6.27, 6.85 μ.

In a second experiment, a mixture of 1 g. of 2,3-dimethylcyclohexane-1,2-dicarboxylic acid, 1 g. of 10% palladium-charcoal and a few drops of acetone was heated in a sealed tube at 320° for 24 hours. The reaction mixture was rinsed out with ether and the catalyst was filtered off. No acidic product was obtained by washing the ethereal solution with sodium bicarbonate solution. The crude neutral fraction obtained after removal of ether showed λ^{EtOH} 263 mμ and an infrared spectrum similar to that of *o*-xylene. The fraction was oxidized directly by heating with 3 g. of potassium permanganate and 50 cc. of water on a steam-bath under reflux for 20 hours. The resulting mixture was treated with sulfur dioxide and extracted with ether. Evaporation of the ethereal extract yielded a crude product m.p. 180°, dec., which gave a sublimate m.p. 120°. The infrared spectrum of the sublimate showed identity with that of authentic phthalic anhydride, λ^{chf} 5.43, 5.65, 6.23, 6.8, 7.4, 8.0, 9.02, 11.1 μ. Contamination with a small amount of the free acid was indicated by the appearance of an associated hydroxy band at 3.3–3.5 μ and a carbonyl band at 5.91 μ due to the free carboxy group. However, further characterization of the product was shown by a positive fluorescein test on fusion with resorcinol and sulfuric acid and conversion to phthalanil, m.p. and mixed m.p. with an authentic sample[13] 205–207°; infrared spectrum identical with that of the authentic specimen, λ^{chf} 5.66, 5.80, 5.84, 6.24, 6.68, 7.25, 9.0, 11.34 μ.

Dimethyl α,β-Dimethyl-β,β'-dicarbomethoxyadipate.—Dimethyl Δ^4-2,3-dimethylcyclohexane-1,2-dicarboxylate (26.5 g.) was ozonized at 0° in portions of about 2 g. dissolved in 30 cc. of chloroform. Each portion of the ozonolysis product was carefully concentrated under reduced pressure at 25° to a sirupy residue, which was then treated with 30 cc. of 5% aqueous sodium hydroxide solution containing a suspension of silver oxide freshly prepared from 5 g. of silver nitrate. The resulting mixture was heated on a steam-bath for 30 minutes, cooled and acidified with dilute sulfuric acid and extracted thoroughly with ether; the ethereal solution was concentrated to a small volume and treated with excess diazomethane. The combined crude ester thus obtained was dissolved in a mixture of petroleum ether-benzene (1:1), filtered through 100 g. of acid-washed alumina, and eluted with 2 l. of benzene to give 22.35 g. of a bright yellow oil. The oil was redissolved in 250 ml. of petroleum ether–benzene (2:1) and again filtered through 100 g. of acid-washed alumina, eluted with about 3 l. of the same solvent mixture. The eluates were combined and concentrated to a yellow sirup, which on triturating with ether deposited colorless crystals of the tetramethyl ester of α,β-dimethyl-β,β'-dicarboxyadipic acid, m.p. 98–101°, λ^{chf} 3.5, 5.77, 5.82, 8.0 μ; yield 10.8 g. (29%).

Anal. Calcd. for $C_{14}H_{22}O_8$ (318.32): C, 52.82; H, 6.97. Found: C, 52.82; H, 6.82.

CAMBRIDGE, MASSACHUSETTS

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