meso- and *dl*-dichlorobutane products were separable by GLPC.

The infrared spectra of the pure isomers were compared with the spectra obtained from the products of the reactions of pure *cis*- and *trans*-2-butenes with cupric chloride on pumice at 290°. It was determined that *dl*-2,3-dichlorobutane was formed from the reaction of *cis*-butene-2 while the *meso*-isomer was predominantly formed by the reaction of *trans*-butene-2 with cupric chloride.

Chlorination of norbornadiene. Forty-six grams (0.5 mole) of norbornadiene was dissolved in 100 ml. of carbon tetrachloride in a black, three neck flask equipped with a stirrer, condenser, and gas inlet tube. At 15°, chlorine was added at a rate of about 150 ml./min. over a 60-min. period (0.4 mole of chlorine). The material was then distilled through a small Vigreux column to give two product fractions: (1) 3.5 g., b.p. 67–78°, at 14 mm.; and (2) 28.5 g., b.p. 79–80°, at 8 mm. Cut (1) was not identified. Cut (2) was identified as 3,5-dichloronortricyclene by analysis of its infrared spectra.[5] This product was the same as the major product (>90%) obtained by the reaction of norbornadiene and cupric chloride on pumice at 285°.

Acknowledgment. The authors are greatly indebted to Dr. Horace A. Ory for infrared analyses and to Professors R. B. Turner and W. H. Urry for helpful discussions during the course of this work.

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[CONTRIBUTION FROM THE DEPARTMENTS OF PHARMACOLOGY AND MEDICINE, LOUISIANA STATE UNIVERSITY, SCHOOL OF MEDICINE; CHEMISTRY DEPARTMENT, TULANE UNIVERSITY AND IMPERIAL COLLEGE, UNIVERSITY OF LONDON, ENGLAND]

Oxidation of Protocatechuic Acid with Peroxyacetic Acid

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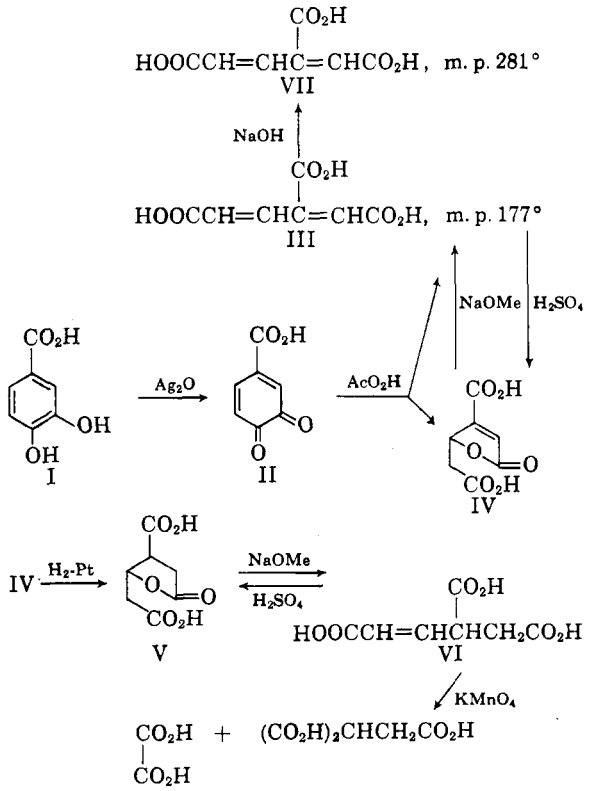
Treatment of protocatechuic acid with peroxyacetic acid has heretofore resulted in fission of the carbocyclic ring and formation of β-carboxy-*cis*, *trans*-muconic acid (III) and β-carboxy-γ-carboxymethyl-$\Delta^{\alpha,\beta}$-butenolide (IV). Evidence has been reported which supports the stereochemical orientation.

We wish to describe at this time the chemical conversion of protocatechuic acid (I) to β-carboxy-*cis*,*trans*-muconic acid (III) and *dl*-β-carboxy-γ-carboxymethyl-$\Delta^{\alpha,\beta}$-butenolide (IV).

The oxidation of protocatechuic acid (I) to 4-carboxybenzoquinone-1,2 (II) is preferably carried out with silver oxide. The absorption spectrum of the quinone exhibits a maximum extinction at 420 mμ (log ε 3.12).[2] Treatment of the freshly prepared quinone with peroxyacetic acid[3] results in a geometrical isomer of β-carboxymuconic acid (III) and β-carboxy-γ-carboxymethyl-$\Delta^{\alpha,\beta}$-butenolide (IV).[4,5] We find in each case that the melting points of III and IV vary with the rate of heating, which probably accounts for apparent discrepancies in the literature.[4a,6]



Hydrogenation of the β-carboxymuconic acid (III) over platinum results in the uptake of two molecules of hydrogen and the formation of β-carboxyadipic acid. Lactonization of III with dilute sulfuric acid affords β-carboxy-γ-carboxymethyl-$\Delta^{\alpha,\beta}$-butenolide (IV) which can be re-

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(2) The quinone chromophor is similar to that of *o*-benzoquinone, λ_{max} 390 mμ (log ε 3.26) [*cf.* F. Ramirez and P. V. Ostwald, *J. Org. Chem.*, **20**, 1676 (1955)] and *N*-benzoyl-6-methoxydopamine, λ_{max} 220 and 375 mμ [*cf.* S. Senoh and B. Witkop, *J. Am. Chem. Soc.*, **81**, 6222 (1959)].

(3) J. H. Boyer and L. R. Morgan, Jr., *J. Am. Chem. Soc.*, **83**, 919 (1961).

(4) (a) D. L. MacDonald, R. Y. Stanier, and J. L. Ingraham, *J. Biol. Chem.*, **219**, 809 (1954). (b) E. L. Tatum and S. R. Gross, *ibid.*, **219**, 707 (1956).

(5) On the basis of physical and chemical properties, III appears to be identical to the biologically inactive (*cis*, *trans*-) β-carboxymuconic acid isolated by MacDonald, Stanier, and Ingrahm and IV, undoubtedly a racemate of their $\Delta^{\alpha,\beta}$-butenolide.

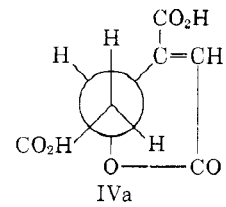
(6) S. R. Gross, R. D. Gafford, and E. L. Tatum, *J. Biol. Chem.*, **219**, 781 1956).

converted into III with sodium methoxide. Hydrogenation of IV over platinum results in β-carboxy-γ-carboxymethylbutanolide (V), which upon treatment with methanolic sodium methoxide affords a $\Delta^{\gamma,\delta}$-dihydro-β-carboxymuconic acid (VI). Treatment of VI with dilute sulfuric acid affords β-carboxy-γ-carboxymethylbutenolide and hydrogenation of VI yields β-carboxyadipic acid, while permanganate oxidation affords carboxysuccinic acid and oxalic acid dihydrate. Refluxing III with dilute sodium hydroxide results in an isomeric acid (VII), which can be hydrogenated to β-carboxyadipic acid, however, all attempts to lactonize the new acid were unsuccessful. While the higher melting acid (VII) is unchanged by sulfuric acid, the lower melting isomer (III) is lactonized to β-carboxy-γ-carboxymethyl-$\Delta^{\alpha,\beta}$-butenolide (IV). The lower melting β-carboxymuconic acid (III) shows no detectable change when an aqueous or ethanolic solution of it is irradiated with ultraviolet light in the presence of iodine.[7]

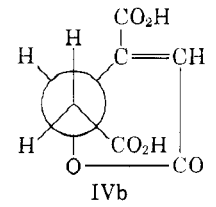
For β-carboxymuconic acid four geometric isomers are theoretically possible, *cis,cis*, *cis,trans*, *trans,cis*, and *trans,trans* and each of these may exist in an *s-cis* and *s-trans* configuration with respect to the β,γ-single bond.[8] The *s-trans* has been demonstrated by Elvidge, Linstead, Sims, and Orkin to be the most stable modification in the muconic acid series.[9]

The observed instability of the naturally occurring β-carboxy-*cis,cis*-muconic acid reported by MacDonald, Stanier, and Ingrahm[10] is in agreement with the observation that the additional carboxyl group in β-carboxymuconic acid gives rise to interference in the *s-trans* form of the *cis,-cis* isomer.

Evidence for a *cis,trans* configuration for β-carboxy-*cis,trans*-muconic acid (III) is supported by the ease of interconversion of III and β-carboxy-γ-carboxymethyl-$\Delta^{\alpha,\beta}$-butenolide (IV) for which a carboxyl group disposed *cis* to an acrylic residue is required. In comparing the possible conformations of IV (A and B) capable of undergoing



IVa



IVb

normal *trans* elimination,[11] conformation B would be expected to lead to a *cis*-olefin (β-carboxy-*cis,cis*-muconic acid) which in comparison with similar homogeneous eliminations would be the least thermodynamically stable isomer, whereas conformation A should lead to the *trans*-olefin and the most stable isomer (β-carboxy-*cis,trans*-muconic acid). In addition the prediction that the less crowded activated complex for conformation A would be more stable than the activated complex for conformation B is consistent with Brewster's principles of conformational and atomic asymmetry.[12]

Oxidation of the dihydro-β-carboxymuconic acid (VI) affords carboxysuccinic acid and oxalic acid dihydrate which when combined with the reduction of VI to β-carboxyadipic acid demonstrates a β-carboxyl and a γ,δ-double bond. The γ,δ-double bond is considered to be *trans* by analogy with the delactonization of VI and similar homogeneous elimination reactions.[10] Isomerization of β-carboxy-*cis,trans*-muconic acid to a higher melting isomer, a shift of absorption [λ_{max} 265 mμ (log ε 4.02) to λ_{max} 270 mμ (log ε 4.25)] and the failure of the new isomer to lactonize indicates a *cis-trans* isomerization resulting in β-carboxy-*trans,trans*-muconic acid (VII).

EXPERIMENTAL[13]

4-Carboxybenzoquinone-1,2 (II). 3,4-Dihydroxybenzoic acid (protocatechuic acid) (3 g., 0.019 mole) was dissolved in 50 ml. of anhydrous methanol containing 1 ml. of 98% formic acid, and added at 0° to a mixture of anhydrous sodium sulfate (6 g.) and freshly prepared dry silver oxide (7 g.). The mixture was vigorously shaken for 2–3 min., filtered through a layer of anhydrous sodium sulfate, and washed twice with methanol. The filtrate was evaporated to dryness under high vacuum and the red residue washed several times with cold acetone. The residue was collected and recrystallized from acetone as metallic red crystals of *4-carboxybenzoquinone-1,2*, 2.1 g. (71%), m.p. 185–187° dec.; $\lambda_{max}^{CH_3OH}$ 420 mμ (log ε 3.12).

Anal. Calcd. for $C_7H_4O_4$: C, 55.27; H, 2.65; O, 42.07. Found: C, 55.20; H, 2.41; O, 41.89.

β-Carboxy-cis,trans-muconic acid (III). A solution of 10 g. (0.066 mole) of 4-carboxybenzoquinone-1,2 in 150 g. of 13%

(7) A similar observation is reported for the *cis, trans*-isomer of β-methylmuconic acid, J. A. Elvidge, R. P. Linstead, and P. Sims, *J. Chem. Soc.*, 3386 (1951).

(8) The terms *cis* and *trans* are given in positional order, *i.e.*, the first cited refers to the lower numbered double bond.

$$CO_2HCH{=}CH{-}CR{=}CHCO_2H$$
trans *cis*

(9) Models show that with a *s-cis* orientation steric interference with a planar configuration occurs in both the *cis,cis-* and *cis,trans*-muconic acid. Intramolecular interference effects are absent from the *s-trans* forms, so that an *s-trans* configuration for the *cis,cis*, *cis,trans* and *trans,trans* isomer of muconic acid is strongly indicated. [*Cf.* J. A. Elvidge, R. P. Linstead, P. Sims, and B. A. Orkin, *ibid.*, 2235 (1950)].

(10) MacDonald, Stanier, and Ingrahm report that the naturally occurring β-carboxymuconic acid (presumably *cis, cis-*), rapidly isomerizes into a more stable or *cis, trans*-isomer (ref. 4a).

(11) For a summary of *trans* eliminations see E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, 1959, pp. 489–497.

(12) J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5491 (1959).

(13) Semimicro analyses by Alfred Bernhardt, Max Planck Institut Microanalytisches Laboratorium, Mülheim (Rühr), Germany. Melting points are uncorrected. Ultraviolet absorption spectra were obtained on the Unicam S. P. 500 spectrophotometer.

peroxyacetic acid[14] was kept for 10 hr. in the dark at room temperature. The yellow amorphous precipitate (0.5 g.) was recrystallized from isopropyl ether and petroleum ether (b.p. 60–70°) to yield 0.41 g. (3.3%) of *β-carboxy-cis, trans*-muconic acid as colorless microcrystals, m.p. 175–177° dec.[5]; λ_{max} 265 mμ (log ε 4.02) in 0.1 *M* phosphate buffer, *p*H 7.

Anal. Calcd. for $C_7H_6O_6$: C, 45.16; H, 3.25. Found: C, 45.11; H, 3.37.

Treatment of the muconic acid with ethereal diazomethane afforded a trimethyl ester as yellow plates, m.p. 91–92°.

Anal. Calcd. for $C_{10}H_{12}O_6$: C, 52.63; H, 5.30; O, 42.07. Found: C, 52.59; H, 5.39; O, 42.33.

β-Carboxy-γ-carboxymethyl-$\Delta^{\alpha,\beta}$-butenolide (IV). Concentration of the original acetic acid filtrate to a volume of approximately 10 ml. afforded β-carboxy-γ-carboxymethyl-$\Delta^{\alpha,\beta}$-butenolide as a yellow amorphous solid, which recrystallized from glacial acetic acid as colorless microcrystals, 7.6 g. (62%), m.p. 179–181°,[2] $[\alpha]^{25}D$ −3° (*c* 1.8, chloroform), λ_{max} 215 mμ (log ε 4.03) in 0.1 *M* phosphate buffer, *p*H 7.

Anal. Calcd. for $C_7H_6O_6$: C, 45.16; H, 3.25. Found: C, 45.12; H, 3.34.

Treatment of the lactonic acid with ethereal diazomethane yielded a dimethyl ester as colorless microcrystals which could be recrystallized from benzene, m.p. 41–142°.

Anal. Calcd. for $C_9H_{10}O_6$: C, 50.47; H, 4.71; O, 44.82. Found: C, 50.37; H, 4.61; O, 44.72.

A solution of 400 mg. (2.3 mmoles) of β-carboxy-γ-carboxymethyl-$\Delta^{\alpha,\beta}$-butenolide in 10 ml. of methanol was treated dropwise with 5 ml. of methanol containing 200 mg. of sodium methoxide. After 1 hr. the solution was diluted with 20 ml. of water, acidified with 0.1 *N* hydrochloric acid (Congo paper), and extracted with ether to yield pale yellow microcrystals of *β-carboxy-cis,trans*-muconic acid, which recrystallized from glacial acetic acid, 260 mg. (65%), m.p. 174–176° dec.

Lactonization of β-carboxy-cis,trans-muconic acid. A slurry of 100 mg. (0.54 mmole) of the acid and 13 ml. of 80% sulfuric acid was allowed to stand for 12 hr., poured over 40 g. of crushed ice, and extracted with ether. Evaporation of the ethereal extract to dryness afforded β-carboxy-γ-carboxymethyl-$\Delta^{\alpha,\beta}$-butenolide which recrystallized from glacial acetic acid as pale yellow microcrystals, 0.81 g. (81%), m.p. and mixture m.p. 180–182°; λ_{max} 215 mμ (log ε 4.03) in 0.1 *M* phosphate buffer, *p*H 7.

Reduction of β-carboxy-cis,trans-muconic acid. Reduction of *β-carboxy-cis,trans*-muconic acid with hydrogen and platinum oxide resulted in β-carboxyadipic acid.[4a] Two recrystallizations from ethyl acetate and ligroin (b.p. 66–75°) afforded colorless crystals, m.p. and mixture m.p. 121–122°.

Reduction of β-carboxy-γ-carboxymethyl-$\Delta^{\alpha,\beta}$-butenolide. A solution of 200 mg. (1 mmole) of the unsaturated acid in 150 ml. of methanol was reduced with hydrogen (one atmosphere of pressure and room temperature) and 100 mg. of platinum oxide. Removal of the catalyst and solvent yielded 150 mg. (81%) of *β-carboxy-γ-carboxymethylbutanolide* (V) which recrystallized from ether–ligroin (b.p. 66–75°) as colorless prisms, m.p. 125–126.5°.

Anal. Calcd. for $C_7H_8O_6$: C, 44.69; H, 4.29; O, 51.03. Found: C, 44.61; H, 4.29; O, 51.21.

trans-$\Delta^{\gamma,\delta}$-Dihydro-β-carboxymuconic acid (VI). A solution of 430 mg. (2.3 mmoles) of β-carboxy-γ-carboxymethylbutanolide in 10 ml. of methanol was treated dropwise with 15 ml. of methanol containing 200 mg. of sodium methoxide. After 30 min. the solution was diluted with 20 ml. of water, acidified with 0.1 *N* hydrochloric acid, and extracted with ether. The ethereal extract yielded colorless slender needles of *trans-$\Delta^{\gamma,\delta}$-dihydro-β-carboxymuconic acid* which were recrystallized from water, 190 mg. (45%), m.p. 155–157°.

Anal. Calcd. for $C_7H_8O_6$: C, 44.69; H, 4.29; O, 51.03. Found: C, 44.67; H, 4.18; O, 51.25.

Hydrogen (1 atm.) over 100 mg. of platinum oxide in 50 ml. of 95% ethanol reduced 100 mg. (0.53 mmole) of *trans-$\Delta^{\gamma,\delta}$*-dihydro-β-carboxymuconic acid to colorless crystals [from ethyl acetate and ligroin (b.p. 66–75°)] of β-carboxyadipic acid, 65 mg. (65%), m.p. and mixture m.p. 121–122°.

A slurry of 100 mg. (0.53 mmole) of *trans-$\Delta^{\gamma,\delta}$*-dihydro-β-carboxymuconic acid and 13 ml. of 80% sulfuric acid was allowed to stand for 12 hr., poured over 40 g. of crushed ice, and extracted with ether. Evaporation of the ethereal extract to dryness afforded δ-carboxy-γ-carboxymethylbutanolide, which recrystallized from ether–ligroin as colorless prisms, 75 mg. (75%), m.p. and mixture m.p. 124–125.5°.

Oxidation of trans-$\Delta^{\gamma,\delta}$-dihydro-β-carboxymuconic acid. Aqueous potassium permanganate (2%, 40 ml.) was added dropwise with stirring during 2 hr. to a solution of 0.32 g. (1.7 mmoles) of the acid in 15 ml. of a saturated aqueous sodium bicarbonate solution. The manganese dioxide was removed, the filtrate acidified, and extracted for 24 hr. with ether. Evaporation of the dried ethereal extract to dryness yielded a brown residue which recrystallized from benzene as colorless prisms of carboxysuccinic acid, m.p. 159–160.5°,[15] 150 mg. (57%).

Anal. Calcd. for $C_5H_6O_6$: C, 37.05; H, 3.73; O, 59.22. Found: C, 37.21; H, 3.65; O, 59.27.

The residue from the benzene mother liquor recrystallized from boiling water as colorless microcrystals of oxalic acid dihydrate, 40 mg. (31%), m.p. and mixture m.p. 100–101°.

β-Carboxy-trans,trans-muconic acid (VII). A solution of 200 mg. (1.1 mmoles) of *β-carboxy-cis,trans*-muconic acid in 15 ml. of 20% sodium hydroxide was refluxed for 4 hr. Upon acidification with 1 *N* hydrochloric acid, *β-carboxy-trans,-trans-muconic acid* separated and was recrystallized from hot water as short colorless needles, m.p. 281–283°, 110 mg. (55%); λ_{max} 270 mμ (log ε 4.25), 275 mμ (log ε 4.28) in 0.1 *M* phosphate buffer, *p*H 7.

Anal. Calcd. for $C_7H_6O_6$: C, 45.17; H, 3.25. Found: C, 45.10; H, 3.31.

Reduction of β-carboxy-trans,trans-muconic acid. Reduction of the *trans,trans*-isomer with platinum oxide and hydrogen in ethanol according to the procedure for the *cis,trans*-isomer afforded β-carboxyadipic acid in 89%, m.p. and mixture m.p. 121–122°.

Attempted lactonization of β-carboxy-trans,trans-muconic acid. A slurry of 1 g. (5.3 mmoles) of the *trans,trans*-isomer and 20 ml. of 80% sulfuric acid was refluxed for 24 hr., cooled and poured over 15 g. of crushed ice. The precipitate was collected and recrystallized from water as unchanged starting material, 0.76 g. (76%), m.p. and mixture m.p. 281–283°.

Acknowledgment. The author wishes to thank Dr. J. H. Boyer for reading the manuscript and for his advice.

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(14) Peroxyacetic acid (40%) was generously supplied by Buffalo Electrochemical Co.

(15) M. Conrad and C. A. Bischoff, *Ann.*, **214**, 71 (1882).