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Studies of Aliphatic Hydroxycarboxylic Acids as Antioxidants. III. The Preparation of Two Isomers of Hydroxycitric Acid Lactone (*erythro*- and *threo*-3,4-dicarboxy-3-hydroxy-γ-butyrolactone)

Kazuo Horikawa and Shinroku Masuyama
The Osaka Municipal Technical Research Institute, Kita-ku, Osaka

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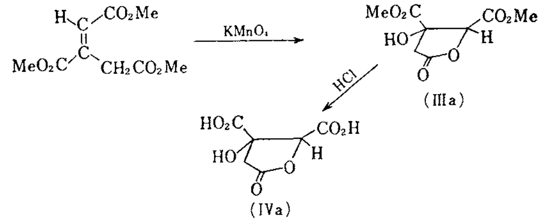
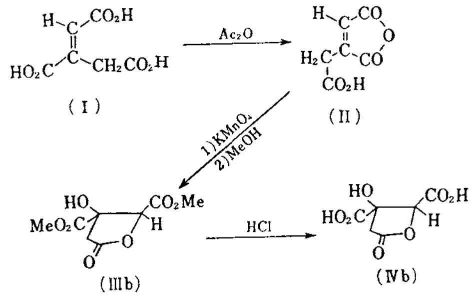
In 1883, Lippmann[1] found a hydroxycarboxylic acid in a by-product of beet sugar. He reported that the formula of this compound corresponded to that of hydroxycitric acid, which had already been synthesized by Pawollek.[2] On the other hand, Martius and Maué[3] prepared the hydroxycitric acid lactone by the addition of hypochlorous acid to calcium aconitate. Two isomers were obtained in this reaction; the one with the lower melting point of 152°C was hydroxycitric acid lactone, while the other, with the higher melting point of 182°C was allohydroxycitric acid lactone. The configurations of these two racemic acids have, however, never been described. Therefore, it seemed worthwhile to confirm the configurations of these lactones, since the configuration might be related to the stabilizing effect on the vegetable oil as an antioxidant.

As has been reported previously from our laboratory,[*1,4] erythro lactonic acid (IVa) was synthesized by the oxidation of *trans*-trimethylaconitate with permanganate and by subsequent hydrolysis (Scheme I).



Scheme I



Scheme II

In this paper, another isomer, *threo* lactonic acid (IVb), was similarly prepared from *cis*-aconitic anhydride (II).[5] The oxidation mixture was separated after methylation, and the obtained dimethyl ester (IIIb) was hydrolysed (Scheme II). As for the relative configurations of these two lactonic acids, it was inferred, on the basis of the *cis*-hydroxylation mechanism of permanganate, that IVa was *erythro* and that IVb was *threo*.[*1] These assignments were supported by the reaction of both lactonic acids with acetic anhydride. Thus, when they were treated with this reagent at 60°C for 1.5 hr, the former gave a lactonic anhydride, which exhibited characteristic bands due to the 5-membered anhydride group at 5.31 and 5.75μ, while the latter did not. The NMR spectra of IIIa and IIIb are of interest in connection with the above assignment. The NMR spectra of IIIa and IIIb in chloroform exhibited signals at τ 6.18, 6.22 (each 3 H, $-OCH_3$) and 6.10, 6.23 (each 3 H, $-OCH_3$), 5.04 (1 H, methin proton) and 4.88 (1 H, methin proton), respectively. The methin proton signal of IIIb appeared in a field lower than that of IIIa. The methin proton of IIIb may be more deshielded by the β methoxycarbonyl group, which is situated closer than in IIIa. The IIIb compound has a larger difference in chemical shifts about the *O*-methyl proton (τ 6.10, 6.23) of the two methoxycarbonyl groups than those in IIIa (τ 6.18, 6.22)

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[1] E. von Lippmann, *Ber.*, **16**, 1078 (1883).

[2] A. Pawollek, *Ann.*, **178**, 155 (1875).

[3] C. Martius and R. Maué, *Z. Phys. Chem.*, **269**, 33 (1941).

[*1] In the preceding paper, the lactonic acid obtained was prefixed with *threo* according to a Fischer projection on the basis of the tartaric acid moiety, but in this paper the lactonic acid obtained was prefixed with *threo* on the basis of the citric acid moiety. Therefore, in order to eliminate this confusion, the authors wish to correct the prefix of the previously-obtained lactonic acid to *erythro*.

[4] K. Horikawa and S. Masuyama, *Yukagaku*, **14**, 179 (1965).

[5] R. Malachowski, M. Giedroyć and Z. Jerzmanowska, *Ber.*, **61**, 2525 (1928).

Experimental

All the melting points are uncorrected. The infrared spectra were measured in Nujol mull using a Shimadzu IR-27 spectrometer in the 2—15 μ region, while the NMR spectra were determined at 100 Mc with a Japan Electron Optics JNM-4H-100 NMR spectrometer, using TMS as the internal reference. The elemental analyses were done at the Microanalytical Laboratory, Faculty of Science, Osaka City University.

The Preparation of *cis*-Aconitic Anhydride (III). To 240 m*l* of acetic anhydride 240 g of *trans*-aconitic acid (I) were added, after which the reaction mixture was maintained at 60°C for 1.5 hr. The reaction solution was then concentrated *in vacuo* to a syrup, which was crystallized upon the addition of dry benzene. Recrystallization from dry benzene gave pure II. Yield, 125 g; mp 76°C. Found: C, 46.20; H, 2.77%. Calcd for $C_6H_4O_5$: C, 46.17; H, 2.58%.

The Oxidation of *cis*-Aconitic Anhydride (II). A solution of II (30 g) dissolved in 300 m*l* of methanol was neutralized by the addition of sodium bicarbonate and was oxidized with 2% aqueous potassium permanganate for 3 hr at 0—5°C. The reaction solution was then allowed to stand at room temperature overnight. The precipitated inorganic salt was removed by filtration; the filtrate was acidified with hydrochloric acid and then evaporated to a syrup, which was esterified by refluxing for 7 hr with 300 m*l* of methanol and 5 m*l* of concentrated hydrochloric acid. After the methanol had been evaporated *in vacuo*, the syrupy residue was treated as will be described below.

Separation of The Lactonic Ester (IIIb). Five grams of the syrup obtained above were chromatographed on a silica-gel column (140 g). Elution with a large amount of chloroform gave 330 mg of IIIb. Recrystallization from chloroform gave pure IIIb as crystals. Yield, 267 mg; mp 97—98°C.

IR: 2.85, 2.95, 5.55, 5.75 μ. NMR($CHCl_3$): τ 4.88 (1H, singlet, methin), 6.10, 6.23 (2 OCH_3, each 3H, singlet), 7.04 (2H, quartet, methylene). Found: C, 43.99; H, 4.81%. Calcd for $C_8H_{10}O_7$: C, 44.03; H, 4.58%.

Hydrolysis of IIIb. A mixture of 9% hydrochloric acid (10 m*l*) and IIIb (125 mg) was maintained at 80°C for 5 hr. The hydrolysate was then evaporated to dryness under a vacuum. The residue was dissolved in ethyl acetate and crystallized by the addition of small amount of carbon tetrachloride. Mp 180—181°C. IR: 2.92, 5.61, 5.75 μ. Found: C, 37.70; H, 3.11%. Calcd for $C_6H_6O_7$: C, 37.89; H, 3.14%.

The Reaction of IVa and IVb with Acetic Anhydride. A mixture of acetic anhydride (0.5 m*l*) and IVa (81 mg) was maintained at 60°C for 1.5 hr. The reaction solution was then evaporated under a vacuum in order to remove the acetic acid and the acetic anhydride. The residue was treated with dry benzene, after which the benzene was removed *in vacuo*. The infrared spectrum of the product showed the characteristic bands due to the 5-membered anhydride group at 5.31 and 5.75 μ. On the other hand, in the case of IVb the characteristic bands were not observed.

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