Syntheses of Gallic Acid and Pyrogallol

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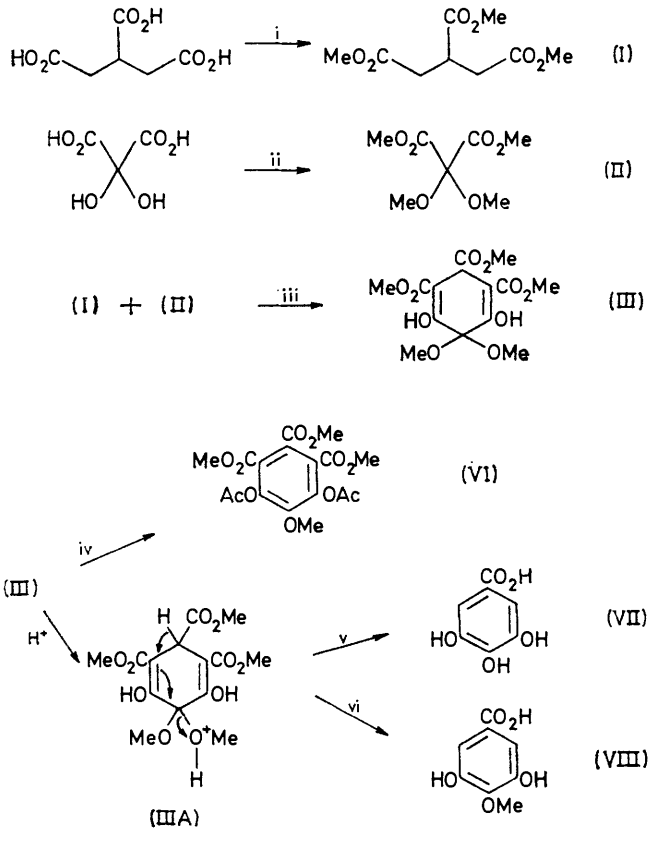
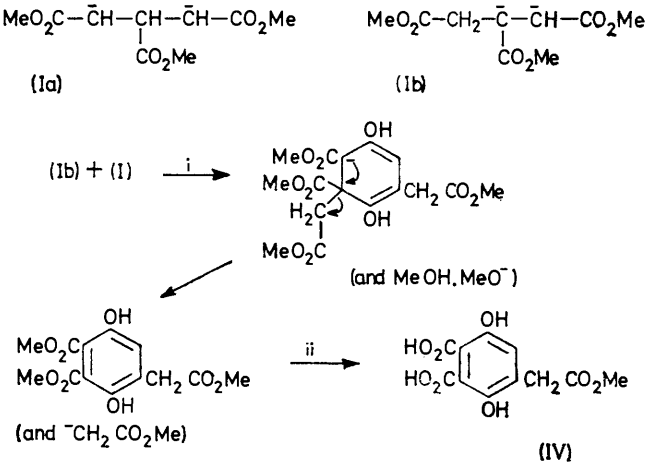
Condensation of trimethyl propane-1,2,3-tricarboxylate (I) with dimethyl dimethoxymalonate (II) gave the cyclic β-keto-ester (III) and a smaller amount of a phenolic acid (IV). Treatment of the ester (III) with acid yielded gallic acid. Condensation of dimethyl glutarate with the diester (II) yielded the cyclic β-keto-ester (V), which was converted into 4,5,6-trihydroxyisophthalic acid (IX) on treatment with acid. The latter decarboxylated smoothly at 200 °C to give pyrogallol.

In the nearly two centuries since Scheele discovered gallic acid no synthesis of it from aliphatic materials has been reported. We now report such a synthesis, with the initial steps shown in Scheme 1. Propane-1,2,3-tricarboxylic acid and dihydroxymalonic acid were both esterified in good yields by metathesis with an acetal [1] or an orthoester,[2] respectively. Base-catalysed condensation of the products (I) and (II) yielded trimethyl 4,6-dihydroxy-5,5-dimethoxycyclohexa-1(6),3-diene-1,2,3-tricarboxylate (III). The latter underwent hydrolysis and decarboxylation to gallic acid (VII) (74% yield) on refluxing with 48% hydrobromic acid, whereas a 5 : 2 mixture of (VII) and its 4-*O*-methyl ether (VIII) resulted from use of refluxing, concentrated hydrochloric acid.



Scheme 1 Reagents: i, $Me_2C(OMe)_2$,HCl; ii, $HC(OMe)_3$; iii, NaH; iv, Ac_2O-C_5H_5N; v, refluxing 48% HBr; vi, refluxing conc. HCl

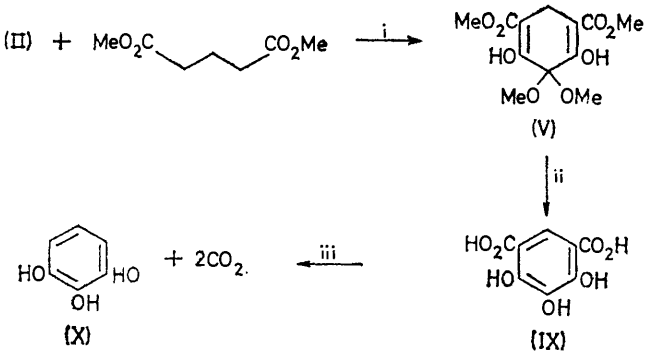


Scheme 2 Reagents: i, NaH; ii, HCl (1 : 1)

[1] N. S. Radin, A. K. Hajra, and Y. Akahori, *J. Lipid Res.*, 1960, **1**, 250.
[2] H. Cohen and J. D. Mier, *Chem. and Ind.*, 1965, 349.

This points to the protonated form (IIIA) as an intermediate. Acetylation of (III) gave trimethyl 4,6-diacetoxy-5-methoxybenzene-1,2,3-tricarboxylate (VI), no doubt by a comparable involvement of an acetylium intermediate with removal of one of the acetal methoxy-groups.

Formation of the cyclic ester (III) involves the dianion (Ia) (Scheme 2), or equivalent monoanions in two steps.



SCHEME 3 Reagents: i, NaH; ii, refluxing 48% HBr; iii, 200 °C in MeOH

The low yield (*ca.* 10%) of (III) indicates competitive condensation reactions but only one by-product (IV) was actually obtained, and in small amount. It resulted from condensation of (I) with the dianion (Ib) and was separated from (III) by making use of its solubility in water at pH 4 or lower; (III) was soluble in benzene or ether.

Pyrogallol too has never been synthesized from aliphatic sources. Much as gallic acid was obtainable from compounds (II) and (I), pyrogallol was obtained from (II) and dimethyl glutarate, *via* dimethyl 4,6-dihydroxy-5,5-dimethoxycyclohexa-1(6),3-diene-1,3-dicarboxylate (V) (Scheme 3). Refluxing with 48% hydrobromic acid converted (V) in 65% yield into 4,5,6-trihydroxyisophthalic acid [3] (IX). Decarboxylation did not occur in a manner comparable to that of (III). Decarboxylation to pyrogallol (X) was practically quantitative, however, when (V) was heated [4] in methanol to 200 °C in an autoclave.

New compounds were characterized by elemental analyses and i.r., ^{1}H n.m.r., and mass spectra.

EXPERIMENTAL

Details are available as Supplementary Publication No. SUP 21369 (6 pp.).†

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† For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1974, Index issue.

[3] H. Voswinckel and F. de Weerth, *Ber.*, 1912, **45**, 1242.
[4] H. Rinderknecht and C. Niemann, *J. Amer. Chem. Soc.*, 1945, **70**, 2605.