

Cyclic Compounds from Acetylpyruvic Esters. Part III

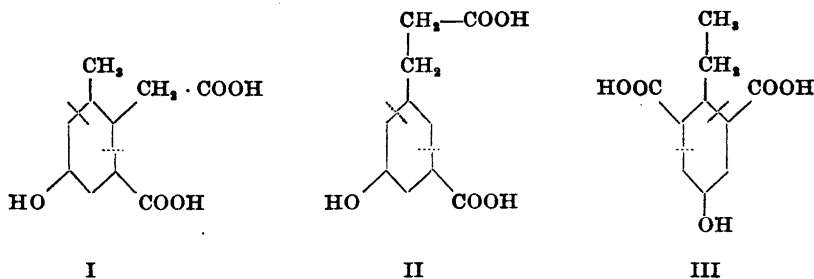
Structure of the Acid $C_{10}H_{10}O_5$

ENDRE BERNER

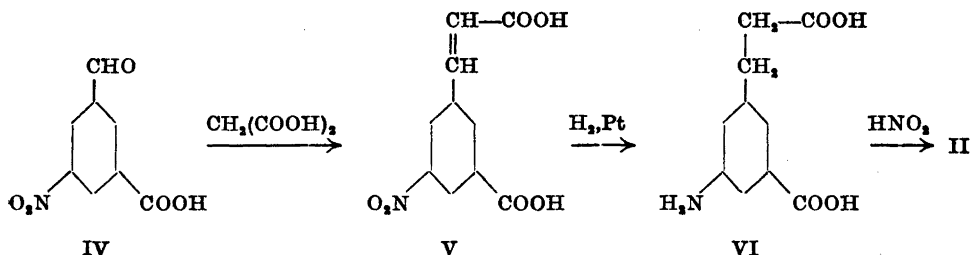
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The following three aromatic hydroxy acids have been synthesized, a) 3-hydroxy-5-carboxyhydrocinnamic acid, b) 2-ethyl-5-hydroxybenzoic acid, and c) 2-ethyl-5-hydroxyisophthalic acid. The acid c was found to be identical with the acid $C_{10}H_{10}O_5$, obtained by treatment of the hydrogenated condensation product of methyl acetylpyruvate with barium hydroxide.

In part I of this series ¹ it was shown that the condensation product of methyl acetylpyruvate (in short called methyl product), first described by Claisen ² as being an open-chained compound, actually must have a cyclic structure. Already Claisen found that the methyl product on heating with barium hydroxide split off oxalic acid and gave 3-methyl-5-hydroxybenzoic acid. Besides verifying this we found that the hydrogenated methyl product, having taken up two moles of hydrogen, on heating with barium hydroxide gave the three compounds: oxalic acid, 3-methylcyclohexanone-5-carboxylic acid, and an aromatic hydroxy-dicarboxylic acid $C_{10}H_{10}O_5$ with m.p. 267°. For the latter we found that the structural formula I would be in agreement with most of the findings, although we were unable to prove the structure by degradation, either by decarboxylation or by oxidation. Later it was found that an acid with the structure I, 5-hydroxy-3-carboxy-*o*-tolueneacetic acid, had been synthesized by Meldrum and Vaidyanathan ³. The synthetic acid, having the m.p. 210°, was quite different from our acid, a fact which was verified by repeating the synthesis, and formula I therefore had to be abandoned.



By further work on the structure of $C_{10}H_{10}O_5$ it was found that the main product obtained on decarboxylating the sodium salt by heating with calcium hydroxide was *p*-ethylphenol, a chromatographic investigation at the same time revealing that small amounts of *m*-ethylphenol and phenol were also formed during the decarboxylation. In order to explain the occurrence of the ethylphenols a structural formula II, 3-hydroxy-5-carboxyhydrocinnamic acid, for the substance $C_{10}H_{10}O_5$ was considered. A corresponding formula for the methyl product would contain the side-chain $-CH_2-CO-COOH$ and thus be able to explain that oxalic acid and 3-methyl-5-hydroxybenzoic acid are formed by treatment with barium hydroxide. The simultaneous occurrence of *p*- and *m*-ethylphenol would at any rate imply that either the ethyl or the hydroxyl group migrates during the decarboxylation. As indicated by dotted lines a skeleton as in formula II would be compatible with the formation of the methyl product from two molecules of acetylpyruvic ester. A synthesis of 3-hydroxy-5-carboxyhydrocinnamic acid (II) also showed, however, that this acid was different from our acid $C_{10}H_{10}O_5$.

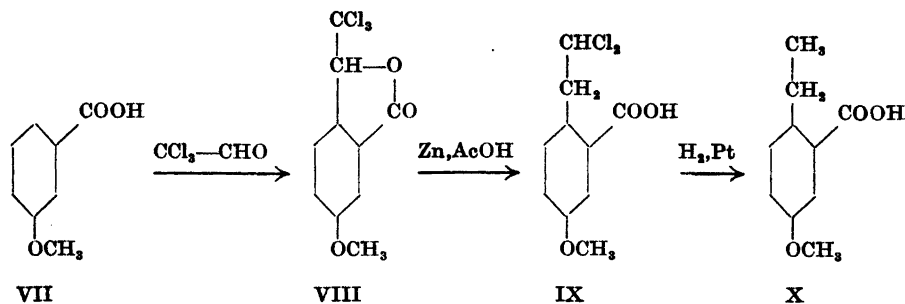


The synthesis was carried out in the following way: *Isophthalaldehydic acid* on nitration gave 5-nitroisophthalaldehydic acid (IV) in which the 5-position of the nitro group was proved by oxidation of IV to the known 5-nitroisophthalic acid. Condensation of IV with malonic acid gave 3-carboxy-5-nitrocinnamic acid (V). On catalytic hydrogenation the latter was transformed into 3-carboxy-5-aminohydrocinnamic acid (VI) which was diazotized to 3-carboxy-5-hydroxyhydrocinnamic acid (II), having m.p. 200—202°.

The third possibility for the structure of $C_{10}H_{10}O_5$ which suggested itself was formula III, representing the 2-ethyl-5-hydroxyisophthalic acid. It is *a priori* difficult to perceive how a skeleton as in formula III could be compatible with the simultaneous occurrence of the 3-methylcyclohexanone-5-carboxylic acid when the hydrogenated methyl product was treated with barium hydroxide, and with the formation of 3-methyl-5-hydroxybenzoic acid by treatment of the methyl product itself with barium hydroxide. A satisfying explanation of this difficulty has, however, been found and will be dealt with in a later communication. Our present aim is to prove the correctness of formula III for the acid $C_{10}H_{10}O_5$.

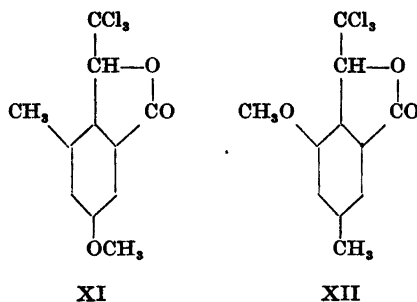
As described in part I of this series a methyl ether of the acid $C_{10}H_{10}O_5$ could easily be prepared. A partial decarboxylation of this methyl ether was achieved by heating it with copper chromite, the main product being a crystalline methyl ether of a monobasic hydroxy acid. The corresponding hydr-

oxy acid, $C_9H_{10}O_3$, m.p. 155° , gave no colour with ferric chloride and on further decarboxylation in the usual way gave *p*-ethylphenol only. The product from the partial decarboxylation must therefore be the methyl ether of 2-ethyl-5-hydroxybenzoic acid (X) which was confirmed by the following synthesis.



According to Fritsch ⁴ the main product of the reaction between *m*-methoxybenzoic acid (VII) and chloral hydrate in the presence of conc. sulphuric acid is 5-methoxy-2-trichloromethylphthalide (VIII). On heating with zinc powder and glacial acetic acid VIII was reduced to 2- β -dichloroethyl-5-methoxybenzoic acid (IX). The substance IX on catalytic dehalogenation gave 2-ethyl-5-methoxybenzoic acid (X) which was found to be identical with the product obtained by partial decarboxylation of the methyl ether of $C_{10}H_{10}O_5$.

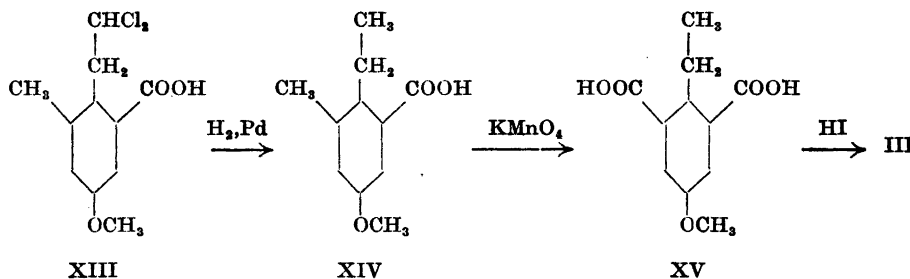
Finally an acid with the structural formula III was synthesized along a similar line as that followed by the synthesis of the acid m.p. 155° . Meldrum ⁵ and later Meldrum and Vaidyanathan ³ showed that 5-methoxy-3-methylbenzoic acid (or its ester) reacted with chloral hydrate to give a mixture of 5-methoxy-3-methyl-2-trichloromethylphthalide (XI) and 3-methoxy-5-methyl-2-trichloromethylphthalide (XII), having m.p. 118° and 143° , respectively.



A complete separation of the two isomers by crystallization is very difficult to achieve. On repeated crystallizations the lowest melting isomer (XI) was, however, accumulated in the mother liquors and could thus be obtained in a sufficient purity so as to ensure that it was really this isomer which formed the basis for the present synthesis. Having established this fact it was in later

experiments found to be practical to separate the isomeric trichloro-compounds only partially and to use the lower melting, more soluble fraction for the synthesis. A final separation of isomeric reaction products was then undertaken at a later stage as described in the experimental part. The structures of the two isomers XI and XII have been ascertained by Meldrum and Vaidyanathan³ by transforming them into 5-hydroxy-3-methylphthalic acid (β -coccinic acid) and 3-hydroxy-5-methylphthalic acid (γ -coccinic acid), respectively.

The isomer XI on treatment with zinc powder in glacial acetic acid gave 2- β , β -dichloroethyl-5-methoxybenzoic acid (XIII) which was dehalogenated, catalytically to 2-ethyl-3-methyl-5-methoxybenzoic acid (XIV).



The oxidation of XIV to 2-ethyl-5-methoxyisophthalic acid (XV) was effected by potassium permanganate in alkaline solution. The fact that the methyl group alone and not the ethyl group was oxidized must be due to steric hindrance. In the oxidation product itself (XV) in which both *ortho* positions to the ethyl group are occupied by carboxyl groups the steric hindrance is so pronounced that the substance cannot be oxidized at all without breaking up the molecule. The methyl ether XV on treatment with hydroiodic acid gave the corresponding hydroxy acid (III) which had the m.p. 267° and was found to be identical with the acid $C_{10}H_{10}O_5$ obtained from the hydrogenated methyl product.

As mentioned above the decarboxylation of $C_{10}H_{10}O_5$ by the classical method led mainly to *p*-ethylphenol with *m*-ethylphenol and phenol as minor products. In view of formula III the explanation of this result must be that the ethyl group migrates. In some cases it will thereby occupy the position of a carboxyl group when this is expelled, in other cases the ethyl group will not re-enter the molecule at all and phenol will be the final product.

EXPERIMENTAL

(Melting points not corrected)

3 - Hydroxy - 5 - carboxyhydrocinnamic acid

(In part with Stud. real. Asbjørn Baklien)

m-Carboxycinnamic acid, prepared by conventional methods from *m*-nitrocinnamic acid, had m.p. 268–270°. (Found: C 62.27; H 4.21; M by titration 194; Calc. for $C_{10}H_8O_4$ (192.2): C 62.50; H 4.20.). Oxidation to *isophthalaldehydic acid*: To a solution of *m*-carboxycinnamic acid in 50 ml N sodium carbonate and 400 ml water were added slowly

at 4–5° 80 ml 5 % potassium permanganate, stirring vigorously. The filtrate from manganese dioxide was concentrated to about 150 ml and acidified with 5 N hydrochloric acid, when a mixture of *isophthalaldehydic acid*, *isophthalic acid* and unoxidized *m*-carboxycinnamic acid separated. In order to isolate the aldehydic acid, the solid mixture as well as the filtrate from it were extracted with ether in which the two last-mentioned acids are sparingly soluble. The crude *isophthalaldehydic acid* (3.6 g) was recrystallized from water and had then m.p. 173°.

Nitration: A solution of *isophthalaldehydic acid* (1.6 g) in conc. sulphuric acid (13 ml) was cooled to +5° and 1.23 g finely powdered potassium nitrate added in small portions. The solution was stirred until all nitrate had dissolved, keeping the temperature below 10°. During half an hour the temperature was raised to 35° and finally to 105–110° where it was kept for 15 min. Pouring the cooled solution on ice some un-nitrated substance (0.7 g) separated. The filtrate from this on extraction with ether gave the nitro*isophthalaldehydic acid* as a yellow oil (1.0 g) which crystallized slowly when kept in a desiccator. The m.p. was not sharp, clear at 150°, but no attempt was made to recrystallize the acid. In order to prove the position 5 for the nitro group a small quantity of the substance (0.2 g) was oxidized with potassium permanganate to the corresponding nitro*isophthalic acid*. The methyl ester of the oxidation product (prepared by means of diazomethane) had m.p. 123° and was identical with the methyl ester of the nitrated *isophthalic acid*.

The 5-nitro*isophthalaldehydic acid* was condensed with malonic acid, using a method given by Brand and Horn⁶: A mixture of the nitro acid (1 g), malonic acid (0.7 g), pyridine (3 ml), and piperidine (0.3 ml) was heated for half an hour to 70–80°. On raising the temperature to 100° carbon dioxide began to evolve. The temperature was finally raised to 140° and the heating discontinued after 2 1/4 hours. By addition of hydrochloric acid the 5-nitro-3-carboxycinnamic acid separated crystalline (1.2 g). It was recrystallized twice from water, using some Carbex E, and had m.p. 207–211°.

The simultaneous saturation of the double bond and the reduction of the nitro group were effected by catalytic hydrogenation. A solution of 5-nitro-3-carboxycinnamic acid (0.46 g) in methanol (25 ml) to which PtO₂ (0.1 g) had been added did not at first take up any hydrogen. Only after adding more PtO₂ (0.1 g) did the solution in the course of two hours consume 154 ml hydrogen (1 1/2 atm.), calculated 160 ml. The filtered solution on evaporation left the amino acid as an oil (0.42 g) which was diazotized directly according to the following method given by Fieser and Lothrop⁷. A solution of the amino acid in 4 ml N sodium carbonate was diluted with water to 6 ml and 0.14 g sodium nitrite in 1 ml water added. The solution was cooled with ice and added slowly under stirring to a mixture of 0.8 ml conc. hydrochloric acid, 4–5 g ice and 0.25 g boric acid. On heating, first on a water-bath, later to boiling, gas evolved. By extraction of the solution with ether the 5-hydroxy-3-carboxyhydrocinnamic acid was obtained as a crystalline, slightly red-coloured mass with m.p. 200°. After recrystallizing twice from water, adding some Carbex E, the acid became practically colourless, m.p. 200–202°. It gave no colour with ferric chloride. (Found: C 57.48; H 4.82. Calc. for C₁₀H₁₀O₅ (210.2): C 57.14; H 4.76.)

2-Ethyl-5-hydroxybenzoic acid

3-Methoxybenzoic acid (5.0 g) and chloral hydrate (5.4 g) were dissolved in conc. sulphuric acid (25 ml) and left at room temperature for 24 hours. On dilution with ice and water an oil separated which immediately crystallized. The crystalline mass was crushed in a mortar and recrystallized from ethanol. The first fraction (5.5 g) had m.p. 139° (Fritsch⁴ gave m.p. 135°) and the second fraction (1.6 g) m.p. 135–138°. A solution of the first fraction in glacial acetic acid (50 ml) was refluxed for 1 1/2 hours with zinc powder (20 g). After adding water (30 ml) the refluxing was continued for half an hour. The clear solution decanted from excess of zinc powder on cooling separated needles (4.0 g) with a somewhat unsharp m.p., clear at 187°. This substance was dissolved in pure methanol (40 ml) and the solution after adding platinum oxide (0.25 g) shaken in an atmosphere of hydrogen. In the course of 1 1/2 hours 1 110 ml hydrogen were absorbed. The filtrate from the platinum on evaporation in a vacuum gave a crystalline, halogen-free product (2.9 g) with m.p. about 65°, being the methyl ether of 2-ethyl-5-hydroxybenzoic acid. It was demethylated by refluxing for 3/4 hour with hydroiodic acid (10 ml,

d 1.7). The free hydroxy acid after crystallizing from water had m.p. 155° and showed no depression on mixing with the acid from the partial decarboxylation of $C_{10}H_{10}O_5$. (Found: C 64.97; H 6.05; M by titration 164. Calc. for $C_9H_8O_5$ (166.2): C 65.05; H 6.07.)

2-Ethyl-5-hydroxyisophthalic acid

3-Methyl-5-methoxybenzoic acid (22.5 g) and chloral hydrate (22.5 g) were dissolved in conc. sulphuric acid (110 ml). The temperature rose slowly to 29° and then fell again. After standing for 24 hours at room temperature the solution was poured in ice-water. The viscous mass which separated crystallized overnight. It was crushed, filtered, washed and dried (38.7 g) and then crystallized from methanol.

Fraction I, filtered after short time	21.6 g	m.p. clear at	115°
» II, filtered next day	7.8 »	» »	112°
» III, after dilution with water	4.2 »	» »	114°

The fractions were treated separately with zinc powder in glacial acetic acid. Fraction I and zinc powder (8 g) in glacial acetic acid (45 ml) reacted on shaking and the solution became warm. In order to finish the reaction the shaking was continued for 3 hours. Afterwards some crystalline material which had separated was redissolved by heating and the solution filtered from excess of zinc. On subsequent addition of water the reduction product (IA, 15.2 g) separated crystalline. Fraction II on treatment in the same way with 3 g zinc powder gave 5.3 g crystalline product (IIA). Equivalent weight by titration 261, calc. for $C_{11}H_{12}O_5Cl_2$ 263. Fraction III on treatment with zinc gave only a partly crystalline reduction product which was discarded.

The fractions IA and IIA were combined and recrystallized from glacial acetic acid and two fractions were collected. Fraction IVA (5.5 g) which separated directly on cooling was not used for further treatment. Fraction IVB (12.8 g) obtained after dilution with water had equiv. wt. 260; it was dehalogenated in the following way. A solution of fraction IVB in 180 ml pure methanol to which had been added 105 ml 25 % methanolic KOH and 6.5 g catalyst (aluminum oxide with 5 % Pd) was shaken in an atmosphere of hydrogen for two hours when about 3 l hydrogen had been adsorbed. On diluting the filtered solution with water the dehalogenated product separated crystalline (7.5 g). It consisted of the methyl ethers of the two isomeric ethylmethylhydroxy-benzoic acids which could be separated by crystallization from petrol ether (45–68°). A solution obtained by refluxing the mixture with 200 ml petrol ether was allowed to evaporate slowly at room temperature in a beaker. The one component crystallizing in thin needles crept up the wall of the beaker. After recrystallization from dilute ethanol it had m.p. 137° and analyzed correctly for a methyl ether of ethylmethylhydroxy-benzoic acid. The other component separated mostly at the bottom of the beaker as clear prisms which could easily be collected (1.7 g). Recrystallized from dilute ethanol, m.p. 90°. (Found: C 68.11; H 7.45; OCH_3 15.98; M by titration 193. Calc. for $C_{11}H_{14}O_5$ (194.2): C 68.02; H 7.27; OCH_3 15.98.) Preliminary experiments had shown that the methyl ether m.p. 90° was derived from the lowest melting of the isomeric trichloro-compounds XI and XII. It must therefore be the 2-ethyl-3-methyl-5-methoxybenzoic acid. Oxidation: The methyl ether (1.6 g) dissolved in 12 ml N sodium hydroxide and 250 ml water was heated on the steam-bath and a solution of 3.1 g potassium permanganate (20 % excess) in water (60 ml) added in small portions. After 6 hours the filtrate from manganese dioxide was concentrated to 100 ml and 5 N hydrochloric acid added. The crystalline precipitate (1.2 g) was recrystallized from glacial acetic acid; m.p. 186°, no depression on admixture. It was demethylated by refluxing 1/4 hour with hydroiodic acid. The crude hydroxy acid had m.p. 267° and the m.p. was not altered either on recrystallization from water or on mixing with $C_{10}H_{10}O_5$ prepared from acetylpyruvic ester. (Found: C 57.03; H 4.82. Calc. for $C_{10}H_{10}O_5$ (210.2): C 57.14; H 4.76.)

Decarboxylation of $C_{10}H_{10}O_5$

(With Magister Odd Leander Johansen and Cand. real. Agnes Thoresen)

The sodium salt of the methyl ether of $C_{10}H_{10}O_5$ (3 g) was mixed with twice its weight of calcium hydroxide and heated in a glass tube through which nitrogen passed slowly. The distillate (0.6 ml) was demethylated by refluxing for half an hour with 3 ml hydro-

iodic acid (1.7). The free phenol was taken up in ether, the solution shaken with sodium carbonate and thiosulphate. On distillation the phenol went over at 200–220°. The following derivatives were prepared. 1) Phenylurethane, after recrystallization from petrol ether, m.p. 117–119°. (Found: C 74.98; H 6.29; N 6.20. Calc. for $C_{11}H_{11}O_2N$ (241.3): C 74.66; H 6.27; N 5.81.) The phenylurethane prepared from authentic *p*-ethylphenol had m.p. 120°, mixed m.p. 118–119°. 2) *p*-Ethylphenoxyacetic acid prepared by reaction with monochloroacetic acid and sodium hydroxide; recrystallized from benzene plus petrol ether, m.p. 94°. Prepared from authentic *p*-ethylphenol, m.p. 96–97°, mixed m.p. 96°. 3) Benzoyl derivative crystallized from dilute ethanol, m.p. 55–57°. Corresponding derivative from *p*-ethylphenol, m.p. 60°.

A chromatographic analysis of the product from the decarboxylation was later carried out according to the method of Hossfeld⁸. The product was coupled with diazotized sulphanilic acid and the dyestuffs extracted with ether. Drops of the concentrated ethereal solution were placed on a filter paper (Whatman no 1) which beforehand had been treated with sodium carbonate. For comparison coupling-products of *p*- and *m*-ethylphenol, *p*- and *m*-cresol and phenol were placed on the same paper. The mobile phase was methyl ethyl ketone saturated with water. The chromatogram showed in all five spots of which two were very weak. One yellow spot corresponded to *m*-ethylphenol, one reddish spot to *p*-ethylphenol and another yellow spot to phenol. The two spots of the ethylphenols were of about the same intensity and control experiments showed that mixtures of *m*- and *p*-ethylphenol containing only a minor quantity of the *meta* isomer (5–10 %) would give spots of about equal intensity. The two very weak spots had the same position as those of *m*- and *p*-cresol.

Partial decarboxylation of the methyl ether of $C_{10}H_{10}O_3$: The methyl ether (1.16 g) was mixed with copper chromite (0.3 g) and heated in a test tube through which a slow current of nitrogen passed. At about 290° decarboxylation set in and the temperature was finally raised to 330°. The liquid distillate (0.83 g) crystallized overnight. A sample pressed on porous tile had m.p. 65°. The rest was demethylated in the usual way. The free hydroxy acid after recrystallization from water had m.p. 154°. (Found: C 64.50; H 5.98; M by titration 165.8. Calc. for $C_9H_{10}O_3$ (166.2): C 65.05; H 6.07.)

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