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Syntheses of Orsellinic Acid and Related Compounds

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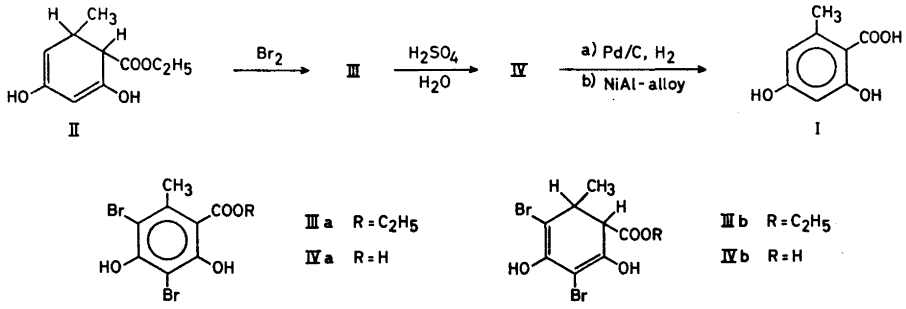
A supposed dibromodihydroorsellinic acid is shown to be dibromoorsellinic acid. This acid can be dehalogenated to orsellinic acid by Raney nickel alloy in sodium hydroxide. Orsellinic acid has also been prepared by magnesium methyl carbonate (MMC) carboxylation of orcinol. Some related compounds were synthesized by MMC carboxylations. Syntheses of 3- and 5-chloroorsellinic acids are reported, the former involving a selective deiodination.

Orsellinic acid (I) is of considerable biochemical interest. It is one of the simplest compounds, which can arise by *in vivo* cyclisation of a polyketide precursor,[1] it is a key intermediate in the biosynthesis of many secondary metabolites,[2] and it can be regarded as a "parent compound" for a large number of lichen substances.[3–5]

Many methods for the preparation of orsellinic acid have been reported. Three main types may be recognized: (1) degradation of suitable lichen compounds,[6] (2) formylation of orcinol and oxidation of the protected orcylaldehyde,[7,8] and (3) condensation of ethyl acetoacetate with ethyl crotonate and aromatization of the ethyl dihydroorsellinate thus formed.[9–12] Methods of type (1) are not very practical, the starting materials being rather inaccessible.

Orsellinic acid from ethyl dihydroorsellinate. In the first synthesis of type (3), Sonn [10] brominated ethyl dihydroorsellinate and dehalogenated the



dibromoester to ethyl orsellinate, which was hydrolyzed. He formulated the dibromo ester as ethyl dibromoorsellinate (IIIa). Recently Kloss and Clayton [12] suggested the dibromo ester to be IIIb, affording dibromodihydroorsellinic acid upon hydrolysis. They did not give any evidence for the revised structure, and their analytical data for the acid IV b are in better agreement with dibromoorsellinic acid (IVa).

Final proof has now been obtained for the structures IIIa for the dibromo ester and IVa for its hydrolysis product. The mass spectra of III and IV showed $M^{+\cdot}$ peaks at *m/e* 356, 354, and 352 and at *m/e* 328, 326, and 324, respectively. In the NMR spectra (in acetone-d_6) the methyl group appeared as a singlet (at τ 7.85 and 7.90 ppm, respectively) and no signals due to methine protons required by the structures IIIb and IVb could be detected.

Furthermore, bromination of ethyl orsellinate afforded a dibromo ester identical with III, while bromination of orsellinic acid gave a dibromo acid, identical with IV. Hence, Sonn's original formulation of the ethyl dihydroorsellinate bromination product as IIIa is correct, and Kloss' and Clayton's dibromo acid is IVa rather than IVb.

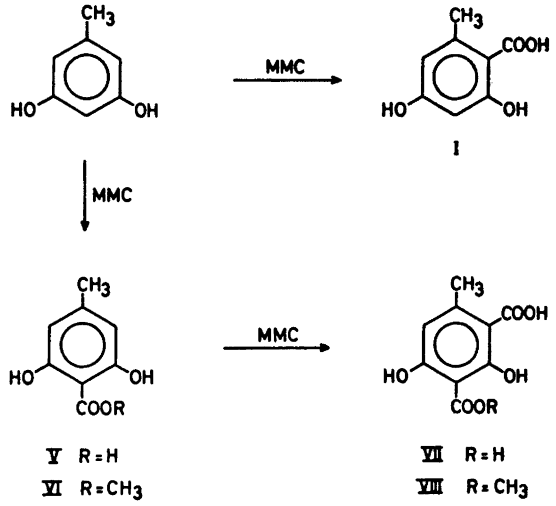
Dehalogenations of IIIa and IVa have earlier been carried out by hydrogenolysis with a palladium-on-carbon catalyst. A convenient method for dehalogenations, using Raney nickel alloy in sodium hydroxide solution, was described by Papa *et al.*[13] and this method has been successfully applied, *e.g.* in studies on halogenated xanthones.[14] By means of this method (slightly modified) IIIa and IVa could be dehalogenated in high yields. The Raney nickel alloy method is easier, more rapid, cheaper, and gives a higher yield than the H_2-Pd/C method.

MMC carboxylations. A direct carboxylation of orcinol with potassium hydrogen carbonate to orsellinic acid is not possible, *p*-orsellinic acid being the sole product of the reaction.[15–17] In contrast, resorcinol under similar conditions does not afford γ-resorcylic acid but β-resorcylic acid.[18]

Magnesium methyl carbonate (MMC) in dimethyl formamide solution [19,20] has been used for the α-carboxylation of ketones,[21,22] nitroalkanes,[19] and, quite recently, resorcinol, phloroglucinol, and cannabidiols.[23] Thus, resorcinol afforded β-resorcylic acid (45 %) and 2,4-dihydroxyisophthalic acid (15 %).

Applying this reaction to orcinol a reaction mixture was obtained, consisting of orsellinic acid (30 %), *p*-orsellinic acid (V) (10 %), 2,4-dihydroxy-6-methylisophthalic acid (VII) (10 %), and orcinol (50 %) (the quantitative composition estimated from thin layer chromatograms). A 10 % yield of I could be isolated, and by conversion of V and VII into orcinol, 67 % of the starting material could be isolated (making the yield of I, calculated on orcinol used, 30 %). The MMC carboxylation of orcinol is thus a convenient one step method for the preparation of smaller quantities of orsellinic acid.

MMC carboxylation of *p*-orsellinic acid afforded the new isophthalic acid VII in 42 % yield. In contrast, MMC carboxylation of orsellinic acid afforded a mixture of starting material and small amounts of orcinol, V, and VII. The two latter compounds are probably formed by carboxylation of orcinol, produced by decarboxylation of orsellinic acid under the alkaline reaction conditions.



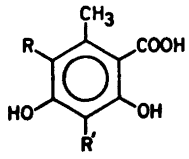
Similarly, MMC treatment of methyl *p*-orsellinate (VI) gave 3-methyl 2,4-dihydroxy-6-methylisophthalate (VIII), while methyl orsellinate did not react.

The acid VII and the half-ester VIII are of special interest in being closely related to degradation products of lichen *β*-orcinol depsides, *e.g.* squamatic and thamnolic acids. Earlier attempts to prepare VII and VIII have been unsuccessful.[24]

Both VII and VIII are easily decarboxylated in a hot aqueous solution, affording *p*-orsellinic acid and methyl *p*-orsellinate, respectively. No traces of orsellinic acid could be detected in the reaction product from the decarboxylation of VII.

Halogenations of I. Monohalogenation of orsellinic acid and its esters takes place exclusively in the 5 position. No 3-monohalogenated derivatives of I have hitherto been prepared.

Chlorination of I with sulphuryl chloride afforded 5-chloroorsellinic acid (IX) in fair yield. The structure was proved by converting the acid into its known [25] methyl ester.



	R	R'
IX	Cl	H
X	I	H
XI	I	Cl
XII	H	Cl

Iodination of I with iodine-mercuric oxide gave 5-iodoorsellinic acid (X), which could be chlorinated to the chloroiodo acid XI. This acid could be deiodinated either by use of Raney nickel alloy in sodium hydroxide solution or by the use of sodium borohydride and palladium-on-carbon [26] to give 3-chloroorsellinic acid (XII). The structure of XII follows from its non-identity with IX.

EXPERIMENTAL

Dibromoorsellinic acid (IVa). Pyridinium hydrobromide perbromide (3.5 g, 11 mmol) was added to a stirred solution of orsellinic acid (0.84 g, 5 mmol) in glacial acetic acid (25 ml). After 1 h at 50°, the solution was cooled, diluted with hydrochloric acid (2 M, 200 ml) and extracted with ether (2 × 50 ml). Evaporation of the ether and recrystallisation of the residue from benzene afforded IVa (1.1 g 65 %), m.p. 207–209° (lit.[12] 213–213.5°), in all respects identical with IV prepared by hydrolysis of III according to Ref. 12.

Ethyl dibromoorsellinate (IIIa) was prepared from ethyl orsellinate (1.0 g, 5 mmol) and Py·HBr·Br_2 (3.5 g, 11 mmol) in the same way as IVa. The product (1.3 g, 75 %), m.p. 142–144° (lit.[27] 144°) was in all respects identical with III, prepared by bromination of II.[10,12]

Orsellinic acid (I). Dibromoorsellinic acid (3.26 g, 10 mmol) was dissolved in aqueous sodium hydroxide (2 M, 70 ml) at 0° and treated with Raney nickel alloy (3.0 g), added in small portions as rapidly as possible (excessive frothing can be controlled by addition of a few drops of ethanol). The Raney nickel was removed by filtration, the filtrate flowing into ice-cold conc. hydrochloric acid (25 ml). Ether extraction of the filtrate, evaporation of the ether, and recrystallisation of the residue from glacial acetic acid-water afforded orsellinic acid (1.51 g, 82 %) as white needles, m.p. 174–175° (lit.[9] 176°).

Ethyl orsellinate. Ethyl dibromoorsellinate (3.54 g, 10 mmol) was debrominated with Raney nickel alloy (3.0 g) in the same way, yielding ethyl orsellinate (1.80 g, 92 %), m.p. 130–132° [27] (lit. 132°).

MMC carboxylation of orcinol. (A) Orsellinic acid. Dry orcinol (12.4 g, 0.1 mol) and MMC in dimethyl formamide (2 M, 150 ml) [19] were heated to 100° for 2 h. The cool reaction mixture was poured onto ice (250 g), water (250 ml), and conc. hydrochloric acid (50 ml) under efficient stirring. The precipitate was collected and dried. (The filtrate was saved for recovery of orcinol.) It was then dissolved in water at 90° under intensive stirring (80 ml per 5 g of precipitate), and the solution was set aside. After 3 h the precipitated needles were collected to afford orsellinic acid (1.9 g, 10 %), m.p. 170–172°.

(B) Recovery of orcinol. Ice (100 g) and conc. hydrochloric acid (100 ml) were added to the above filtered reaction mixture. Ether extraction (1 × 300 ml, 3 × 100 ml), evaporation of the ether, refluxing the residue with the above mother liquor for 15 h, and evaporation of the water afforded a slightly oily residue, which was recrystallised from benzene to afford orcinol (8.3 g, 67 %).

2,4-Dihydroxy-6-methylisophthalic acid (VII). Dry *p*-orsellinic acid [28] (16.8 g, 0.1 mol) and MMC in DMF (2 M, 150 ml) [19] were heated to 110° for 2 h. The cool reaction mixture was poured onto ice (400 g) and conc. hydrochloric acid (100 ml). The precipitate was dried and repeatedly recrystallised from ethyl acetate to afford VII (9.0 g, 42 %), m.p. 164–165°. (Found: C 51.2; H 3.89. Calc. for $C_9H_8O_6$: C 51.0; H 3.80.) Evaporation of the combined mother liquors afforded a 1:1 mixture of VII and V (9.2 g, about 50 %), suitable as starting material for a repeated synthesis.

3-Methyl 2,4-dihydroxy-6-methylisophthalate (VIII). Methyl *p*-orsellinate [29] (1.82 g, 10 mmol) and MMC in DMF (2 M, 20 ml) were heated to 120° for 2 h, cooled, and poured onto ice (150 g) and conc. hydrochloric acid (20 ml). The reaction mixture was extracted with ether (3 × 100 ml) and the combined ethereal extracts were extracted with aqueous sodium hydrogen carbonate (5 %, 2 × 100 ml). Evaporation of the ether afforded starting material (1.12 g, 62 %). Acidification of the $NaHCO_3$ solution, ether extraction, and evaporation of the ether gave a solid, which was refluxed with chloroform (20 ml) for 1 h. After cooling, the residue was collected and recrystallised from chloroform to afford VIII (0.30 g, 13 %) as long, white needles, m.p. 177–178°. (Found: C 53.1; H 4.48. Calc. for $C_{10}H_{10}O_6$: C 53.1; H 4.46.)

Decarboxylations. VII (10 mg) in water (2 ml) was heated to 90° for 10 min. By TLC, only the presence of *p*-orsellinic acid could be demonstrated. In the same way VIII afforded only methyl *p*-orsellinate.

5-Chloroorsellinic acid (IX). Dry orsellinic acid (8.40 g, 50 mmol) in dry ether (200 ml) was treated at room temp. with sulphuryl chloride (5 ml, 55 mmol) in ether (50 ml). After 2 h, the ether was evaporated and the residue recrystallised from benzene to afford IX (6.8 g, 67 %), m.p. 182.5–184°. (Found: C 47.3; H 3.59. Calc. for $C_8H_7ClO_4$: C 47.4; H 3.48.)

Methyl 5-chloroorsellinate. Methylation of IX with the calculated amount of diazomethane at −10° afforded the ester, m.p. 133−134° (lit.[25] 134°).

5-Iodoorsellinic acid (X). Dry orsellinic acid (8.4 g, 50 mmol) and iodine (12.6 g, 50 mmol) in ether (200 ml) was treated with yellow mercuric oxide (10.8 g, 50 mmol) in small portions. After 15 min reflux and 1 h at room temp., the reaction mixture was filtered, washed with aqueous potassium iodide (10 %, 50 ml) and water (50 ml), and the ether was evaporated. Recrystallisation of the residue from benzene afforded X (9.08 g, 55 %) as needles, m.p. 172.5−174°. (Found: C 33.0; H 2.40; I 42.5. Calc. for $C_8H_7IO_4$: C 32.7; H 2.40; I 43.1.)

3-Chloro-5-iodoorsellinic acid (XI). X (4.75 g, 16 mmol) in dry ether (150 ml) was treated with sulphuryl chloride (6 ml, 70 mmol) in ether (50 ml). After 15 h at room temp., the reaction mixture was washed with water (5 × 100 ml) and the ether was evaporated. Recrystallisation from benzene gave XI (2.95 g, 56 %) as stump needles, m.p. 198−200°. (Found: C 29.9; H 1.82; I 37.3. Calc. for $C_8H_6ClIO_4$: C 29.3; H 1.84; I 38.6.)

3-Chloroorsellinic acid (XII). (A). XI (1.37 g, 4.2 mmol) was dissolved in aqueous sodium hydroxide (2 M, 25 ml). Portions of Raney nickel alloy (25−50 mg each time) were added to the solution until the very slow gas evolution suddenly turned rapid. The mixture was immediately filtered into cold conc. hydrochloric acid (7 ml), water (75 ml) was added to the filtrate, and it was extracted with ether (3 × 50 ml). The water-washed ether extracts were evaporated and the residue recrystallised from benzene to give XII (0.67 g, 80 %) as needles, m.p. 172−174°, not identical with IX (mixed m.p., IR). (Found: C 48.0; H 3.58; Cl 16.7. Calc. for $C_8H_7ClO_4$: C 47.4; H 3.48; Cl 17.5.)

(B). XI (0.65 g, 2 mmol) and 10 % palladium-on-carbon (10 mg) in aqueous sodium hydroxide (2 M, 10 ml) were treated with sodium borohydride (0.15 g, 2 mmol) in NaOH (2 M, 2 ml) at 0° for 30 min. After filtration and acidification, the precipitate was collected and recrystallised from benzene to afford XII (0.25 g, 62 %), m.p. 171−173°.

Thin layer chromatography of the reaction products from the MMC carboxylations was carried out using Merck's DC Fertigplatten Kieselgel F 254 and chloroform-glacial acetic acid 7:2 (v/v). R_F values: orcinol 0.46, I 0.51, V 0.25, VII 0.07, VIII 0.68.

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