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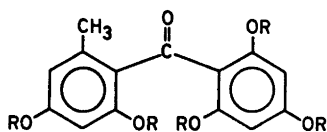
Received September 10, 1974.

Synthesis of 2,2',4,4',6'-Pentahydroxy-6-methylbenzophenone*

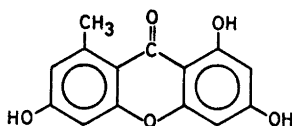
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2,2',4,4',6'-Pentahydroxy-6-methylbenzophenone (I) has often been postulated as a precursor of certain polyketides in lower plants, viz. xanthenes¹ and griseofulvin.^{1,2}



- I R=H
II R=CH₃
III R=CH₂C₆H₅



IV

For biosynthetic studies on lichen xanthenes (all of which are related to norlichexanthone,

* Part 33 of the series Chemical Studies on Lichens. Part 32 in press.

IV)³ I was needed. There appears, however, to be no record of its synthesis in the literature.

In an attempt to synthesize I, *O,O*-dimethylorsellinoyl chloride was reacted with 2,4,6-trimethoxyphenyl lithium in diethyl ether⁴ to give the methylated benzophenone II in ~50% yield. During demethylation of II with boron tribromide in dichloromethane, I was formed (15%) together with partially demethylated benzophenones and xanthenes.

In another synthesis, *O,O,O*-tribenzylphloroglucinol carboxylic acid was condensed with *O,O*-dibenzylorcinol using trifluoroacetic anhydride in dichloromethane⁵ to give the benzylated benzophenone III in high yield. 2,2',4,4'-Tetrabenzyloxy-6,6'-dimethylbenzophenone was formed as a by-product. Hydrogenolysis of III afforded I quantitatively.

The spectral data (NMR, UV, IR, MS) are in agreement with the pentahydroxy benzophenone I structure. (Cooling of the KBr disc prevented thermally induced formation of IV during the registering of the IR spectrum of I. When recording the mass spectrum of I, the main part of the sample dehydrated to IV in the direct inlet system before evaporation; however peaks at *m/e* 276, 151, and 153 were present).

The compound is sensitive to moisture even at room temperature. Other 2,2',6'-hydroxylated benzophenones are known to dehydrate fairly easily under alkaline conditions, even as the methyl ethers.²

Because of its great instability, it would be difficult to demonstrate the presence of I in plant material even if appreciable amounts should occur.

Experimental. All melting points are uncorrected. Elemental analyses were performed by the Analytical Department, Institute of Chemistry, Uppsala. All solvents used were of analytical grade. Petroleum ether refers to the fraction boiling at 43–55 °C. Column chromatography was done using Merck Silica Gel 60 (70–230 mesh); TLC was carried out using Merck's precoated silica gel plates. IR spectra were recorded with a Perkin-Elmer 157. NMR-spectra were recorded on a Varian A-60D, using TMS as the internal standard. UV-spectra were recorded on a Unicam SP 1800.

O,O-Dimethylorsellinoyl chloride.⁶ *O,O*-Dimethylorsellinic acid⁷ (7.2 g) in dry benzene (20 ml) was reacted with oxalyl chloride (3.5 ml) under nitrogen and left overnight at room temperature. Distillation (b.p. 123–128 °C/2 mmHg) gave 6.7 g (79%) product which was extremely sensitive to moisture. NMR (CCl₄): δ 2.28 (s 3 H), 3.71 (s 3 H), 3.79 (s 3 H), 6.17 (s 2 H); IR ν_{\max} (CCl₄) 1785 cm⁻¹ (C=O).

2,2',4,4',6'-Pentamethoxy-6-methylbenzophenone (II). 1,3,5-Trimethoxybenzene (3.60 g)⁸ in ether (25 ml) was treated with butyl lithium (14.3 ml, 16.7 mmol/ml in hexane) under nitrogen at room temperature (1 h). The slurry was slowly added to an ethereal solution (20

ml) of *O,O*-dimethylorsellinoyl chloride during 40 min at 0 °C under nitrogen. Water (20 ml) was added, the precipitate dissolved in benzene, washed with water, dried (MgSO₄), and evaporated to give a pale yellow oil. Recrystallization from benzene/petroleum ether afforded 2.8 g (47 %) of colourless needles, m.p. 126.5–127 °C. *R_F* 0.7 [silica gel, dichloromethane-acetone (4:1)]. NMR (CDCl₃): δ 2.32 (t 3 H, *J* = 0.5 Hz), 3.54 (s 3 H), 3.64 (s 6 H), 3.78 (s 3 H), 3.80 (s 3 H), 6.07 (s 2 H), 6.31 (m 2 H, *J* = 2.2 Hz, *J* = 0.5 Hz). IR, ν_{\max} (KBr) 1667 cm⁻¹ (C=O). (Found C 65.6; H 6.4; MW (MS) 346. C₁₉H₂₂O₆ requires C 65.8; H 6.4).

Demethylation of benzophenone II. Boron tribromide (750 mg, 6 equiv.) in dichloromethane (7 ml) was added dropwise during 15 min to a stirred solution of II (173 mg, 0.5 mmol) in dichloromethane (6 ml) at room temperature. After 1.5 h an orange product precipitated and the reaction was continued for 6.5 h. Additional boron tribromide (750 mg) was added and stirring continued overnight. Water (50 ml) was added at 0 °C with stirring. After work-up the crude material was separated by TLC [silica gel 0.5 mm, dichloromethane-acetone (4:1) to yield I (*R_F* 0.10, 20 mg, 15 %; identical with I prepared by hydrogenation of III, see below). IV (*R_F* 0.28, 35 mg, 27 %), and griseoxanthone C² (*R_F* 0.45, 15 mg, 11 %)]. The identities of the xanthenes were confirmed by comparison with authentic samples. The other bands contained mono-, di-, and trimethoxybenzophenones.

Benzyl-O,O,O-tribenzylphloroglucinol carboxylate. To a solution of anhydrous phloroglucinol carboxylic acid (2 g)⁹ and benzyl bromide (8.5 g) in acetone (50 ml) was added freshly roasted K₂CO₃ (13.8 g). The mixture was stirred at room temperature (48 h). After pouring into ether-water, the ether layer was washed with water, dried and evaporated. The product crystallized from hexane/tetrahydrofuran to give colourless needles (3.1 g, 50 %) m.p. 102–103 °C. NMR (C₃D₆O): δ 5.08 (s 2 H), 5.10 (s 4 H), 5.26 (s 2 H), 6.44 (s 2 H), 7.10–7.55 (m 20 H); IR ν_{\max} (KBr) 1725 cm⁻¹ (C=O). (Found C 79.3; H 5.7; MW (MS) 530. C₃₅H₃₀O₅ requires C 79.3; H 5.6).

O,O,O-Tribenzylphloroglucinol carboxylic acid. Benzyl-O,O,O-tribenzylphloroglucinol carboxylate (0.53 g) was added to a solution of KOH (1.2 g in 2 ml water) and ethylene glycol (12 ml) and the mixture refluxed (48 h). Water (25 ml) was then added, the solution extracted with ether and the ether layer washed with water. The aqueous extracts were combined, acidified (pH ~2) with 2 M hydrochloric acid, extracted with ether, washed, dried and evaporated. Recrystallization from benzene/petroleum ether gave colourless needles (0.39 g, 89 %); m.p. 134–35 °C. NMR (C₃D₆O): δ 5.12 (s 2 H), 5.16 (s 4 H), 6.47 (s 2 H), 7.12–7.62 (m 15 H); IR ν_{\max} (KBr) 3560–2210 (OH), 1700 (sh), and 1690 cm⁻¹ (C=O). (Found C 76.3; H 5.5;

MW (MS) 440. C₂₃H₂₄O₅ requires C 76.4; H 5.5).

2,2',4,4',6'-Pentabenzyl-oxy-6-methylbenzophenone (III). *O,O,O*-Tribenzylphloroglucinol carboxylic acid (1.32 g) and *O,O*-dibenzylorcinol (4.56 g)⁵ were dissolved in dry dichloromethane (25 ml) and freshly distilled trifluoroacetic anhydride (1.5 ml) was dropwise added. After 10 min, the mixture was evaporated and chromatographed on silica gel (750 g, petroleum ether-ether (2:1)) to give unreacted *O,O*-dibenzylorcinol (3.67 g), 2,2',4,4'-tetrabenzyl-oxy-6,6'-dimethylbenzophenone [170 mg, recrystallized from benzene/petroleum ether to give colourless needles (50 mg); m.p. 124–125 °C (lit. 116–120 °C)¹], and pentabenzyl-oxybenzophenone (III) (1.81 g, 83 %, recrystallized from methanol, filtered at -20 °C, dried over P₂O₅ to give 1.44 g of a glassy product that starts melting at 33 °C). NMR (C₃D₆O): δ 2.14 (s 3 H), 4.78 (s 2 H), 4.80 (s 4 H), 5.11 (s 4 H), 6.30 (s 2 H), 6.45 (q 2 H, *J* = 1.8 Hz), 6.85–7.50 (m 25 H); IR ν_{\max} (CCl₄) 1665 cm⁻¹ (C=O). (Found C 80.8; H 5.8; MW (MS) 726. C₄₉H₄₂O₆ requires C 81.0; H 5.8).

2,2',4,4',6'-Pentahydroxy-6-methylbenzophenone (I). The benzophenone III (73 mg) was hydrogenated at room temperature in ethyl acetate over 10 % palladium-carbon (20 mg) at atmospheric pressure until hydrogen uptake ceased. Filtration, evaporation and trituration with petroleum ether yielded I (28 mg, ~100 %) as a pale yellow powder. NMR (C₃D₆O): δ 2.12 (t 3 H, *J* = 0.6 Hz), 5.91 (s 2 H), 6.28 (t 2 H, *J* = 0.6 Hz), 3.5 (broad 2 H), and 10.8 (broad 3 H); IR ν_{\max} (KBr) 3900–2900 (strong, OH), 1625 (sh), and 1605 cm⁻¹ (C=O); UV (MeOH) ν_{\max} 300 (ϵ 15 000), 310 nm (ϵ 6 300).

Acknowledgements. I wish to thank my teacher Dr. Johan Santesson for many stimulating and helpful discussions. The costs of this investigation were defrayed by a grant from the Swedish Natural Science Research Council to Dr. Gerd Bendz at this Institute.

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Received September 17, 1974.