

The Synthesis of 2,5-Bis(*p*-methoxycinnamoyl)-1,3,4,6,7,8- and 4,5-Bis(*p*-methoxycinnamoyl)-1,2,3,6,7,8-hexamethoxyxanthene¹⁾

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Synopsis. In connection with studies of the structure of carthamin derivatives, 2,5-bis(*p*-methoxycinnamoyl)-1,3,4,6,7,8- and 4,5-bis(*p*-methoxycinnamoyl)-1,2,3,6,7,8-hexamethoxyxanthene were synthesized. The comparison of these two hexamethoxyxanthenes with carthamin derivatives is described.

Recently, we have obtained two hexamethoxyxanthene isomers, A-1 (mp 74—76 °C) and A-2 (mp 190—191 °C), which are presumed to be 2,5-bis(*p*-methoxycinnamoyl)-1,3,4,6,7,8-hexamethoxyxanthene (**1**) and 4,5-bis(*p*-methoxycinnamoyl)-1,2,3,6,7,8- or 2,7-bis(*p*-methoxycinnamoyl)-1,3,4,5,6,8-hexamethoxyxanthene (**2** or **3**) produced by the methylation of the hydrolysis products of carthamin, the red coloring matter of the flowers of safflower (*Carthamus tinctorius* L.).¹⁾

In this paper, the synthesis of **1** and **2** and the comparison of the synthetic samples with carthamin derivatives will be described.

An equimolecular mixture of 2,3,4,6-tetrahydroxyacetophenone (**4**)²⁾ and 3-formyl-2,4,5,6-tetrahydroxyacetophenone (**5**), obtained by the formylation of **4**, was refluxed in methanol containing a small amount of 50% sulfuric acid to afford the condensation product (**6**) as dark violet crystals. Compound **6** was hydrogenated in ethanol using 5% palladium charcoal as a catalyst. The reduction product was then methylated with dimethyl sulfate-potassium carbonate in acetone to give 2,5-diacetyl-1,3,4,6,7,8-hexamethoxyxanthene (**7**). The unsymmetrical structures of **6** and **7** were supported from the observation of the two separate signals of their acetyl groups in their ¹H-NMR spectra.

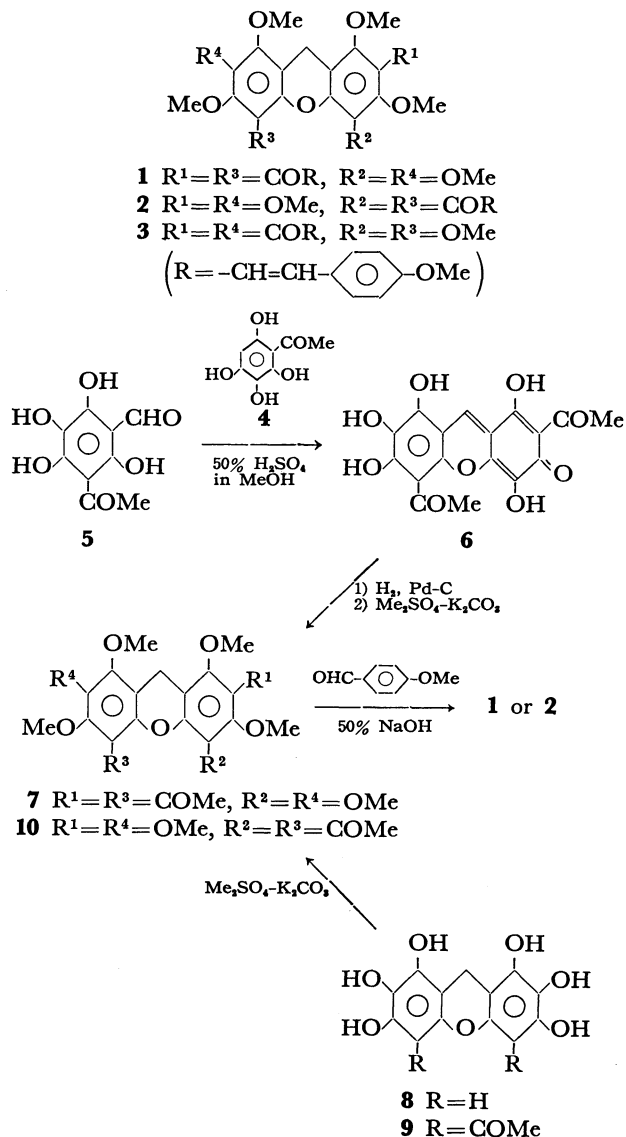
The condensation of **7** with *p*-methoxybenzaldehyde in methanol containing a 50% aqueous potassium hydroxide solution afforded **1** (mp 74—76 °C) in a 57% yield. The IR and ¹H-NMR spectra of **1** were completely identical with those of one of the natural derivatives, A-1.

Since the condensation of **4** with **5** did not give the other symmetrical compound, **2** was synthesized by the alternative method described below.

4,5-Diacetyl-1,2,3,6,7,8-hexamethoxyxanthene (**10**) was obtained by the methylation of 4,5-diacetyl-1,2,3,6,7,8-hexahydroxyxanthene (**9**), prepared by the C-acetylation of 1,2,3,6,7,8-hexahydroxyxanthene (**8**)³⁾ with the boron trifluoride-acetic acid complex. 4,5-Bis(*p*-methoxycinnamoyl)-1,2,3,6,7,8-hexamethoxyxanthene (**2**) (mp 157—158 °C) was afforded by the condensation of **10** with *p*-methoxybenzaldehyde by a manner similar to that of **1**.

From the disagreement of this compound, **2**, with the natural derivative, A-2, it is assumed that the structure of another isomer, 2,7-bis(*p*-methoxycinnamoyl)-1,3,4,6,7,8-hexamethoxyxanthene (**3**), should be assigned for A-2.

5,6,8-hexamethoxyxanthene (**3**), should be assigned for A-2.



Experimental

All the melting points are uncorrected. The UV and IR spectra were recorded on a Hitachi 135 spectrophotometer, and a Hitachi EPI-S2 spectrophotometer respectively. The ¹H-NMR spectra were measured with a Hitachi R-22 spectrometer (90 MHz), using tetramethylsilane as the internal standard. The mass spectra were obtained on a Hitachi RMU-6M mass spectrometer.

3-Formyl-2,4,5,6-tetrahydroxyacetophenone (5). Into a solution of 2,3,4,6-tetrahydroxyacetophenone (**4**)²⁾ (20 g), zinc cyanide (16 g), and anhydrous aluminium chloride (18 g) in dry ether (300 ml), dry hydrogen chloride gas was stirred for

8 h under cooling with ice water. The reaction mixture was then allowed to stand overnight at 0 °C. After the solvent had been removed by decantation, the residue was refluxed with water (100 ml) for 3 h and then filtered. After cooling, **5** (9.2 g, 40%) was obtained from the filtrate. Mp 232–236 °C, ¹H-NMR (DMSO-*d*₆) δ 2.61 (3H, s, -COCH₃), 9.97 (1H, s, -CHO). Found: C, 50.67; H, 3.82%; M⁺, 212. Calcd for C₉H₈O₆: C, 50.94; H, 3.77%; M, 212.

Condensation Product of 4 with 5. A mixture of **4** (500 mg), **5** (570 mg), and 50% sulfuric acid (1 ml) in methanol (30 ml) was refluxed for 10 h. After cooling, the condensation product (**6**) was obtained as dark violet crystals (mp 280 °C) in a 19% yield. UV_{max} (EtOH) 352 and 540 nm, IR (KBr) 1700 and 1620 cm⁻¹ (C=O), ¹H-NMR (DMSO-*d*₆) δ 2.67 and 2.82 (each 3H, s, -COCH₃ × 2), 8.27 (1H, s, -CH=), MS *m/e* 360 (M⁺). This compound was used without purification for the next reaction.

2,5-Diacetyl-1,3,4,6,7,8-hexamethoxyxanthene (7). Compound **6** (5.0 g) was hydrogenated in ethanol (300 ml), using 5% palladium charcoal (0.8 g) as the catalyst. The reaction mixture was filtered, and the filtrate was evaporated *in vacuo* to afford an unstable reduction product (4.8 g).

A mixture of the reduction product (300 mg), dimethyl sulfate (3 ml), and potassium carbonate (5 g) in dry acetone (70 ml) was refluxed for 3 h. The reaction mixture was then worked up in the usual manner, and the crude product was chromatographed on a column of silica gel with benzene-ethyl acetate (4 : 1) to give **7** in a 27% yield. Mp 119–120 °C (from methanol), IR (KBr) 1647 cm⁻¹ (C=O), ¹H-NMR (CDCl₃) δ 2.49 and 2.61 (each 3H, s, -COCH₃ × 2), 3.77 and 3.87 (each 3H, s, -OMe × 2), 3.84 and 3.90 (each 6H, s, -OMe × 4), 3.97 (2H, s, -CH₂-). Found: C, 61.79; H, 5.95%; M⁺, 446. Calcd for C₂₃H₂₆O₉: C, 61.87; H, 5.87%; M, 446.

2,5-Bis(p-methoxycinnamoyl)-1,3,4,6,7,8-hexamethoxyxanthene (1). Into a mixture of **7** (500 mg) and *p*-methoxybenzaldehyde (1 ml) in methanol (10 ml), we added a 50% aqueous potassium hydroxide solution (2.0 g) at room temperature. The reaction mixture was warmed to 50–60 °C for 1 h and then extracted with ether. The ether was evaporated *in vacuo*, and the residue was chromatographed on a column of silica gel with benzene-ethyl acetate (9 : 1) to afford crude **1**, which was further chromatographed on silica gel with chloroform-ethyl acetate (40 : 3). Compound **1** (380 mg, 50%), mp 74–76 °C, IR (KBr) 1632 cm⁻¹ (C=O), ¹H-NMR (CDCl₃) δ 3.75 (2H, s, -CH₂-), 3.80–4.10 (24H, m, -OMe × 8), 6.95–7.60 (12H, m, *p*-substituted cinnamoyl × 2). Found: C, 68.63; H, 5.64%; M⁺, 682. Calcd for C₃₉H₃₈O₁₁: C, 68.61; H, 5.61%; M, 682. This compound was completely identical with the natural derivative A-1.

1,2,3,6,7,8-Hexahydroxyxanthene (8). This compound was prepared by the reduction of the condensation product of

1,2,3,5-benzenetetrol⁴⁾ with ethyl formate as has previously been reported.³⁾ Although this reduction product contained a small amount of an isomer, 1,3,4,6,7,8-hexahydroxyxanthene, it was used without purification for the next reaction.

4,5-Diacetyl-1,2,3,6,7,8-hexamethoxyxanthene (10). A mixture of 1,2,3,6,7,8-hexahydroxyxanthene (**8**) (2.5 g), containing a small amount of 1,3,4,6,7,8-hexahydroxyxanthene and the boron trifluoride-acetic acid complex (10 ml) was heated on a water bath for 2 h. The reaction mixture was then stirred into an aqueous potassium acetate solution, drop by drop. The resulting precipitate was filtered, and the filtrate was concentrated to dryness to afford 4,5-diacetyl-1,2,3,6,7,8-hexahydroxyxanthene (**9**) (mp > 280 °C), containing a small amount of 2,5-diacetyl-1,3,4,6,7,8-hexamethoxyxanthene.

A mixed solution of the above crude **9** (1.0 g), dimethyl sulfate (3.2 ml), potassium carbonate (4.6 g), and dry acetone (50 ml) was refluxed for 6 h. The reaction mixture was worked up in the usual manner, and the crude product was chromatographed on a column of silica gel with benzene-ethyl acetate (8 : 1) to afford **10** (550 mg, 45%); mp 130–131 °C, IR (KBr) 1710 cm⁻¹ (C=O), ¹H-NMR (CDCl₃) δ 2.44 (6H, s, -COCH₃ × 2), 3.79 (2H, s, -CH₂-), 3.85, 3.87, and 3.96 (each 6H, s, -OMe × 6). Found: C, 61.58; H, 5.86%; M⁺, 446. Calcd for C₂₃H₂₆O₉: C, 61.88; H, 5.87%; M, 446.

4,5-Bis(p-methoxycinnamoyl)-1,2,3,6,7,8-hexamethoxyxanthene (2). To a solution of **10** (50 mg) in methanol (0.3 ml), we added *p*-methoxybenzaldehyde (50 mg) and a 50% aqueous potassium hydroxide solution (0.2 g) at room temperature. The reaction mixture was then warmed to 50–60 °C for 1 h, and the resulting precipitate was recrystallized from methanol to give **2** as colorless needles (48 mg, 63%); mp 157–158 °C, IR (KBr) 1646 cm⁻¹ (C=O), ¹H-NMR (CDCl₃) δ 3.80 (12H, s, -OMe × 4), 3.84 (2H, s, -CH₂-), 3.86 and 3.99 (each 6H, s, -OMe × 4), 6.68 and 7.22 (each 2H, d, *J* = 16.0 Hz, -CH=CH-), 6.76 and 7.32 (each 4H, d, *J* = 8.5 Hz, *p*-substituted phenyl × 2). Found: C, 68.42; H, 5.63%; M⁺, 682. Calcd for C₃₉H₃₈O₁₁: C, 68.61; H, 5.61%; M, 682.

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