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-hexamethoxyxanthene[1)]

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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.

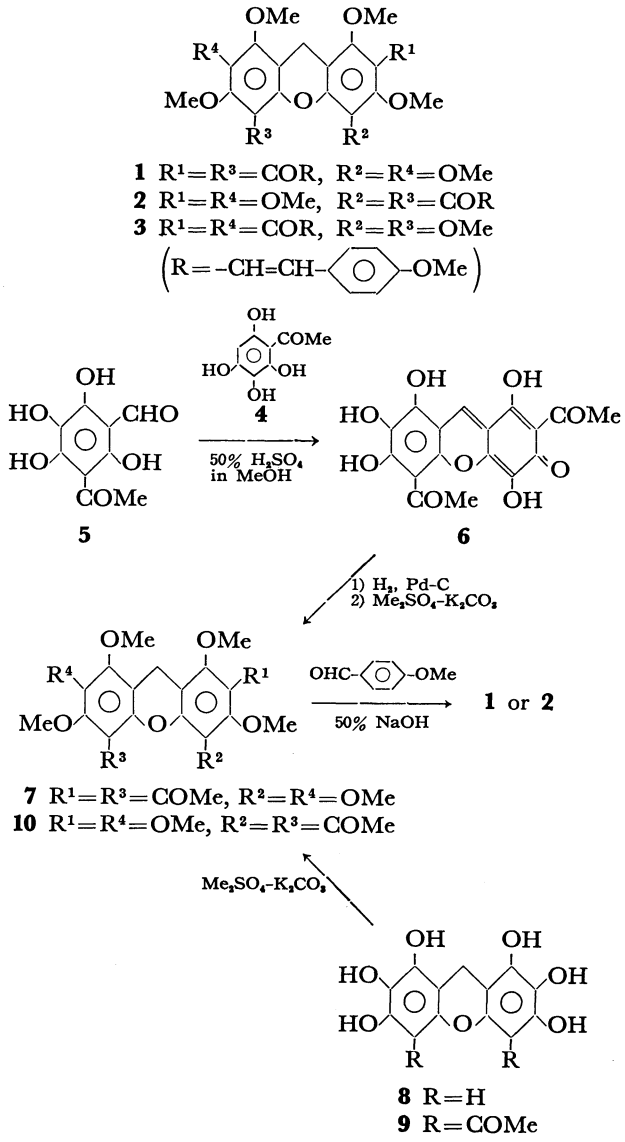
An equimolecular mixture of 2,3,4,6-tetrahydroxyacetophenone (**4**)[2)] and 3-formyl-2,4,5,6-tetrahydroxyacetophenone (**5**), obtained by the formylation of **4**, was refluxed in methanol containing a small amount of 50% sulfuric acid to afford the condensation product (**6**) as dark violet crystals. 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 ^{1}H-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 ^{1}H-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)-1,3,4,5,6,8-hexamethoxyxanthene (**3**), should be assigned for A-2.



1 $R^1=R^3=COR$, $R^2=R^4=OMe$
2 $R^1=R^4=OMe$, $R^2=R^3=COR$
3 $R^1=R^4=COR$, $R^2=R^3=OMe$
$\left(R=-CH=CH-\langle\bigcirc\rangle-OMe\right)$

7 $R^1=R^3=COMe$, $R^2=R^4=OMe$
10 $R^1=R^4=OMe$, $R^2=R^3=COMe$

8 R=H
9 R=COMe

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 ^{1}H-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 chlroride (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, ^{1}H-NMR (DMSO-d_6) δ 2.61 (3H, s, $-COCH_3$), 9.97 (1H, s, -CHO). Found: C, 50.67; H, 3.82%; M$^+$, 212. Calcd for $C_9H_8O_6$: 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), ^{1}H-NMR (DMSO-d_6) δ 2.67 and 2.82 (each 3H, s, $-COCH_3\times2$), 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), ^{1}H-NMR ($CDCl_3$) δ 2.49 and 2.61 (each 3H, s, $-COCH_3\times2$), 3.77 and 3.87 (each 3H, s, $-OMe\times2$), 3.84 and 3.90 (each 6H, s, $-OMe\times4$), 3.97 (2H, s, $-CH_2-$). Found: C, 61.79; H, 5.95%; M$^+$, 446. Calcd for $C_{23}H_{26}O_9$: 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) ot 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), ^{1}H-NMR ($CDCl_3$) δ 3.75 (2H, s, $-CH_2-$), 3.80—4.10 (24H, m, $-OMe\times8$), 6.95—7.60 (12H, m, *p*-substituted cinnamoyl$\times2$). Found: C, 68.63; H, 5.64%; M$^+$, 682. Calcd for $C_{39}H_{38}O_{11}$: C, 68.61; H, 5.61%; M, 682. This compounds 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-benzenetetrol[4] 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-hexahydroxyxanthene.

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). ^{1}H-NMR ($CDCl_3$) δ 2.44 (6H, s, $-COCH_3\times2$), 3.79 (2H, s, $-CH_2-$), 3.85, 3.87, and 3.96 (each 6H, s, $-OMe\times6$). Found: C, 61.58; H, 5.86%; M$^+$, 446. Calcd for $C_{23}H_{26}O_9$: 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), ^{1}H-NMR ($CDCl_3$) δ 3.80 (12H, s, $-OMe\times4$), 3.84 (2H, s, $-CH_2-$), 3.86 and 3.99 (each 6H, s, $-OMe\times4$), 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$\times2$). Found: C, 68.42; H, 5.63%; M$^+$, 682. Calcd for $C_{39}H_{38}O_{11}$: C, 68.61; H, 5.61%; M, 682.

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References

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