Synthesis of 1,2,3,6,7,8-, 1,3,4,5,6,8-, and 1,2,3,5,6,8-Hexamethoxyxanthene

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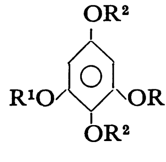
Synopsis. Three hexamethoxyxanthene isomers, 1,2,3,6,7,8-, 1,3,4,5,6,8-, and 1,2,3,5,6,8-hexamethoxyxanthene, were synthesized from the condensation products of 2,6-dimethoxyhydroquinone, 2,5-dimethoxyresorcinol, or 1,2,3,5-benzenetetrol respectively with formaldehyde or ethyl formate.

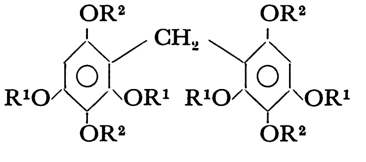
In connection with the synthetic studies of carthamin,[1] the synthesis of three isomers of hexamethoxyxanthene, 1,2,3,6,7,8-, 1,3,4,5,6,8-, and 1,2,3,5,6,8-hexamethoxyxanthene (**4**, **9**, and **12**), was accomplished. Although many methods of preparing xanthenes have been known,[2] no detailed study has been reported on the synthesis of hexahydroxyxanthene derivatives.

1,2,3,6,7,8-Hexamethoxyxanthene (**4**) was obtained by the methylation of 1,3,6,8-tetramethoxy-2,7-xanthenediol (**3**), which had itself been prepared by the dehydration of 2,2′,4,4′-tetramethoxydiphenylmethane-3,3′,6,6′-tetrol (**2**), obtained by the condensation of 2,6-dimethoxyhydroquinone (**1**)[3] with formaldehyde. Two aromatic protons of this symmetrical hexamethoxyxanthene, **4**, appeared as a singlet at 6.33 ppm in its ^{1}H-NMR spectrum.

In a similar manner, we attempted the synthesis of 1,3,4,5,6,8-hexamethoxyxanthene (**9**) from 2,5-dimethoxyresorcinol (**5**),[4] however, the attempt at the dehydration of 3,3′,6,6′-tetramethoxydiphenylmethane-2,2′,4,4′-tetrol (**6**) was unsuccessful.



1 R^1 = Me, R^2 = H
5 R^1 = H, R^2 = Me
13 R^1 = R^2 = H



2 R^1 = Me, R^2 = H
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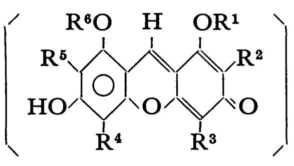
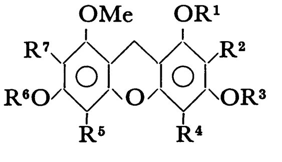


7 R^1 = R^6 = Me, R^2 = R^5 = H, R^3 = R^4 = OMe
10 R^1 = R^3 = R^5 = H, R^2 = R^4 = OMe, R^6 = Me
14 R^1 = R^3 = R^5 = R^6 = H, R^2 = R^4 = OH
15 R^1 = R^3 = R^4 = R^6 = H, R^2 = R^5 = OH



3 R^1 = R^3 = R^6 = Me, R^2 = R^7 = OH, R^4 = R^5 = H
4 R^1 = R^3 = R^6 = Me, R^2 = R^7 = OMe, R^4 = R^5 = H
8 R^1 = Me, R^2 = R^3 = R^6 = R^7 = H, R^4 = R^5 = OMe
9 R^1 = R^3 = R^6 = Me, R^2 = R^7 = H, R^4 = R^5 = OMe
11 R^1 = R^3 = R^4 = R^6 = R^7 = H, R^2 = R^5 = OMe
12 R^1 = R^3 = R^6 = Me, R^2 = R^5 = OMe, R^4 = R^7 = H

Compound **9** and, an unsymmetrical isomer, 1,2,3,5,6,8-hexamethoxyxanthene (**12**), were obtained by the methylation of 1,4,5,8-tetramethoxy-3,6-xanthenediol (**8**) and 2,5,8-trimethoxy-1,3,6-xanthenetriol (**11**), respectively, obtained by the hydrogenation of the condensed-ring compound of 2,5-dimethoxyresorcinol (**5**) with ethyl formate. Two aromatic protons of **9** in the 2- and 7-positions appeared as a singlet at 6.21 ppm, while the 4- and 7-protons of **12** were observed at 6.18 and 6.48 ppm respectively in their ^{1}H-NMR spectra. Consequently, it is thought that the above crude condensed-ring compound was a mixture of 6-hydroxy-1,4,5,8-tetramethoxy- and 1,6-dihydroxy-2,5,8-trimethoxy-3*H*-xanthen-3-one (**7** and **10**).

Compound **12** was also obtained, along with **4**, by the methylation of the unstable hydrogenated products of the crude condensed-ring compound of 1,2,3,5-benzenetetrol (**13**)[5] with ethyl formate. The formation of 1,2,5,6,8- and 1,2,6,7,8-pentahydroxy-3*H*-xanthen-3-one (**14** and **15**) is also assumed in the above condensation.

From these results, significant information regarding the synthetic studies of hexamethoxyxanthene derivatives of carthamin[6] was obtained.

Experimental

All the melting points are uncorrected. 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.

2,2′,4,4′-Tetramethoxydiphenylmethane-3,3′,6,6′-tetrol (2). To a mixed solution of 2,6-dimethoxyhydroquinone (**1**) (3.7 g) and formalin (37%) (1.2 g) in ethanol (20 ml), we added one drop of concd hydrochloric acid. The reaction mixture was allowed to stand overnight, and the resulting colorless needles (**2**) were filtered and washed with water. Mp 180 °C (dec), 2.4 g (63%). Found: C, 57.67; H, 5.80%; M$^+$, 352. Calcd for $C_{17}H_{20}O_8$: C, 57.95; H, 5.72%; M, 352.

1,3,6,8-Tetramethoxy-2,7-xanthenediol (3). A mixed solution of **2** (240 mg) and phosphoryl chloride (100 mg) in dry toluene (140 ml) was refluxed for 2 h. The reaction mixture was then washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo*, and the residue was chromatographed on silica gel. Elution with benzene–ethyl acetate (4 : 1) afforded **3** as light yellow needles; mp 204 °C (38 mg, 17%). Found: C, 60.81; H, 5.45%; M$^+$, 334. Calcd for $C_{17}H_{18}O_7$: C, 61.07; H, 5.43%; M. 334.

1,2,3,6,7,8-Hexamethoxyxanthene (4). A mixed solution of **3** (50 mg), dimethyl sulfate (47 mg), and anhydrous potassium carbonate (65 mg) in dry acetone (6.5 ml) was refluxed for 10 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 (10 : 1) to give **4** (10 mg, 18%) (mp 115—116 °C (from ether–petroleum ether)) as colorless needles. ^{1}H-NMR (CDCl$_3$) δ 3.76 (2H, s, -CH$_2$-), 3.82 (12H, s, -OMe$\times$4), 3.93 (6H, s, -OMe $\times$2), 6.33 (2H, s, C$_{4,5}$-H), Found: C, 62.87; H, 6.12%; M$^+$,

362. Calcd for $C_{19}H_{22}O_7$: C, 62.98; H, 6.07%; M, 362.

3,3′,6,6′-Tetramethoxydiphenylmethane-2,2′,4,4′-tetrol (6). This compound was prepared from 2,5-dimethoxyresorcinol (**5**) and formalin (37%) in a 72% yield by a manner similar to that used for **2**; mp 195 °C. Found: C, 57.89; H, 5.73%; M+, 352. Calcd for $C_{17}H_{20}O_8$: C, 57.95; H, 5.73%; M, 352. The dehydration of this compound by a manner similar to that used for **2** was, however, unsuccessful.

1,4,5,8-Tetramethoxy-3,6-xanthenediol (8) and 2,5,8-Trimethoxy-1,3,6-xanthenetriol (11). Into a solution of 2,5-dimethoxyresorcinol (**5**) (1.0 g) in ethyl formate (8.0 ml), dry hydrogen chloride gas was stirred for 4 h under cooling with ice water. The reaction mixture was then allowed to stand for 2 d at 0 °C. The resulting deep purple-red ppt (850 mg) was filtered and washed with ether. The above condensation product was hydrogenated in ethanol (40 ml) with 5% palladium charcoal (980 mg) for 6 h. The reaction mixture was then filtered, and the solvent was removed *in vacuo*. The residue was chromatographed on a column of silica gel with benzene–ethyl acetate (2 : 1) to give **8** (85 mg, 10%) (mp 183 °C (from ether–petroleum ether)) from the first eluent. Found: C, 60.78; H, 5.41%; M+, 334. Calcd for $C_{17}H_{18}O_7$: C, 61.07; H, 5.43%; M, 334. Compound **11** (400 mg, 49%) (mp 239°C (dec) (from toluene)) was obtained from the second eluent. Found: C, 59.72; H, 4.96%; M+, 320. Calcd for $C_{16}H_{16}O_7$: C, 60.00; H, 5.03%; M, 320.

1,3,4,5,6,8-Hexamethoxyxanthene (9). A mixed solution of **8** (100 mg), dimethyl sulfate (0.12 ml), and anhydrous potassium carbonate (200 mg) in dry acetone (13 ml) was refluxed for 6 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 (10 : 1) to afford **9** (70 mg, 65%); mp 138—139 °C (from ether–petroleum ether). ^{1}H-NMR ($CDCl_3$) δ 3.65 (2H, s, $-CH_2-$), 3.82, 3.88, and 3.94 (each 6H, s, $-OMe\times6$), 6.21 (2H, s, $C_{2,7}$–H). Found: C, 62.60; H, 6.14%; M+, 362. Calcd for $C_{19}H_{22}O_7$: C, 62.98; H, 6.07%; M, 362.

1,2,3,5,6,8-Hexamethoxyxanthene (12). This compound, **12**, was obtained by the methylation of **11** in a manner similar to that used for **9**; mp 120—121 °C (from ether–petroleum ether). ^{1}H-NMR ($CDCl_3$) δ 3.72 (2H, s, $-CH_2-$), 3.82 (9H, s, $-OMe\times3$), 3.85 and 3.87 (each 3H, s, $-OMe\times2$), 3.93 (3H, s, -OMe), 6.18 (1H, s, C_7–H), 6.48 (1H, s, C_4–H). Found: C, 62.94; H, 6.12%; M+, 362. Calcd for $C_{19}H_{22}O_7$: C, 62.98; H, 6.07%; M, 362.

1,2,3,6,7,8- and 1,2,3,5,6,8-Hexamethoxyxanthene (4 and 12) from 1,2,3,5-Benzenetetrol (13). The condensation product (2.6 g) of 1,2,3,5-benzenetetrol (**13**) with ethyl formate, which was obtained in a manner similar to that used for **8**, was hydrogenated in ethanol (240 ml) with 5% palladium charcoal (20 g) for 6 h. The reaction mixture was then filtered, and the solvent was removed *in vacuo* to give an unstable reduction product (1.7 g), a mixture of **14** and **15**. A mixed solution of the above reduction product (100 mg), dimethyl sulfate (0.32 ml), and anhydrous potassium carbonate (460 mg) in dry acetone (15 ml) was refluxed for 6 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 (10 : 1). From the first eluent, **4** (59 mg, 44%) (mp 115—116 °C) was obtained. Similarly, **12** (6.0 mg, 4.6%) (mp 120—121 °C) was obtained from the second eluent.

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