The Synthesis of 3'-Methoxy-2',4,4',6'- and 2'-Methoxy-3',4,4',6'-tetrahydroxychalcone and Some Quinochalcones and a Comparison of Them with Carthamin[1]

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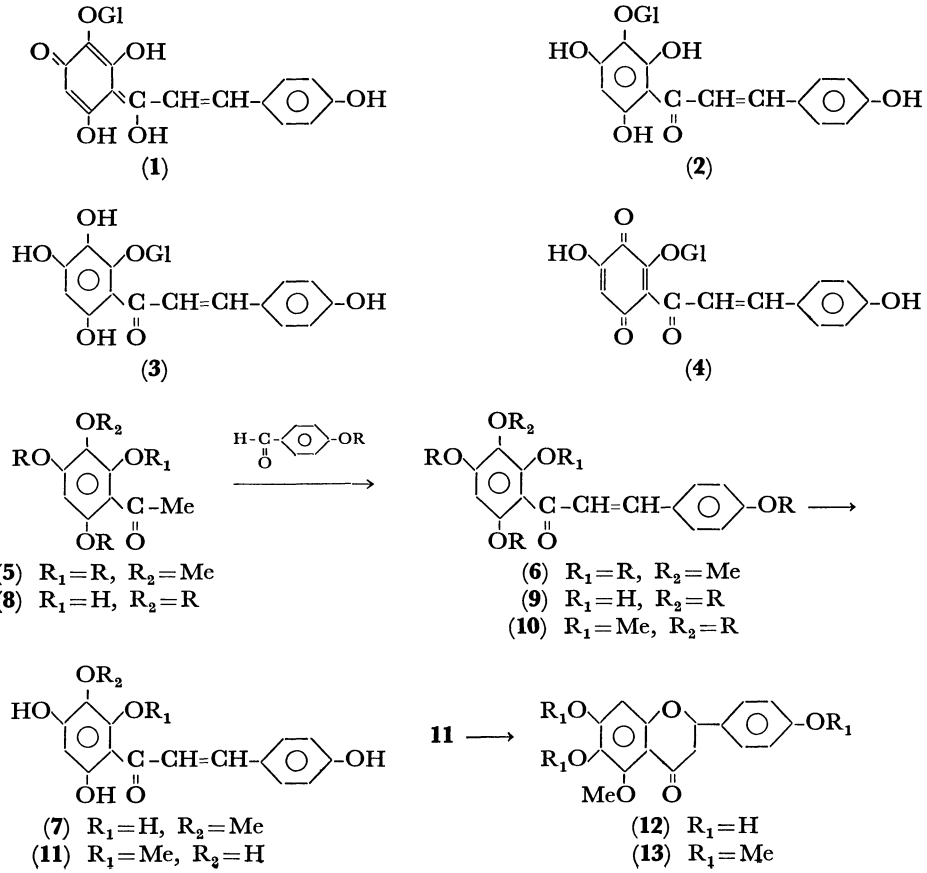
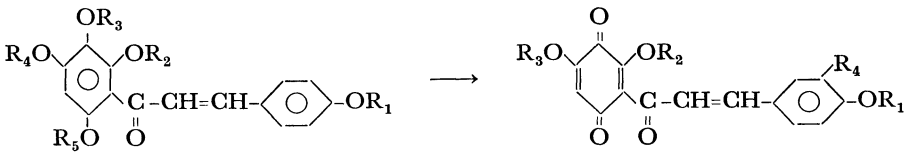
3'-Methoxy-2',4,4',6'- and 2'-methoxy-3',4,4',6'-tetrahydroxychalcone, 2',4,4'-trihydroxy-, 2',4-dihydroxy-4'-methoxy-, and 2'-hydroxy-4,4'-dimethoxy-3',6'-quinochalcone have been synthesized, and their properties have been compared with those of carthamin.

In 1930, Kuroda[2] proposed Structure **1** for carthamin, the red coloring matter of the flowers of the Safflower (*Carthamus tinctorius* L.); she also reported a yellow unstable tautomeric form, isocarthamin (**2**), which is very liable to be converted into the stable carthamin. On the other hand, Seshadri *et al.*[3] reported that the yellow hydroxychalcone (**3**), which is the main component of the flowers, should be called carthamin, while they gave the red pigment which was conventionally called "carthamin" by Kuroda, the constitution of the quinochalcone, carthamone (**4**); they also reported that **4** was obtained by the oxidation of **3** in the presence of peroxidase.

In connection with the synthetic studies of carthamin, we have reported the synthesis of 2',3',4,4',6'-pentahydroxychalcone (**14**),[4] corresponding to the aglycon of **2** or **3**, and its isomerization into 4',5,6,7- and 4',5,7,8-tetrahydroxyflavanone (carthamidin and isocarthamidin).[5] In this paper, the syntheses of some analogs of **2**, **3**, and **4**, *i.e.*, 3'-methoxy-2',4,4',6'- and 2'-methoxy-3',4,4',6'-tetrahydroxychalcone (**7** and **11**), 2',4,4'-trihydroxy-, 2',4-dihydroxy-4'-methoxy-, and 2'-hydroxy-4,4'-dimethoxy-3',6'-quinochalcone (**17**, **21**, and **23**), and a comparison of their properties with those of carthamin will be described.

The condensation of 3-methoxy-2,4,6-tris(methoxymethoxy)acetophenone (**5**) with *p*-(methoxymethoxy)-benzaldehyde afforded 3'-methoxy-2',4,4',6'-tetrakis-(methoxymethoxy)chalcone (**6**), which was then hydrolyzed with dilute hydrochloric acid in methanol to give **7** as yellow crystals. Similarly, 2'-methoxy-3',4,4',6'-tetrahydroxychalcone (**11**) was obtained by the hydrolysis of 2'-methoxy-3',4,4',6'-tetrakis(methoxymethoxy)chalcone (**10**), prepared by the methylation of the condensation product (**9**) of 2-hydroxy-3,4,6-tris(methoxymethoxy)acetophenone (**8**) with *p*-(methoxymethoxy)benzaldehyde. The structures of these chalcones were identified by elemental analyses and by studies of their UV, IR, and PMR spectra. The structure of **11** was further confirmed by its conversion





(**14**) $R_1=R_2=R_3=R_4=R_5=H$
(**15**) $R_1=R_2=R_3=R_4=R_5=CH_2OMe$
(**18**) $R_1=CH_2OMe$, $R_2=R_3=R_4=R_5=Me$
(**19**) $R_1=R_2=R_3=R_4=R_5=Me$
(**22**) $R_1=H$, $R_2=R_3=R_4=R_5=Me$

(**16**) $R_1=R_3=CH_2OMe$, $R_2=R_4=H$
(**17**) $R_1=R_2=R_3=R_4=H$
(**20**) $R_1=CH_2OMe$, $R_2=R_4=H$, $R_3=Me$
(**21**) $R_1=R_2=R_4=H$, $R_3=Me$
(**23**) $R_1=R_3=Me$, $R_2=R_4=H$
(**24**) $R_1=R_2=H$, $R_3=Me$, $R_4=NO_2$

($R=CH_2OMe$)

into 5-methoxy-4′,6,7-trihydroxyflavanone (**12**) with acid. The trimethyl ether (**13**) of **12** was completely indentical with an authentic sample of 4′,5,6,7-tetramethoxyflavanone.[6]

2′,4,4′-Trihydroxy-3′,6′-quinochalcone (**17**) was obtained by the oxidation of **14**[4] with silver oxide in ether, or by the demethoxymethylation of 2′-hydroxy-4,4′-bis(methoxymethoxy)-3′,6′-quinochalcone (**16**), prepared by the nitric acid oxidation of 2′,3′,4,4′,6′-pentakis(methoxymethoxy)chalcone (**15**)[4] in acetic acid containing 6 M hydrochloric acid. Since this chalcone (**17**) was unstable in solution, and since we failed in our attempt at methylation in a usual way, its mono and dimethyl ethers were prepared by the following method. 2′,4-Dihydroxy-4′-methoxy-3′,6′-quinochalcone (**21**) was obtained by the demethoxymethylation of 2′-hydroxy-4′-methoxy-4-methoxymethoxy-3′,6′-quinochalcone (**20**), prepared by the nitric acid oxidation of 4-methoxymethoxy-2′,3′,4′,6′-tetramethoxychalcone (**18**), which had itself been obtained by the condensation of 2,3,4,6-tetramethoxyacetophenone[4] with *p*-(methoxymethoxy)benzaldehyde. Similarly, 2′-hydroxy-4,4′-dimethoxy-3′,6′-quinochalcone (**23**) was obtained by the oxidation of 2′,3′,4,4′,6′-pentamethoxychalcone (**19**)[4] with nitric acid in acetic acid. On the other hand, the direct nitric acid oxidation of 2′,3′,4′,6′-tetramethoxy-4-hydroxychalcone (**22**), itself prepared by the demethoxymethylation of **18**, gave nitroquinochalcone, 2′,4-dihydroxy-4′-methoxy-3-nitro-3′,6′-quinochalcone (**24**). The structures of these quinochalcones were determined by studies of their UV, IR, and PMR spectra and by elemental analyses.

The electronic spectra of these synthetic analogs (**7**, **11**, and **17**) and carthamin are shown in Fig. 1. Since a tautomerism was expected between carthamin (**1**) and isocarthamin (**2**), as was described at the beginning, the absorption spectrum of **7** was expected to be similar to that of carthamin, in fact, however, these two spectra did not resemble each other at all. Actually, the **7** chalcone is a stable compound and does not show any unstable behavior such as carthamin does. Further, carthamin showed a characteristic absorption band at 520 nm in its electronic spectrum, but the synthetic quinochalcones do not exhibit absorption maxima in such a long-wavelength region. From these results, it is thought that the structures of the red pigment proposed by Kuroda or Seshadri are not reasonable and that carthamin must have a longer conjugated system.

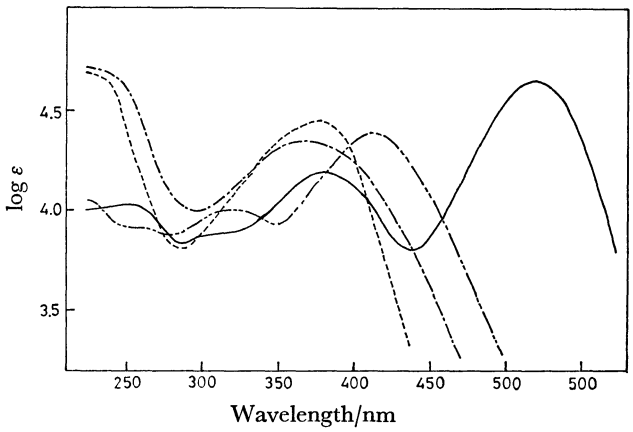


Fig. 1. The electronic spectra of **7** (----), **11** (——-), **17** (———-), and carthamin (——) in ethanol.

Experimental

All the melting points are uncorrected. The UV and IR spectra were recorded with a Hitachi 135 spectrophotometer and a Hitachi EPI-S2 spectrophotometer respectively. The PMR spectra were measured with a Hitachi R-22 spectrometer (90 MHz), using tetramethylsilane as the internal standard.

3-Methoxy-2,4,6-tris(methoxymethoxy)acetophenone (**5**). Into a solution of 3-methoxy-2,4,6-trihydroxyacetophenone[7] (2.0 g, mp 169—170 °C, lit,[7] mp 168 °C) in 37 ml of absolute ethanol we vigorously stirred a one-fourth volume of a solution of sodium (3.3 g) in 53 ml of absolute ethanol under a nitrogen atmosphere and under cooling with ice-cold water. After 30 s, a one-fourth volume of chloromethyl methyl ether (11.5 g) was stirred into the above solution over a 5-min interval at 40 °C; this operation was repeated three times under the same conditions. After the addition had been completed, the reaction mixture was evaporated *in vacuo* and the residue was poured into water and extracted with ether. The ether layer was washed with a 5% aqueous $NaHCO_3$ solution and water. The ether was evaporated to give an oily residue, which was then chromatographed over silica gel. Elution with benzene–ethyl acetate (4:1) afforded **5** (1.1 g, 33%) as a light yellow viscous oil, which was used immediately in the subsequent reaction.

3′-Methoxy-2′,4,4′,6′-tetrakis(methoxymethoxy)chalcone (**6**). Into a mixed solution of **5** (0.5 g) and *p*-(methoxymethoxy)-benzaldehyde (0.4 g) in 11 ml of methanol we stirred a 50% aqueous sodium hydroxide solution (5.5 ml) at room temperature. After it had stood overnight, the mixture was poured into cold water and extracted with ether, and then

the ether layer was washed with water. The evaporation of the solvent gave an oily residue, which was then chromatographed over silica gel. Elution with benzene–ethyl acetate (4:1) afforded **6** (0.6 g, 83%). UV (EtOH) λ_{max} 328 nm (log ε=4.38); IR ($CHCl_3$) 1630 cm^{-1} (C=O); PMR ($CDCl_3$) δ 3.41, 3.43, 3.50, and 3.58 (each 2H, s, $-CH_2-\times4$), 3.89 (3H, s, -OMe), 5.12, 5.17, 5.24, and 5.29 (each 3H, s, $-CH_3\times4$), 6.87 (1H, s, $C_{5'}$–H), 7.10 (2H, d, J=8.5 Hz, $C_{3,5}$–H), 7.56 (2H, d, J=8.5 Hz, $C_{2,6}$–H), 6.98 (1H, d, J=16.0 Hz, C_α–H), 7.45 (1H, d, J=16.0 Hz, C_β–H), Found: C, 59.87; H, 6.44%. Calcd for $C_{24}H_{30}O_{10}$: C, 60.24; H, 6.32%.

3'-Methoxy-2',4,4',6'-tetrahydroxychalcone (7). A mixture of **6** (0.4 g), 6 M hydrochloric acid, and methanol (17 ml) was refluxed for 30 s. After cooling, the reaction mixture was poured into 30 ml of cold brine and extracted with ether. The ether layer was dried over anhydrous Na_2SO_4 and concentrated to about 10 ml *in vacuo*. A small quantity of petroleum ether was added to the concentrated solution to give crude **7**, which was then chromatographed over silica gel. Elution with CCl_4–ether–acetic acid (20:10:1) afforded **7** (70 mg, 28%) as yellow crystals; mp 169—171 °C. UV (EtOH) λ_{max} 377 nm (log ε=4.47); IR (KBr) 1620 cm^{-1} (C=O); PMR (acetone-d_6) δ 3.78 (3H, s, -OMe), 6.00 (1H, s, $C_{5'}$–H), 6.92 (2H, d, J=8.5 Hz, $C_{3,5}$–H), 7.57 (2H, d, J=8.5 Hz $C_{2,6}$–H), 7.76 (1H, d, J=16.0 Hz, C_α–H), 8.13 (1H, d, J=16.0 Hz, C_β–H), 8.93, 9.24, 11.10, and 12.18 (each 1H, s, $-OH\times4$). Found: C, 63.15; H, 4.72%. Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.64%.

2-Hydroxy-3,4,6-tris(methoxymethoxy)acetophenone (8). To a solution of 2,3,4,6-tetrahydroxyacetophenone[4] (6.0 g) in 150 ml of absolute ethanol, we vigorously stirred a one-fourth volume of a solution of sodium (8.8 g) in 140 ml of absolute ethanol under a nitrogen atmosphere, and under cooling with ice-cold water. After 30 s, a one-fourth volume of chloromethyl methyl ether (31 g) was stirred into the above solution over a 5-min interval at 40 °C; this operation was repeated three times under the same conditions. After the addition had been completed, the reaction mixture was worked up in a manner similar to that used in the preparation of 3-methoxy-2,4,6-tris(methoxymethoxy)acetophenone (**5**) described above. Elution with benzene–ethyl acetate (4:1) afforded **8** (1.34 g, 13%) as a yellow oil. IR ($CHCl_3$) 1620 cm^{-1} (C=O); PMR ($CDCl_3$) δ 2.68 (3H, s, -Ac), 3.55 (6H, s, $-CH_3\times2$), 3.66 (3H, s, $-CH_3$), 5.13 (2H, s, $-CH_2-$), 5.29 (4H, s, $-CH_2-\times2$), 6.51 (1H, s, C_5–H), 13.80 (1H, s, -OH). Found: C, 53.46; H, 6.44%. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.33%.

2'-Methoxy-3',4,4',6'-tetrahydroxychalcone (11). Into a mixed solution of **8** (1.5 g) and *p*-(methoxymethoxy)benzaldehyde (1.2 g) in methanol (8 ml) we stirred a 50% aqueous sodium hydroxide solution (4 ml) at room temperature. After standing overnight, the reaction mixture was poured into cold 10% acetic acid and extracted with ether. The evaporation of the solvent gave an oily residue, which was then chromatographed over silica gel. Elution with benzene–ethyl acetate (3:1) afforded 2'-hydroxy-3',4,4',6'-tetrakis(methoxymethoxy)chalcone (**9**) (1.66 g, 76%) as yellow crystals; mp 74—76 °C. UV (EtOH) λ_{max} 367 nm (log ε=4.42); IR (KBr) 1622 cm^{-1} (C=O); PMR ($CDCl_3$) δ 3.56 and 3.73 (each 3H, s, $-CH_3\times2$), 3.60 (6H, s, $-CH_3\times2$), 5.22 and 5.30 (each 2H, s, $-CH_2-\times2$), 5.36 (4H, s, $-CH_2-\times2$), 6.56 (1H, s, $C_{5'}$–H), 7.16 (2H, d, J=8.5 Hz, $C_{3,5}$–H), 7.65 (2H, d, J=8.5 Hz, $C_{2,6}$–H), 7.89 (2H, s, $C_{\alpha,\beta}$–H), 13.80 (1H, s, -OH). This chalcone, **9**, was methylated with dimethyl sulfate–potassium carbonate in acetone, and the resulting oily product was chromatographed over silica gel. Elution with benzene–ethyl acetate (4:1) afforded 2'-methoxy-3',4,4',6'-tetrakis(methoxymethoxy)chalcone (**10**) (74%) as an unstable oil, which was used immediately in the subsequent reaction.

A mixture of the above chalcone, **10** (640 mg), and 6 M hydrochloric acid (4.5 ml) in 11 ml of methanol was refluxed for 1.5 min. After cooling, the reaction mixture was poured into 60 ml of cold brine and extracted with ether. The solvent was evaporated *in vacuo*, and the residue was recrystallized from dilute methanol to give **11** (280 mg, 69%) as bright yellow needles; mp 190—192 °C. UV (EtOH) λ_{max} 368 nm (log ε=4.36); IR (KBr) 1620 cm^{-1} (C=O); PMR (DMSO-d_6) δ 3.76 (3H, s, -OMe), 6.15 (1H, s, $C_{5'}$–H), 6.86 (2H, d, J=8.7 Hz, $C_{3,5}$–H), 7.57 (2H, d, J=8.7 Hz, $C_{2,6}$–H), 7.62 (2H, s, $C_{\alpha,\beta}$–H), 8.23, 10.00, 10.40, and 12.80 (each 1H, s, $-OH\times4$). Found: C, 63.16; H, 4.65%. Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.64%.

5-Methoxy-4',6,7-trihydroxyflavanone (12). A mixture of **11** (60 mg) and 6 M hydrochloric acid (1.5 ml) in 8 ml of methanol was refluxed for 8 h. The reaction mixture was then evaporated *in vacuo*, and the residue was extracted with ethyl acetate. The evaporation of the solvent gave a crude product, which was subsequently chromatographed over silica gel. Elution with benzene–ethyl acetate–acetic acid (30:10:1) afforded **12** (26 mg, 43%) as light yellow crystals; mp 232—234 °C. UV (EtOH) λ_{max} 287 nm (log ε=4.16) and 350 nm (log ε=3.67); IR (KBr) 1650 cm^{-1} (C=O); PMR (DMSO-d_6) δ 2.54 (1H, q, J=17.0 and 2.5 Hz, C_3–H), 2.94 (1H, q, J=17.0 and 13.3 Hz, C_3–H), 5.29 (1H, q, J=13.3 and 2.5 Hz, C_2–H), 3.76 (3H, s, -OMe), 6.22 (1H, s, C_8–H), 6.85 (2H, d, J=8.5 Hz, $C_{3',5'}$–H), 7.32 (2H, d, J=8.5 Hz, $C_{2',6'}$–H), 8.25, 9.41, and 10.07 (each 1H, s, $-OH\times3$). Found: C, 63.46; H, 4.65%. Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.64%. The methylation of this compound with dimethyl sulfate–potassium carbonate in acetone afforded 4',5,6,7-tetramethoxyflavanone (**13**), which was completely identical with an authentic sample.[6]

2',4,4'-Trihydroxy-3',6'-quinochalcone (17). A mixture of **14**[4] (100 mg), silver oxide (200 mg), and magnesium sulfate (200 mg) in 5 ml of dry ether was stirred for 4 h at room temperature. The reaction mixture was then filtered, and the filtrate was evaporated. The residue was chromatographed over silica gel with toluene–ethyl formate–formic acid (5:2:1) to give crude products. Recrystallization from acetic acid gave **17** (3 mg) as orange needles; mp 234—236 °C. UV (EtOH) λ_{max} 260 nm (log ε=3.90), 310 nm (log ε=3.97), and 412 nm (log ε=4.41); IR (KBr) 1690, 1635, and 1605 cm^{-1} (C=O). Found: C, 62.20; H, 3.80%; M^+, 286. Calcd for $C_{15}H_{10}O_6$: C, 62.94; H, 3.52%; M, 286.

2'-Hydroxy-4,4'-bis(methoxymethoxy)-3',6'-quinochalcone (16). Into a mixed solution of 2',3',4,4',6'-pentakis(methoxymethoxy)chalcone (**15**)[4] (1.0 g), acetic acid (4 ml), and ether (4 ml) we added 1 ml of nitric acid (d=1.38) under cooling with ice-cold water; the reaction mixture was then kept at 0—5 °C for 10 h. The resulting crystals were filtered and recrystallized from acetic acid–ether to afford **16** (230 mg, 30%); mp 142—143 °C. UV (EtOH) λ_{max} 266, 294, and 406 nm; IR (KBr) 1700, 1630, and 1600 cm^{-1} (C=O); PMR ($CDCl_3$) δ 3.74 (6H, s, $-CH_3\times2$), 5.23 and 5.26 (each 2H, s, $-CH_2-\times2$), 6.40 (1H, s, $C_{5'}$–H), 7.08 (2H, d, J=8.5 Hz, $C_{3,5}$–H), 7.66 (2H, d, J=8.5 Hz, $C_{2,6}$–H), 8.05 (1H, d, J=16.0 Hz, C_α–H), 8.28 (1H, d, J=16.0 Hz, C_β–H), 17.76 (1H, s, -OH). Found: C, 60.67; H, 5.02%. Calcd for $C_{19}H_{18}O_8$: C, 60.96; H, 4.85%.

The demethoxymethylation of **16** by warming at 50—60 °C in acetic acid containing 6 M hydrochloric acid af-

forded a small amount of **17**.

*4-Methoxymethoxy-2',3',4',6'-tetramethoxychalcone (**18**).* Into a mixture of 2,3,4,6-tetramethoxyacetophenone[4] (480 mg) and *p*-(methoxymethoxy)benzaldehyde (400 mg) in 5 ml of methanol we added 5 ml of a 50% aqueous sodium hydroxide solution; the reaction mixture was then left to stand over 2 nights at room temperature. The reaction mixture was subsequently worked-up in a manner similar to that of **9**. The resulting products were chromatographed over silica gel with benzene–ethyl acetate (4:1) to give **18** as a light yellow oil (760 mg, 98%). Found: C, 64.36; H, 6.44%; M^+, 388. Calcd for $C_{21}H_{24}O_7$: C, 64.93; H, 6.23%; M, 388.

*2'-Hydroxy-4-methoxymethoxy-4'-methoxy-3',6'-quinochalcone (**20**).* To a mixture of **18** (200 mg) and acetic acid (1.5 ml) in 1.5 ml of ether we added 0.2 ml of nitric acid (d=1.38), after which the reaction mixture was left to stand overnight in a refrigerator. The resulting product was recrystallized from acetic acid–ether to afford **20** (45 mg, 25%); mp 155—156 °C. IR (KBr) 1702, 1665, and 1620 cm^{-1} (C=O). Found: C, 62.36; H, 4.88%. Calcd for $C_{18}H_{16}O_7$: C, 62.79; H, 6.48%.

*2',4-Dihydroxy-4'-methoxy-3',6'-quinochalcone (**21**).* To a solution of **20** (100 mg) in 3 ml of acetic acid we added 0.5 ml of 6 M hydrochloric acid, after which the mixture was warmed at 40—50 °C for 3 min. After cooling, the resulting crude product was recrystallized from acetic acid to afford **21** (55 mg, 63%); mp 252—254 °C. UV (EtOH) λ_{max} 264, 300, and 414 nm; IR (KBr) 1706, 1630, and 1600 cm^{-1} (C=O); PMR (DMSO-d_6) δ 3.82 (3H, s, –OMe), 6.18 (1H, s, $C_{5'}$–H), 6.84 (2H, d, J=8.5 Hz, $C_{3,5}$–H), 7.58 (2H, d, J=8.5 Hz, $C_{2,6}$–H), 7.92 (2H, s, $C_{\alpha,\beta}$–H), 10.30 (bs, –OH). Found: C, 63.60; H, 4.19%. Calcd for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03%.

*2'-Hydroxy-4,4'-dimethoxy-3',6'-quinochalcone (**23**).* To a solution of 2',3',4,4',6'-pentamethoxychalcone (**19**)[4] (150 mg) in 1.5 ml of acetic acid we added 0.15 ml of nitric acid (d=1.42); the reaction mixture was then left to stand overnight in a refrigerator. The resulting product was filtered and recrystallized from acetic acid to afford **23** (55 mg, 42%); mp 188—189 °C. UV ($CHCl_3$) λ_{max} 261, 297, and 412 nm; IR (KBr) 1714, 1658, and 1630 cm^{-1} (C=O); PMR (DMSO-d_6) δ 3.83 (6H, s, –OMe×2), 6.26 (1H, s, $C_{5'}$–H), 7.08 (2H, d, J=8.5 Hz, $C_{3,5}$–H), 7.71 (2H, d, J=8.5 Hz, $C_{2,6}$–H), 8.00 (2H, s, $C_{\alpha,\beta}$–H). Found: C, 64.96; H, 4.46%. Calcd for $C_{17}H_{14}O_6$: C, 64.82; H, 4.49%.

*2',4-Dihydroxy-4'-methoxy-3-nitro-3',6'-quinochalcone (**24**).* This chalcone was obtained by the oxidation of 4-hydroxy-2',3',4',6'-tetramethoxychalcone (**22**) (mp 120—121 °C), which had been prepared by the demethoxymethylation of **18** in a manner similar to that described above. Orange plates from acetic acid; mp 202—204 °C (39%). UV ($CHCl_3$) λ_{max} 277 nm ($\log\varepsilon$=4.32) and 382 nm ($\log\varepsilon$=4.54); PMR (DMSO-d_6) δ 3.84 (3H, s, –OMe), 6.19 (1H, s, $C_{5'}$–H), 7.15 (1H, d, J=8.5 Hz, C_5–H), 7.90 (1H, q, J=8.5 and 2.0 Hz, C_6–H), 7.88 (2H, s, $C_{\alpha,\beta}$–H), 8.20 (1H, d, J=2.0 Hz, C_2–H). Found: C, 55.35; H, 3.26; N, 4.31%. Calcd for $C_{16}H_{11}O_8N$: C, 55.66; H, 3.21; N, 4.06%.

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