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THE PHENOLIC OXIDATION OF A β-METHYLCHALCONE

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Abstract—The phenolic oxidation of 2',4-dihydroxy-4'-methoxy-β-methylchalcone using alkaline potassium ferricyanide gives an aurone rather than an isoflavone. This result is discussed in the context of current theories regarding the biosynthesis of flavonoid and isoflavonoid compounds.

We have previously shown that oxidation of 2',4 - dihydroxy - 4' - methoxychalcone (**1**) with alkaline potassium ferricyanide gives the flavone (**2**),[1] and this reaction was considered to be an *in vitro* analogy for the biosynthesis of flavonoids. In an attempt to assess the possible role of phenolic oxidation in the formation of isoflavones[2] we have carried out a similar oxidation of the β-methylchalcone (**3**) in which flavone formation is precluded by the presence of the β-Me group.

The β-methylchalcone (**3**) was prepared by conjugate addition of lithium dimethyl cuprate to 2',4-dibenzyloxy-4'-methoxychalcone (**4**) followed by reaction of the enolate so formed with phenylselenenyl bromide which gave an α-phenylselenenyl ketone. Oxidation followed by elimination of the selenoxide afforded the dibenzyloxy-β-methylchalcone (**5**), which on treatment with boron trichloride gave the required β-methylchalcone (**3**). Oxidation of **3** with alkaline potassium ferricyanide gave a product which was rapidly identified as an aurone on the basis of its ^{13}C NMR[3,4] and other spectral data (Experimental). The precise structure of the product (**6**) was established by carrying out an independent synthesis of the β-methyl aurone by acid-catalysed condensation of 6-methoxybenzofuran-3-one with 4-hydroxyacetophenone.

The formation of an aurone by phenolic oxidation of a chalcone is not unduly surprising since it has been previously shown that some chalcones (e.g. **7**, **8**) can be oxidised by potassium ferricyanide to give aurones[5] and indeed such reactions represent yet another facet of the overall scheme presented to account for flavonoid biosynthesis.[1]

In order to demonstrate the role of phenolic oxidation in the conversion of **3** into **6** the 4-methoxy-β-methylchalcone (**9**) was required. This was prepared by acylation of 1,3-dimethoxybenzene by the β-methylcinnamic acid (**10**) using polyphosphoric acid followed by selective demethylation of the 2'-OMe group by boron trichloride. Treatment of **9** with alkaline potassium ferricyanide under identical conditions to those used for the oxidation of **3** gave no trace of the corresponding aurone. Thus the oxidation of **3** and **6** does involve phenolic oxidation of the 4-phenolic group, as previously postulated.

Unfortunately these results fail to provide an *in vitro* analogy to the *in vivo* phenolic oxidation of chalcones, with rearrangement, to give isoflavones.[1,2] Under our conditions the intermediate diradical undergoes direct intramolecular coupling to yield aurone (**6**) rather than cyclisation followed by rearrangement to give the desired isoflavone (**11**).

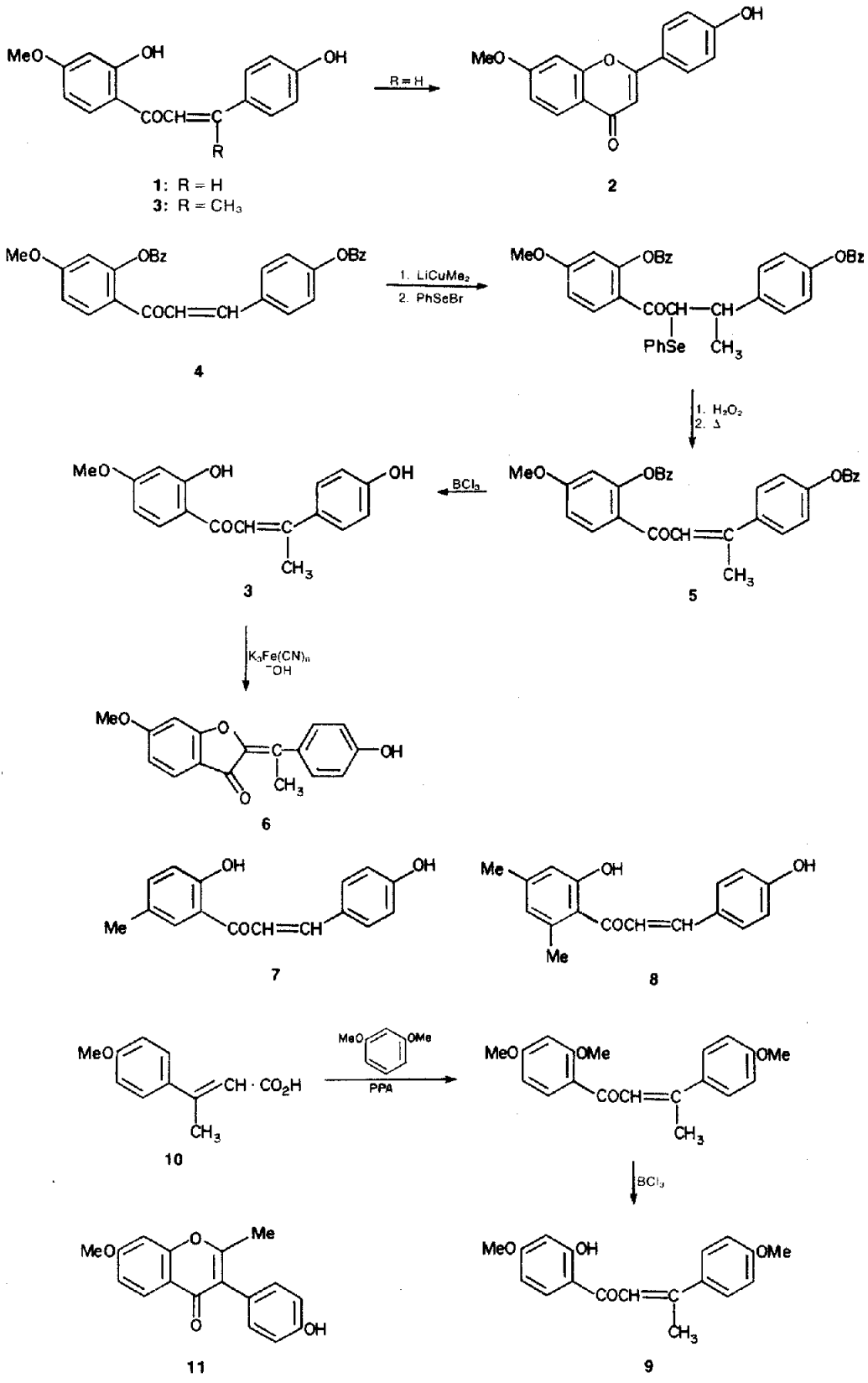
EXPERIMENTAL

IR and UV spectra were recorded using Perkin-Elmer 257 and 402 spectrophotometers respectively. Mass spectra were obtained using an AEI MS9 double-focussing spectrometer, and ^1H and ^{13}C NMR spectra were obtained using Varian HA-100 and XL-100 instruments, the latter being coupled to a 620L-100 computer.

2',4-Dibenzyloxy-4'-methoxychalcone (**4**). 2 - Benzyloxy - 4 methoxyacetophenone (12.8 g) and 4-benzyloxy-benzaldehyde (10.1 g) were dissolved in the minimum quantity of cold (5°) MeOH. An aqueous soln of KOH (13 g; 60% w/w) was added and any solid ppt redissolved by adding MeOH. After 24 hr a light yellow solid separated out and was removed by filtration and washed with cold MeOH. Recrystallisation from MeOH gave the desired product (50% yield), m.p. 145–8°(lit.[6] 146°) $\lambda_{max}^{CH_2Cl_2}$ 235 and 345 nm. γ_{max}^{KBr} 1650, 1623 and 1607 cm^{-1}. *m/e* 450 (100%), 360(24), 359(73), 331(22), 273(21), 254(16), 253(50), 240(16), 197(39), 154(10), 152(10), 151(88). τ($CDCl_3$): 2.13 d (5Hz, 1H), 2.4–3.0 m (14H), 3.18 d (9Hz, 2H), 3.42 m (2H), 4.91 s (2H), 4.94 s (2H), 6.17 s (3H). Accurate mass measurement: *m/e* 450.1831 ($C_{30}H_{26}O_4$ requires: 450.18310).

2',4-Dibenzyloxy 4'-methoxy-β-methylchalcone (**5**). Cuprous iodide (253 mg) was dried and placed in a 3-necked flask with anhyd ether (50 ml). MeLi (2.67 mmoles) in ether was added and the mixture maintained at 0°. A yellow ppt (CuMe) formed initially but after all the MeLi had been added the soln was colourless. 2',4 - Dibenzyloxy - 4' - methoxychalcone (450 mg) was added as a solid by rotating a sealed side-arm and the mixture allowed to stir at 0° in a N_2 atmosphere for 10 min. Phenylselenyl bromide, prepared from bromine (0.054 ml) in THF (2 ml) and diphenyldiselenide (314 mg), was added dropwise and the mixture left to stir for 30 min at room temp. after which water (2 ml), AcOH (0.3 ml) and H_2O_2 (10 equiv) were added. Sat $NaHCO_3$ aq (50 ml) was then added and the organic layer separated and dried over $MgSO_4$. Recrystallisation of the crude product from diethyl ether gave the required β-methylchalcone (55% yield), m.p. 125–6°. λ_{max}^{EtOH} 233(20,523), 283(10,708) and 322(14,277) nm. $\gamma_{C=O}^{KBr}$ 1648 and 1610 cm^{-1}. *m/e* 464 (6%), 449(5), 373(13), 359(14), 241(12), 211(18), 165(17), 151(43), 102(16), 91(100). τ($CDCl_3$): 2.25 d (10Hz, 1H), 2.6–3.0 m(13H), 3.27 d (8Hz, 2H), 3.52 m (2H), 5.04 s (4H), 6.28 s (3H), 7.53 s (3H) (Found: C,79.98; H,6.02. $C_{31}H_{30}O_4$ requires: C, 80.17; H, 6.03%.

2',4-Dihydroxy-4'-methoxy-β-methylchalcone (**3**). Chalcone **5** (300 mg) was dissolved in dichloromethane (100 ml) at −78° and excess BCl_3/CH_2Cl_2 (2 ml, 1.25 mmoles) was added *via* a syringe under N_2. The mixture was stirred and allowed to warm to room temp. when it was quenched in water and extracted with EtOAc. Purification by thick layer chromatography on silica gel using CH_2Cl_2 gave the required dihydroxy-chalcone (150 mg, 80% yield), m.p. 103–5°. $\lambda_{max}^{CH_2Cl_2}$ 350 nm. *m/e* 284 (10%), 283(8), 269(100), 191(12), 151(69), 134(16), 121(25). Accurate mass measurements: *m/e* 284.1049 ($C_{17}H_{16}O_4$ requires: 284.10485), *m/e* 269.0814 ($C_{16}H_{13}O_4$ requires: 269.08138). τ($CDCl_3$): 0.49 s (1H, D_2O exch.), 2.30 d (10Hz, 1H), 2.58 d (8Hz, 2H), 2.97 br.s (1H), 3.16 d(8Hz, 2H), 3.62 m (2H), 6.25 s (3H), 7.50 br.s (3H).



Oxidation of 2',4-dihydroxy-4'-methoxy-β-methylchalcone. Chalcone **3** (26 mg) was dissolved in MeOH (0.6 ml) and 2N NaOH (1 ml) added, giving a red soln. Potassium ferricyanide (70 mg) in water (1 ml) was added and the mixture left for 10 min at room temp. Quenching in excess water and acidification to pH4 with glacial AcOH gave a yellow ppt which was recrystallised from aqueous EtOH to give **6** (10 mg, 40%), m.p. 185–6°. λ_{max}^{EtOH} 259(13,883), 290(10,846) and 368(18,438) nm. γ_{max}^{KBr} 1635,

1610 cm^{-1}. *m/e* 282(95%), 218(100), 151(32), 121(24). Accurate mass measurements: *m/e* 282.0892 ($C_{17}H_{14}O_4$ requires: 282.0892) and *m/e* 281.0814 ($C_{17}H_{13}O_4$ requires: 281.08138). τ($CDCl_3$/$(CD_3)_2SO$): 0.07 br.s (1H, D_2O exch.), 3.13 d (9Hz, 2H), 2.41 d (9Hz, 2H), 2.43 d (10Hz, 1H), 3.36 m(2H), 6.20 s(3H), 7.36 s(3H). (For ^{13}C NMR, see Ref. 4.) (Found: C,72.39: H,5.34. $C_{17}H_{14}O_4$ requires: C, 72.33; H, 5.00%).

4'-Acetoxy-6-methoxy-β-methylaurone. Aurone **6** (10 mg) was dissolved in pyridine (1 ml) Ac_2O (0.1 ml) added, and the mixture left at room temp. for 12 hr. Quenching in water and extraction with CH_2Cl_2 gave the acetate. γ_{max}^{KBr} 1760, 1683, 1640 and 1600 cm^{-1}. $\lambda_{max}^{CH_2Cl_2}$ 247 and 333 nm. *m/e* 324(47%), 282(91), 281(100), 272(56), 223(21), 151(84), 149(44), 121(40). τ($CDCl_3$): 2.31 d (9Hz, 2H), 2.33 d (9Hz, 1H), 2.93 d (9Hz, 2H), 3.31 dd (2,9Hz, 1H), 3.41 d (2Hz, 1H). 6.16 s (3H), 7.33 s (3H), 7.69 s (3H).

6-Methoxybenzofuran-3-one. 3-Methoxyphenoxyacetic acid (1 g) was added with stirring to polyphosphoric acid (25 g) at 100°. After 5 min at this temp. the mixture was allowed to cool and after a further 5 min the mixture was poured onto ice. The solid which formed was dissolved in $CHCl_3$ and extracted with $NaHCO_3$ aq and water. Evaporation of the $CHCl_3$ and recrystallisation from EtOH gave the benzofuranone (0.5 g), m.p. 114–6° (lit.[7] 122.4°). τ($CDCl_3$): 2.45 d (10 Hz, 1H), 3.37 m (2H), 5.42 s (2H), 6.15 s (3H). γ_{max}^{KBr} 1712 cm^{-1}.

4'-Hydroxy-6-methoxy-β-methylaurone (**6**). 4-Methoxybenzofuranone (82 mg) was mixed with 4-hydroxyacetophenone (68 mg) and heated in 95% aqueous EtOH. Conc HCl (1 ml) was added and the mixture heated under reflux for 4 hr. The crude product was purified by thick-layer chromatography and recrystallused from aqueous EtOH to give the β-methylaurone, m.p. 185–6°, identical in every respect with the product obtained by ferricyanide oxidation of 2',4-dihydroxy-4'-methoxy-β-methylchalcone.

4-Methoxy-β-methylcinnamic acid (**10**). 4-Methoxyacetophenone (30 g), THF (50 ml) and powered Zn (14.4 g, activated by washing with 2% HCl, water, EtOH, acetone and ether, and drying at 100° for 10 min) were placed in a 3-necked flask equipped with dropping funnel and reflux condenser. Ethyl α-bromoacetate (36.7 g) was slowly added and the mixture stirred at 50° for 6 hr. The product was then hydrolysed by slow addition of 20% H_2SO_4 (100 ml). The crude hydroxyester was dehydrated by heating for 5–6 hr under reflux in benzene with a catalytic amount of toluene-4-sulphonic acid in a Dean and Stark apparatus. The product obtained was hydrolysed by adding 50% NaOH aq and 95% EtOH and refluxing for 1 hr. Acidification with HCl at 0° gave the unsaturated acid which was recrystallised from EtOH (yield 37%), m.p. 149–152° (lit.[8] 156–7°). *m/e* 192(100%), 191(20), 175(20), 174(20), 146(20), 108(53), 103(20).

2',4,4'-Trimethoxy-β-methylchalcone. 4-Methoxy-β-methylcinnamic acid (1.92 g) and 1,3-dimethoxybenzene (1.38) g were mixed, added to polyphosphoric acid (100 g), and the mixture heated to 76° for 1 hr. Quenching the mixture in water gave the desired product which was purified on a column of neutral alumina using chloroform as the eluent. Recrystallisation from MeOH gave the chalcone (yield 72%), m.p. 80–84°. *m/e* 312(46%), 311(78), 297(48), 295(16), 281(44), 175(18), 165(100), 148(19), 135(33), 122(19), 115(13). Accurate mass measurements: *m/e* 312.1348 ($C_{19}H_{20}O_4$ requires: 312.1361), 311.1284 ($C_{19}H_{19}O_4$ requires: 311.1283). τ($CDCl_3$): 2.2–3.6 m (8H), 6.17 and 6.24 s (9H), 7.45 br.s (3H). (Found: C, 73.10; H, 6.30. $C_{19}H_{20}O_4$ requires: C. 73.06; H, 6.45%).

2'-Hydroxy-4,4'-dimethoxy-β-methylchalcone (**9**). A soln of BCl_3 in CH_2Cl_2 was cooled to 0° and added to a cooled soln of the above chalcone in CH_2Cl_2. The mixture was allowed to warm to room temp. and allowed to stand at this temp for 10 min before being quenched with ice. Solvent extraction followed by a column chromatography on silica gel using benzene/acetone (9:1) as eluent gave the 2'-hydroxy-4,4'-dimethoxy-β-methylchalcone which was recrystallised from MeOH, m.p. 110–113°. λ_{max}^{EtOH} 354(59,600) *m/e* 298(9), 297(8), 284(21), 283(100), 191(13); 151(27), 148(26). Accurate mass measurements: *m/e* 298.1176 ($C_{18}H_{18}O_4$ requires 298.1205). τ($CDCl_3$): −3.37 s(1H, D_2O exch.), 3.2–3.7 m (8H), 6.20 and 6.21 s (6H), 7.46 d (3H, 1Hz). (Found: C, 72.92; H, 6.20. $C_{18}H_{18}O_4$ requires: C, 72.47; H, 6.08%).

Oxidation of 2'-hydroxy-4,4'-dimethoxy-β-methylchalcone. Chalcone **9** (30 mg) was dissolved in 2N NaOH aq (250 ml) and potassium ferricyanide (70 mg) in water (1 ml) added. After 10 hr the mixture was acidified to pH4 with glacial AcOH. Work-up gave a single product whose UV spectrum showed a band at 282 nm corresponding to the isomeric flavanone.

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