First Observed Oxidative Phenol Coupling to the β-Position of a Chalcone

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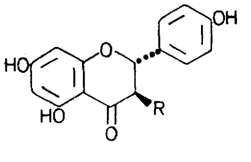
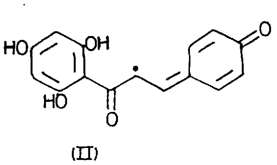
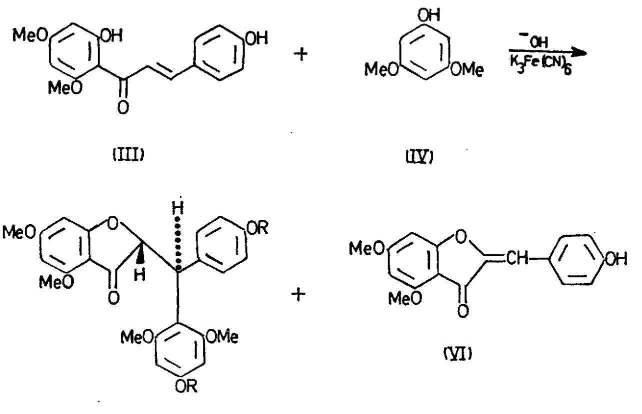
Summary 2′,4-Dihydroxy-4′,6′-dimethoxy-*trans*-chalcone couples at the β-position with 3,5-dimethoxyphenol under oxidative conditions to form stereoisomeric 2-[α-(4-hydroxy-2,6-dimethoxyphenyl)-4-hydroxybenzyl]-4,6-dimethoxybenzo[*b*]furan-3(2*H*)-ones.

THE 3,8-linked biflavonoids in which, *e.g.* a 4′,5,7-trihydroxyflavanone unit is joined to an analogous unit (I; R = dihydroflavonol,[1] flavanone,[1] flavone[2] or 2-hydroxy-2-benzylcoumaranone[3] units) are considered[1] to have their biogenetic origins in the oxidative coupling of the canonical form (II) of the chalcone radical with the phenolic A-ring of a second flavonoid unit. However, no synthetic attempt has been made to simulate the reaction. We now report that while reaction proceeds when using a substituted phenol in place of flavonoid units, it adopts a course which differs from that anticipated.

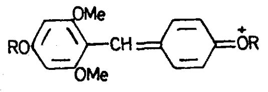

(I)


(II)

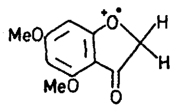


(III) (IV) (V) (VI)

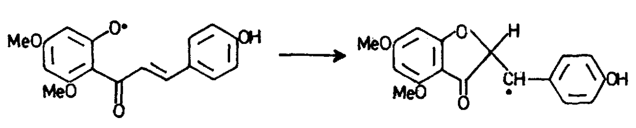
Reaction of 2′,4-dihydroxy-4′,6′-dimethoxy-*trans*-chalcone (III) with 3,5-dimethoxyphenol (IV; phloroglucinol dimethylether) in aqueous alkali–$K_3Fe(CN)_6$[4] under specific experimental conditions gives a high yield (25·5%) of a diastereoisomeric mixture of 2-[α-(4-hydroxy-2,6-dimethoxyphenyl)-4-hydroxybenzyl]-4,6-dimethoxybenzo[*b*]furan-3(2*H*)-ones (V; R=H) and 4′-hydroxy-4,6-dimethoxyaurone (VI) (23%) after separation by t.l.c. (R_F 0·10, 0·24 respectively) in benzene–ethyl acetate (7:3 v/v). The amorphous mixture of diastereoisomers (V; R=H), ν_{max} $CHCl_3$ 1700 cm^{-1}, M^+ 452 (< 1%), *m/e* 298(83), 259(100), 154(74), 153(97), R_F 0·03, 0·09, 0·12 and 0·17 by t.l.c. in dichloroethane–acetone (97:3 v/v; 4 successive developments), was acetylated and the mixed diacetates (V; R = Ac) resolved into two pairs of amorphous enantiomers R_F 0·44 (7% yield), 0·50 (11%) in the same system, [ν_{max} $CHCl_3$ 1705 cm^{-1}, τ ($CDCl_3$), 2·48, 2·48 [d, *J* 8·5, H(2′) +H(6′)], 3·02, 2·98 [d, *J* 8·5, H(3′) + H(5′)], 3·65, 3·63 [s, H(3″) + H(5″)], 3·90, 3·84 [d, *J* 2·0, H(7)], 4·02, 3·99 [d, *J* 2·0, H(5)], 4·23, 4·22 [d, *J* 10·6 H(2)], 5·12, 5·25 (d, *J* 10·6, H_α), 6·15, 6·15 (s, OMe), 6·20, 6·18 (s, OMe), 6·23, 6·23 (s, 2 × OMe), 7·83, 7·83 (s, 2 × OAc), M^+ 536 (1·9%), *m/e* 344 (6·3), 343 (100), 301 (99·7), 259 (99·7), 194 (13·8), 153 (93), 107 (33)]. Mass fragmentation spectra of each of the pair of racemates were identical, as were their accurate mass values; 536·166 (calculated for $C_{29}H_{28}O_{10}$, 536·168).



(VII)



(VIII)



(IX) (X)

The general structure for (V) was assigned mainly on the basis of carbonyl absorptions indicative of 5-membered rings, and on mass spectral fragmentation. The hydroxyl form, and each of the enantiomeric pairs of the diacetates give fragments consistent with diphenylmethanes [VII; *m/e* 259 (R=H), 343 (R=Ac) respectively] as base peaks. The molecular ions of both diacetates yield fragments corresponding to (VII; R = Ac) and (VIII) (*m/e* 194: H-transfer) as indicated by daughter ion analysis. Evidence of RDA-fragmentation as anticipated from structures of type (I) was lacking, thus excluding 6-membered rings. The point of attachment of the dimethoxyphenol is evident from the chemical equivalence of its 3″- and 5″-protons. The molecular conformation (V) may be assigned from the *trans*-diaxial orientation of the 2- and α-protons (*J* 10·6 Hz).

Coupling at the β-position of the chalcone (III) indicates preferential free radical formation at the 2′-hydroxyl [*cf.* (IX)], instead of at the 4-position [*cf.* (II)] when both are available. On this premise, attack by the former on the α,β-double bond leads to the resonance-stabilized radical (X), which undergoes phenol coupling to give (V). Initial steps involving the same mechanism presumably also lead to the formation of the aurone (VI). This represents the first instance of intermolecular oxidative coupling of a phenol with the C_3-portion of a C_6-C_3-C_6 flavonoid structure.

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