Spectral Evidence for the Formation of Quinone Methide Intermediates from 5- and 7-Hydroxyflavonoids

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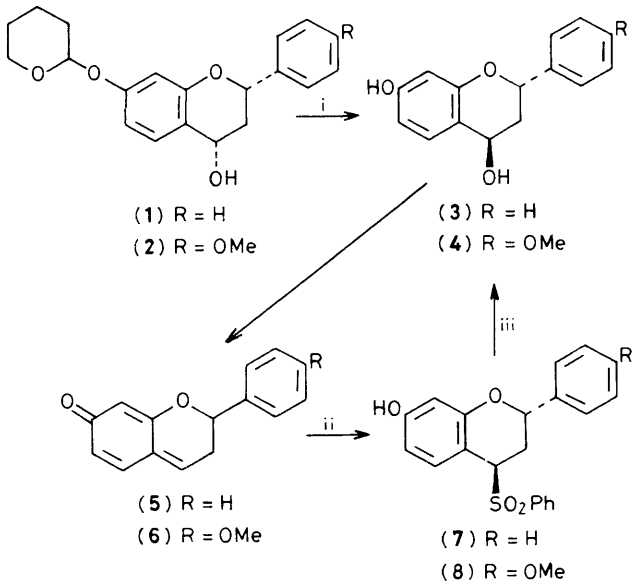
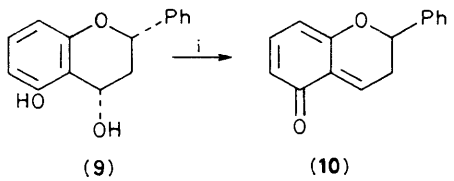
The u.v. spectra of 5- and 7-hydroxyflavan-4-ols in acid solution are interpreted in terms of the π–π^* transition of quinone methide intermediates; the enhanced reactivity of 4-substituted 7-hydroxyflavans compared to 4-substituted 7-methoxyflavans supports this mechanism which may be operative in the biosynthesis of polyflavonoids (*e.g.* condensed tannins).

Having observed that an ethereal solution of 2,3-*trans*-7-hydroxy-3,4-*cis*-dibenzoyloxy-3′,4′-dimethoxyflavan decomposes in contact with silica whereas 2,3-*trans*-3,4-*cis*-dibenzoyloxy-3′,4′,5,7-tetramethoxyflavan is stable under the same conditions, we decided to examine other 4-substituted 7- and 5-hydroxyflavans. It seemed likely that a flavonoid quinone methide, *e.g.* (**5**), (**6**), or (**10**), could be an intermediate in the reactions of such compounds and could account for the observed enhanced reactivity. Haslam[1] has suggested that quinone methides may play a part in the biosynthesis of polyflavonoids from 5- and 7-hydroxyflavonoids, although this view has been questioned by Botha *et al.*[2] who consider that the available evidence is consistent with carbocations as intermediates in the acid-catalysed polymerisation of 4-substituted flavans. In a recent communication Hemingway and Foo[3] concluded that the occurrence of flavonoid quinone methide intermediates could account for the rapid condensations of 4-substituted 5- and 7-hydroxyflavonoids in alkaline solutions. We now report spectral evidence in addition to evidence from enhanced reactivity for the formation of such quinone methide intermediates.

We have synthesised 7-tetrahydropyranyloxyflavan-4β-ol (**1**) and its 4′-methoxy analogue (**2**). Removal of the tetrahydropyranyl group from the 4β-ol (**1**) by careful treatment with acid gave 7-hydroxyflavan-4α-ol (**3**), the stereochemistry at the 4-position being that expected after treatment of a 4β-ol



Scheme 1. *Reagents*: i, H_3O^+; ii, $PhSO_2H$; iii, aq. NaOH–dioxane, 20 °C. All compounds are racemic. Relative stereochemistry is shown here and in Scheme 2.



Scheme 2. *Reagent*: i, H_3O^+.

with acid.[4] Demethylation of 5-methoxyflavan-4-one[5] and reduction with sodium borohydride gave 5-hydroxyflavan-4β-ol (**9**).

Solutions of the 7-tetrahydropyranyloxy-4β-ols (**1**) and (**2**) in aqueous dioxane absorb at 280 and 286 nm in the ultraviolet. On addition of hydrochloric acid, a band was observed in each solution at 305 nm which gradually increased in intensity to a maximum in 3—4 h (see Figure 1). We believe that this is the result of hydrolysis of the tetrahydropyranyl ethers (**1**) and (**2**) (Scheme 1) and the formation of equilibrium concentrations of quinone methides (**5**) and (**6**) by elimination of water from the 7-hydroxyflavan-4α-ols (**3**) and (**4**). The band at 305 nm is in the range quoted for other *p*-quinone methides[6] and is in agreement with estimates from the application of Woodward's rules.[7] On the addition of an excess of sodium benzenesulphinate to the solutions of the quinone methides, the band at 305 nm gradually disappeared and after 8 h a band at 289 nm due to the sulphones (**7**) and (**8**) and a band below 275 nm from the excess of benzenesulphinic acid were apparent; the band at 305 nm had become indistinct (see Figure 1). Treatment of 3',4',7-trihydroxyflavan-4β-ol with acid similarly caused the appearance of a band at *ca.* 305 nm in about 4 h. Treatment of 5-hydroxyflavan-4β-ol (**9**) with acid caused, in about 19 h, the appearance of a band at 395 nm from the π–π^* transition of the *o*-quinone methide (**10**).[8] The addition of sodium benzenesulphinate caused the band to disappear. In contrast to the 5- and 7-hydroxyflavan-4-ols, 7-methoxyflavan-4β-ol, which cannot form a quinone methide, showed no change in its u.v. spectrum when a solution of it in aqueous dioxane was acidified.

Several reactions of the 4-ols and 4-sulphones confirm the occurrence of quinone methides as intermediates. 7-Tetrahydropyranyloxyflavan-4β-ol (**1**) reacted completely with benzenethiol in acidic aqueous dioxane at room temperature in 1.5 h to give 7-hydroxy-4α-phenylthioflavan, whereas 7-methoxyflavan-4β-ol was unchanged under the same conditions after 1.5 h. This striking difference in reactivity is an indication that 7-hydroxyflavan-4α-ol (**3**) from the tetrahydropyranyl compound (**1**) is not reacting through a carbocation as would 7-methoxyflavan-4β-ol,[9] but through another reactive intermediate such as the quinone methide (**5**).

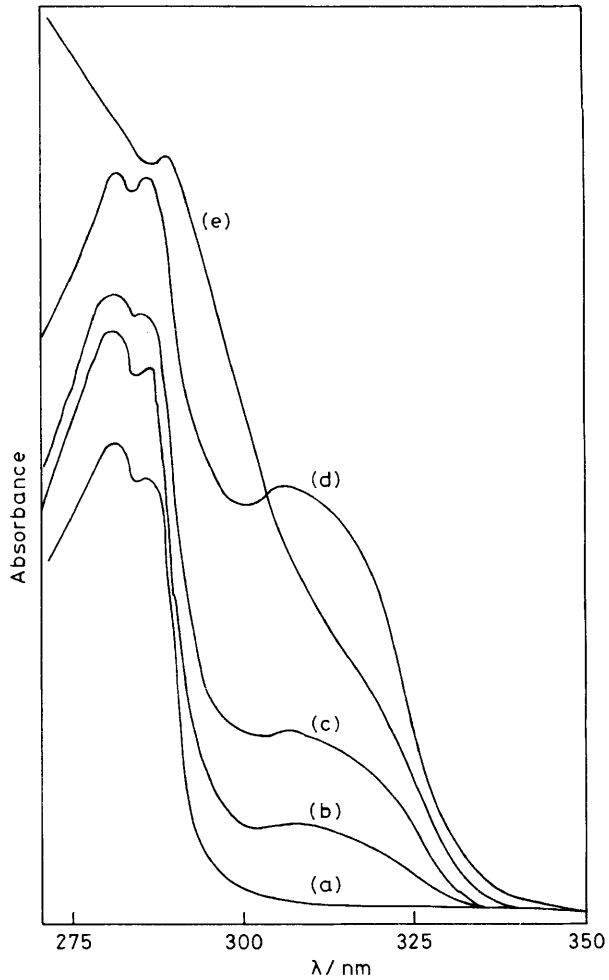


Figure 1. U.v. spectra of 7-tetrahydropyranyloxyflavan-4-β-ol (a), in aqueous dioxane; (b—d) after addition of HCl; (b), 30 min after; (c), 1 h after; (d), 3 h after; (e) 20 min after addition of sodium benzenesulphinate.

We have also found, as did Hemingway and Foo,[3] that in alkaline solution 7-hydroxyflavonoids only show the reactivity expected of quinone methides when they carry a good leaving group at the 4-position. 7-Hydroxy-4α-phenylsulphonylflavan (**7**) is completely destroyed in less than 30 min by sodium hydroxide in aqueous dioxane at room temperature. 7-Hydroxyflavan-4α-ol (**3**) (15%) was the only monomeric product isolated. This reaction is so rapid that we have not been able to observe the u.v. spectrum of the quinone methide intermediate; the u.v. spectrum of 7-hydroxy-4α-phenylsulphonyl-4'-methoxyflavan (**8**) (265, 273, 281, and 289 nm in ethanol) was replaced by a spectrum with one band at 283 nm and shoulders at 290 and 277 nm within 45 seconds when a few drops of 2M-sodium hydroxide were added. By contrast, 7-methoxy-4α-phenylsulphonylflavan,[9] which cannot form a quinone methide, was quite stable to sodium hydroxide in aqueous dioxane at room temperature.

From this evidence we conclude, in agreement with Hemingway and Foo,[3] that the formation of quinone methide intermediates constitutes a viable mechanism for the condensation of 4-substituted flavans over wide range of pH values.

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