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SYNTHESIS OF A FLAV-3-EN-3-OL *VIA* CINNAMYLPHENOL

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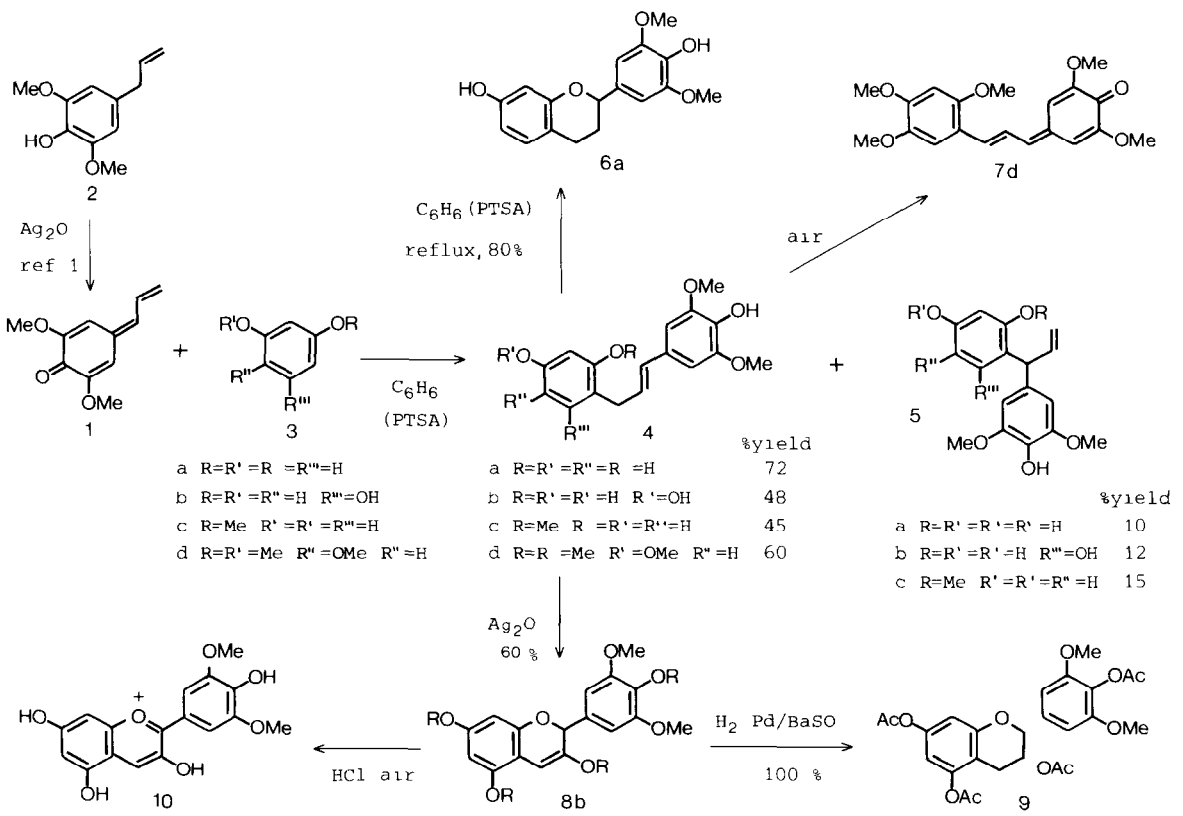
Abstract — Vinyl quinone methide (1) reacts with polyphenols to give cinnamylphenols (4) and neoflavanoids (5) Oxidation of cinnamylphenol (4b) leads to malvidin (10) *via* the isolated intermediate flav-3-en-3-ol (8b)

In a preceding paper[1] it has been shown that vinyl quinone methide (1), prepared from (2) by treatment with Ag_2O, easily reacts with hydroxy compounds to give sinapyl alcohol derivatives This communication deals with the reactions of vinyl quinone methide (1) with polyphenols.[2]
Thus, allowed to react with polyphenols (3), in the presence of catalytic amounts of *p*-toluenesulfonic acid (PTSA), vinyl quinone methide (1) gave *trans*-cinnamylphenols (4) and dalbergiquinol-type neoflavanoids (5) [3] *trans*-Cinnamylphenol (4a), when heated in benzene in the presence of PTSA, slowly cyclized to flavan (6a), while the trimethoxy compound (4d), by exposure to air, gave the obtusaquinone-type quinone methide (7d).



By oxidation with Ag_2O in benzene-acetone for two days, (4b) yielded the unstable flav-3-en-3-ol (8b) (R=H) which was isolated as its acetyl derivative (8b) (R=Ac), the latter compound gave the *epi*catechin-type flavan-3-ol (9) upon catalytic hydrogenation

Compound (8b), which showed a hydroxyl group at C-3, most likely introduced *via* a radical intermediate, is particularly interesting from a biological point of view In fact, flav-3-en-3-ols, not characterized so far, are considered to play a key rôle in flavanoid biogenesis they are thought to derive from chalcones and to be the immediate precursors of anthocyanidins, catechins and 'proanthocianidins'.[4] The last step of the postulated pathway proved to be chemically sound the pure acetyl derivative (8b) (R=Ac) was hydrolized back to flav-3-en-3-ol (8b) (R=H) in CH_3OH containing small amounts of aqueous HCl, the colourless solution so obtained, when stirred in the presence of air, turned slowly mauve and showed the same electronic spectrum of the anthocyanidin malvidin (10) ($\lambda_{max}^{MeOH-HCl}$ 542 nm)

On the basis of the present results, it appears that vinyl quinone methide (1) behaves like a C_6-C_3 intermediate[3,5] in the synthesis of neoflavanoids and cinnamylphenols and that the latter compounds, by oxidation, form anthocyanidins by way of flav-3-en-3-ols.

The shown chemical pathway is so economical that, in my view, it raises the questions whether vinyl quinone methides might be the intermediates in the biosynthesis of cinnamylphenols and whether the latter compounds, rather than chalcones, might be, in some cases, the biological precursors of flav-3-en-3-ols and therefore of anthocyanidins, catechins and 'proanthocyanidins'

REFERENCES AND NOTES

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2 All compounds, with the exception of the unstable quinone methide (7d), have been characterized as such and/or as their acetyl or methyl derivatives by ^1H NMR, UV, IR spectroscopy and mass spectrometry The yields, given in figure, refer to isolated products and are calculated on the starting allylphenol (2) Experimental details are given for the reaction of (1) with (3b) and for the synthesis of (8b). A benzene solution (150 ml) of (1) (2 g) was added to a solution of (3b) (5 g in 500 ml of benzene and 20 ml of DMF) containing 10 mg of PTSA. when the reaction was complete (2 min), the solvent was removed *in vacuo* and the products were separated by flash chromatography, under nitrogen pressure, with hexane-ethyl acetate (4b) and (5b) were fully characterized as their acetyl derivatives

Cinnamylphenol (4b) (800 mg) was dissolved in benzene-acetone (500+100 ml) and stirred with Ag_2O (2 g) at room temperature over two days after which the suspension was filtered through Celite and concentrated *in vacuo* to 100 ml, dry toluene was then added (200 ml) and again concentrated to 100 ml Ac_2O and pyridine were added, the acetylation was complete within 24 h at 0 °C (8b) (R=Ac) was obtained as white crystals, mp 174 °C (EtOAc), ^1H NMR (DMSO-d_6) δ vs int TMS 2 10, 2 18, 2 20, 2 31 (3H each, s, Ac), 3 70 (6H, s, OCH_3), 5 91 (1H, s, H-2), 6 63 (3H, s, H-2',6' and H-4), 6 72 (2H, s, H-6,8) In DMSO-d_6/C_6D_6 the singlet at 6 63 was split 6 73 (2H, s, H-2',6'), 6 83 (1H, s, H-4), λ_{max}^{EtOH} 304 (log ε 3 59), 274 (3 88) and 225 (4 43) nm, ν_{max} (nujol) 1760, 1605, 1425 and 1370 cm^{-1} m/e 500 (M^+, 17%), 457 (63), 415 (42), 372 (26), 331 (flavylim ion) (15), 304 (13), 209 (18), 206 (21) and 167 (100)

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