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EPIMERIZATION OF (±)-4',5,7-TRIMETHOXYFLAVAN-4β-OL TO THE -4α-OL WITH ACETIC ANHYDRIDE AND PYRIDINE.

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Attempted acetylation of (±)-4',5,7-trimethoxyflavan-4β-ol (I), m.p. 159°, with acetic anhydride and pyridine at room temperature for 48 hr. gave a product (II), m.p. 117°, which was considered to be isomeric with I from comparison of their ultra-violet and infra-red spectra[1]. General similarity of their nuclear-magnetic-resonance spectra led to the tentative conclusion that the product was (±)-4',5,7-trimethoxyflavan-4α-ol (II)[1]. Present re-examination of the n.m.r. spectra of both compounds using a Varian HA-100 spectrometer has provided the necessary resolution of absorption lines due to protons at C-2 and C-4 (unresolved at 60Mc), and detailed analysis of their spectra (Table 1) now affords unequivocal proof of the above configurations, and of the unique epimerization.

TABLE 1.

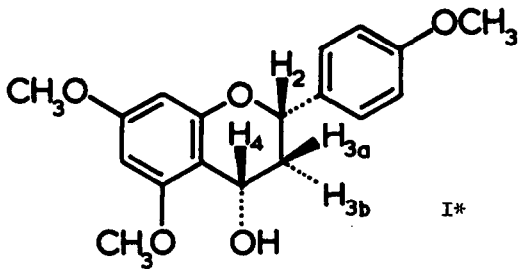
N.m.r. spectra of (±)-4',5,7-trimethoxyflavan-4α-and-4β-ol *

τ-values (p.p.m.).

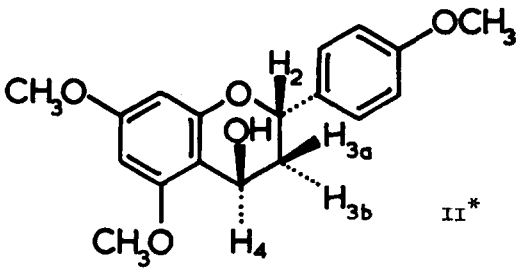
Compound	$H_{2'}+H_{6'}$	$H_{3'}+H_{5'}$	H_6	H_8	H_4	H_2	Methoxyl protons 4'-	7-	5-	H_{3a+3b}	OH
4α-ol	2.56 (2)	3.05 (2)	3.82 (1)	3.88 (1)	5.01 (1)	4.89 (1)	6.18 (3)	6.20 (3)	6.26 (3)	7.92 (2)	7.85 (1)
4β-ol	2.57 (2)	3.05 (2)	3.86 (2)		4.75 (1)	5.04 (1)	6.16 (3)	6.21 (3)	6.28 (3)	7.72 (2)	7.85 (1)

*In deuterochloroform with tetramethylsilane as internal standard at 100 Mc.

+The intensities of the resonance lines are in parenthesis.



I*



II*

The heterocyclic ring protons at C-2 and C-4 of I and II are in each instance coupled with the vicinal methylene protons at C-3, and considered independently, each forms the X portion of an ABX system. Assuming that $J_{2,3a}$ has the same relative sign as $J_{2,3b}$, and $J_{3a,4}$ as $J_{3b,4}$ (cf.[2,3]), then for the flavan-4β-ol (I) $J_{2,3a} + J_{2,3b} = 13.4$ and $J_{3a,4} + J_{3b,4} = 16.7$ c.p.s., and for the flavan-4α-ol (II) $J_{2,3a} + J_{2,3b} = 14.4$ and $J_{3a,4} + J_{3b,4} = 6.0$ c.p.s. These values show that the 2- and 4- protons are both axial in the flavan-4β-ol, whereas for the flavan-4α-ol they are likely to be axial and equatorial respectively[4,5]. Comparison with other flavan-4β-ol acetates[6,7] ($J_{2,3a} + J_{2,3b} = 12.8 - 13.1$ and $J_{3a,4} + J_{3b,4} = 14.8 - 16.5$ c.p.s.) and benzoate[6,8] ($J_{2,3a}$ +

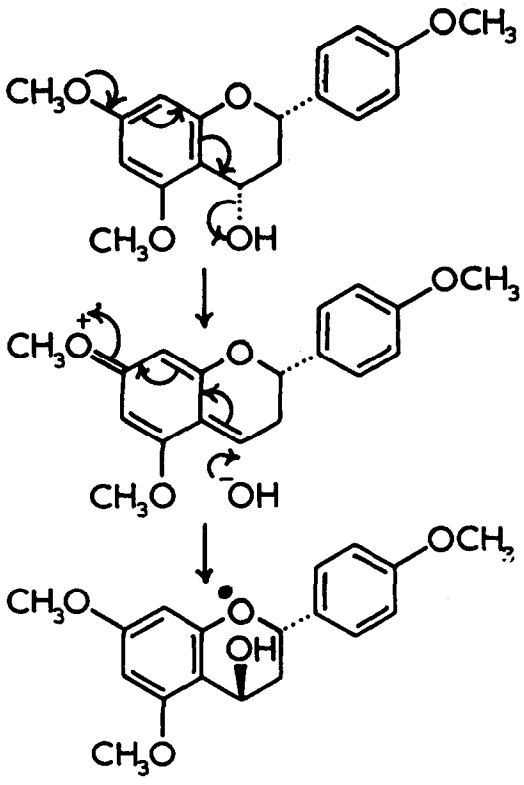
* Only 2S configurations are illustrated in these formulae.

$J_{2,3b}$ = 13.7 and $J_{3a,4} + J_{3b,4}$ = 16.2 c.p.s.), and with a flavan-4α-ol[9] ($J_{2,3a} + J_{2,3b}$ = 14.3 and $J_{3a,4} + J_{3b,4}$ = 5.8 c.p.s.), its acetate[9] ($J_{2,3a} + J_{2,3b}$ = 14.3 and $J_{3a,4} + J_{3b,4}$ = 6.0 c.p.s.) and a benzoate[6,8] ($J_{2,3a} + J_{2,3b}$ = 14.9 and $J_{3a,4} + J_{3b,4}$ = 6.0 c.p.s.) confirm their 2,4-cis (I) 2(eq):4(eq) arrangement of substituents and 2,4-trans (II) 2(eq):4(ax) configurations respectively.

The protons at C-2 and C-4 appear as quartets at 100 Mc, an exception being the triplet of the C-4 proton of I which has small secondary splitting ($J < 1$ c.p.s.). The methylene resonance of the flavan-4β-ol (I) shows an anticipated 16 absorption lines (vicinal plus geminal coupling) reduced to 14 in the flavan-4α-ol (II) due presumably to overlap resulting from narrower spin-spin splittings.

Considering the benzenoid protons, the 4(eq)- or 4(ax)-orientation of the free hydroxyl affects the chemical shift of the A-ring protons, the singlet due to 6-H + 8-H in the flavan-4β-ol (I) being converted into a typical meta-coupled AB quartet ($J_{6,8}$ = 2.5 c.p.s.) in the flavan-4α-ol (II), in which the doublet due to the 6-proton is presumed to be downfield. The 4'-methoxyl group in the B-ring gives rise to an A_2B_2 system ($J_{2',3'} = J_{5',6'} \approx 9.0$ c.p.s.) which is typical of a 1,4-disubstituted benzenoid ring.

The lack of reactivity of the 4-hydroxyl of both I and II with acetic anhydride-pyridine, as opposed to its ready acetylation[6,7,9] and benzoylation[8] in unsubstituted and in 6-methyl and 7-methoxyl flavan-4α- and -4β-ols, indicates that steric repulsion due to the 5-methoxyl is responsible,



as suggested[1]. By comparison, flavan-3,4-diols with 5-methoxyl substitution undergo ready acetylation with acetic anhydride-pyridine[10,11,12], showing that other factors control the course of their acetylation.

The relative ease of epimerization of I indicates that electron-release from the 7-methoxyl is possible, thus enabling inversion according to the mechanism outlined by Drewes and Roux[13] for flavan-3,4-diols (cf. scheme). The presence of the 5-methoxyl reinforces this effect. This

explanation finds a parallel in the observation[14], from comparative studies[14,15,16,17], that inversion of 4(eq)-hydroxyls of flavan-3,4-diols during the course of formation of isopropylidene derivatives is facilitated by methoxyl groups in the 5- and 7- positions.

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