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2,3-CIS-3,7,8,3',4'-PENTAMETHOXYFLAVANONE: A STABLE CIS-DIHYDROFLAVONOL DERIVATIVE

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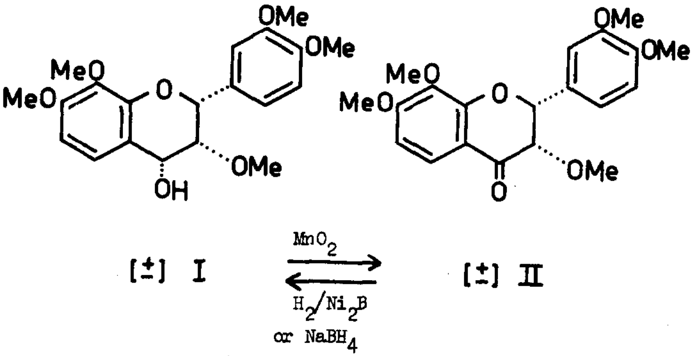
Hydrogenation of 3,7,8,3',4'-pentamethoxyflavone, m.p. 153° [lit. (1) m.p. 151°], for 12 hr. at 80° and 70 atm. over a nickel boride catalyst (P1) (2) gave dimorphic 2,3-cis-3,4-cis-3,7,8,3',4'-pentamethoxyflavan-4-ol (I) (69%) in prisms (from methanol), m.p. 151-152°, or needles (from chloroform or carbon tetrachloride), m.p. 127-128°. The m.p. of the higher melting form was not depressed by admixture with that of m.p. 127-128°, and the i.r. and n.m.r. spectra of both forms were indistinguishable (2H, δ 5.13; 3H, δ 3.72; 4H δ 4.98 p.p.m.; $J_{2,3}$ ca. 0.9 c/s, $J_{3,4}$ 4.5 c/s, consistent (3) with the assigned configuration). Oxidation of the 3-methoxyflavan-4-ol (I) with manganese dioxide in chloroform gave 2,3-cis-3,7,8,3',4'-pentamethoxyflavanone (II), m.p. 109.5-110.5°. Its n.m.r. spectrum showed the 2H signal as a doublet (δ 5.42 p.p.m., $J_{2,3}$ 2.5 c/s) and the 3H doublet at δ ca. 3.93 p.p.m. partly obscured by aromatic methoxyl absorptions; the 3-methoxyl peak occurred at δ 3.41 p.p.m. Coupling constants for 2,3-cis-dihydroflavonols have not previously been reported but the observed value ($J_{2,3}$ 2.5 c/s) is similar to values for two 2,3-cis-3-bromoflavanones ($J_{2,3}$ 1.7 c/s and 1.8 c/s)(3,5) and for flavan-4-ols ($J_{2,3}$ 2.2. c/s)(6). Catalytic hydrogenation



[±] I [±] II

$J_{2,3}$ ca. 0.9 c/s $J_{2,3}$ 2.5 c/s

of the cis-flavanone (II) over nickel boride, or reduction with sodium borohydride, gave 2,3-cis-3,4-cis-3,7,8,3',4'-pentamethoxyflavan-4-ol (I) once more. The apparently analogous 2,3-cis-3,7,3',4'-tetramethoxyflavanone, m.p. 89-90°, has been reported (7).

The 2,3-configuration of naturally occurring dihydroflavonols (3-hydroxyflavanones) is known to be trans (8), and dihydroflavonols synthesised by chemical reduction of flavonols and by ring closure of chalcones also possess the 2,3-trans-configuration (3,9,10), so that the pentamethoxyflavanone (II) and its 3,7,3',4'-tetramethoxy analogue (7) appear to be the first authentic 2,3-cis-3-hydroxyflavanone derivatives (11).

Equilibration of cis-3,7,8,3',4'-pentamethoxyflavanone at 40° in deuterochloroform containing trifluoroacetic acid (4.5%) gave in 8 days an equilibrium mixture of cis-(34%) and trans-methoxyflavanone (66%) ($J_{2,3}$ 10.6 c/s). The free-energy change (ΔG^{o}_{40} = -410 cal.), evaluated from the equilibrium constant, reflects the greater stability of the diequatorial arrangement of the 2-aryl and 3-methoxyl substituents in the preferred conformation of the *trans*-isomer. In 3-hydroxyflavanones hydrogen bonding of the 3-hydroxyl with the 4-carbonyl group, or with the 2-aryl substituent (2-phenylethanol type), may be expected to enhance the stability of *trans*- compared with *cis*-dihydroflavonols. This view, which prompted preparation of the flavanone (II), is supported by the observations that racemisation of (+)-2,3-*trans*-dihydroquercetin with acids or bases gives (±)-2,3-*trans*-dihydroquercetin (8), and that oxidation of 2,3-*cis*-flavan-3,4-diol with chromic acid in acetic acid gives 2,3-*trans*-dihydroflavonol, presumably by inversion of the *cis*-isomer at the centre adjacent to the carbonyl group (12).

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