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SYNTHESIS AND STEREOCHEMISTRY OF FLAVAN-3,4-DIOL DIACETATES

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Abstract—Two hitherto unknown racemates of flavan-3,4-diol diacetate have been prepared and NMR data now available for the complete set of four racemates establish the stereochemistry of these compounds.

OF THE four possible racemic forms of flavan-3,4-diol (I–IV; R = H) only two have been fully characterized in regard to structure and stereochemistry. These are the 2,3-*trans*-3,4-*trans*-diol (I; R = H), m.p. 145°, and the 2,3-*trans*-3,4-*cis*-diol (II; R = H), m.p. 160°. Assignments of geometrical configuration were based upon the NMR spectra of the cyclic carbonates and dibenzoates,[1] and of the diacetates.[2] Use has also been made of the IR absorption spectra of the diols[3] and of the rates of reaction of the diols with lead tetra-acetate.[2] The present communication describes the preparation of the remaining two racemates (III; R = H, Ac and IV; R = Ac) and sets out the spectroscopic evidence on which the stereochemical assignments are based.

As Clark-Lewis *et al.* have pointed out,[4] hydrogenation of flavonols is the only reaction which has been successful for the synthesis of 2,3-*cis*-flavan-3,4-*cis*-diols. Mozingo and Adkins[5] first reported the synthesis of a flavan-3,4-diol, m.p. 123–124°, by reduction of flavonol with hydrogen over copper chromite. The paucity of information concerning this compound led Fujise *et al.*[6] to repeat Mozingo and Adkins' work. Their product, obtained in 3% yield, melted at 152–153° and, since it formed an 0,0-isopropylidene derivative (m.p. 135·5–136·5°), it was regarded tentatively as a flavan-3,4-*cis*-diol. In the present work, however, hydrogenation of flavonol over copper chromite provided a diol (25% yield) of m.p. 111–113°, crystallized from dioxan–cyclohexane. This product also gave rise to an isopropylidene derivative, m.p. 137–138°, which, on hydrolysis with acetic acid afforded the diol, m.p. 111–113°. Retention of the flavanoid structure was confirmed by oxidation of the diol to *trans*-3-hydroxyflavanone,[7] a reaction which apparently involves inversion at position 3. The reason for the disparity in m.p. between Fujise's diol and the diol of the present

[1] E. J. Corey, E. M. Philbin, and T. S. Wheeler, *Tetrahedron Letters* 429 (1961).
[2] M. M. Bokadia, B. R. Brown, P. L. Kolker, C. W. Love, J. Newbould, G. A. Somerfield, and P. M. Wood, *J. Chem. Soc.* 4663 (1961).
[3] E. M. Philbin, T. S. Wheeler, F. V. Brutcher, jun., and W. Bauer, jun., *J. Org. Chem.* **27**, 4114 (1962).
[4] J. W. Clark-Lewis, L. M. Jackman, and L. R. Williams, *J. Chem. Soc.* 3858 (1962).
[5] R. Mozingo and H. Adkins, *J. Amer. Chem. Soc.* **60**, 669 (1938).
[6] S. Fujise, T. Munekata, E. Ishikawa, T. Kobayashi, I. Sakai, M. Ueno, T. Yuki, and S. Hishida, *J. Chem. Soc. Japan* **84**, 81 (1963).
[7] Cf. R. Bognar, M. Rakosi, H. Fletcher, E. M. Philbin, and T. S. Wheeler, *Tetrahedron* **19**, 391 (1963).

study is not clear. The *trans-trans*-diol (I; R = H) was first isolated as the hydrate[8] and thus solvent of crystallization may be the cause of the discrepancy now observed. Indeed, the diol, m.p. 111–113°, when crystallized from methanol, had the composition $C_{15}H_{14}O_3 . \frac{1}{2}CH_3OH$, although no difference in m.p. from that of a sample crystallized from dioxan–cyclohexane was noted. The alternative possibility of dimorphism, however, cannot be excluded. Assignment of the 2,3-*cis*-3,4-*cis*-configuration follows from a study of (*a*) the IR absorption spectrum measured in dilute (0·005 M) solution in carbon tetrachloride, in which the peak at 3570 cm^{-1} characteristic of OH· · ·O bonding is much more intense than that attributed to OH· · ·π bonding at 3605 cm^{-1} (cf. Philbin *et al.*[3]), and (*b*) the NMR spectrum of the diacetate which is discussed in the sequel.

2,3-*cis*-Flavan-3,4-*trans*-diols are known only as the diacetates and in this form were first prepared by Kulkarni and Joshi.[9] Application of their method to the present work involved reduction of 3-bromoflavanone (V)[10] with lithium aluminium hydride to the 3- bromoflavan-4-ol (VI) which on treatment with potassium acetate and acetic anhydride gave *trans*-3,4-diacetoxy-2,3-*cis*-flavan (IV; R = Ac).

The configurations assigned to the flavan-3,4-diol diacetates (III and IV; R = Ac) are confirmed by the NMR data assembled in Table 1. For comparison the Table includes results for the diacetates (I and II; R = Ac). The relationship of spin-spin

TABLE 1

Compound	Melting point (°C)	τ-Values: Acetyl Me		2H	3H	4H	Spin-spin coupling constants (c/s): $J_{2,3}$	$J_{3,4}$
(I; R = Ac)	90–91	8·17,	8·03[a]	4·84	4·41	3·70	8·7	7·0
(II; R = Ac)	97–98	8·16,	7·87[b]	4·70	4·47	3·77	10·0	3·0
(III; R = Ac)	114–115	8·14,	7·89	4·62	4·30	3·60	1·0	4·0
(IV; R = Ac)	169–170	8·15,	7·85	~4·68	~4·68	4·04	3·0	2·5

[a] Brown *et al.*[2] report 8·16, 8·02. [b] Brown *et al.*[2] report 8·16, 7·87.

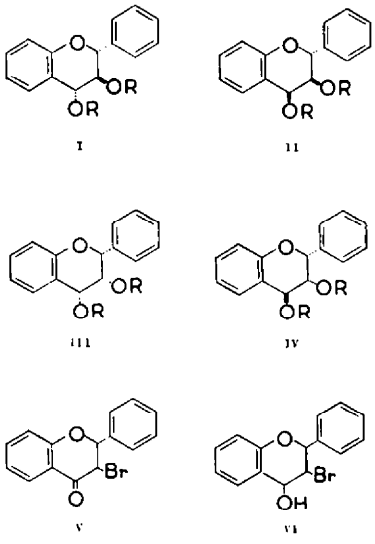
coupling constant to dihedral angle[11] clearly defines the 2,3-*cis*-configuration of the diacetates (III and IV; R = Ac) since the values observed ($J_{2,3}$ = 1·0, 3·0 c/s) are much smaller than those for the 2,3-*trans*-compounds ($J_{2,3}$ = 8·7, 10 c/s). Corey *et al.*[1] report $J_{2,3}$ = 7·3, 10 c/s respectively for the dibenzoates (I and II; R = $C_6H_5 . CO$). Clark-Lewis *et al.*[4] record $J_{2,3}$ = 9·5, 10 c/s respectively for the 2,3-*trans*-3,4-*trans*- and 2,3-*trans*-3,4-*cis*-isomers and $J_{2,3}$ = 0·9, 1·0 c/s respectively for the 2,3-*cis*-3,4-*cis*- and 2,3-*cis*-3,4-*trans*-isomers of 3′,4′-dimethoxy-6-methylflavan-3,4-diol diacetate. Assignment of stereochemistry to the 3,4-*trans*- ($J_{3,4}$ = 7·0 c/s) and the 3,4-*cis*- ($J_{3,4}$ = 3·0 c/s) pair of 2,3-*trans*-flavan-3,4-diol diacetates (I and II; R = Ac) and also to the 3,4-*cis*- ($J_{3,4}$ = 4·0 c/s) and 3,4-*trans*- ($J_{3,4}$ = 2·5 c/s) pair of 2,3-*cis*-flavan-3,4-diol diacetates (III and VI; R = Ac) is based upon similar reasoning. Observed values of the spin-spin coupling constants are consistent with the adoption of a half-chair conformation by the heterocyclic ring.

[8] R. Bognar and M. Rakosi, *Chem. & Ind.* 188 (1956).

[9] A. B. Kulkarni and C. G. Joshi, *Chem. & Ind.* 124 (1956); *J. Sci. Ind. Res., India* **16 B,** 355 (1957); see also Clark-Lewis *et al.*, Ref. 4; J. W. Clark-Lewis, T. McL. Spotswood, and L. R. Williams, *Austral. J. Chem.* **16,** 107 (1963).

[10] R. Bognar, M. Rakosi, and Gy. Litkei, *Acta Chim. Hung.* **34,** 353 (1962).

[11] M. Karplus, *J. Chem. Phys.* **30,** 11 (1959).



Only the 2-*R* enantiomer of each racemate is shown.

EXPERIMENTAL

NMR spectra were determined with a Varian A-60 spectrometer at 60 Mc/s. $CDCl_3$ was used as solvent with tetramethylsilane as internal reference. IR absorption measurements were recorded with a Perkin-Elmer 21 instrument, using 1 cm NaCl cells.

3,4-trans-*Diacetoxy*-2,3-trans-*flavan* (I; R = Ac), m.p. 90–91°, and 3,4-cis-*diacetoxy*-2,3-trans-*flavan* (II; R = Ac), m.p. 97–98°, were prepared by the methods described in the literature.[2]

2,3-cis-*Flavan*-3,4-cis-*diol* (III; R = H). Flavonol (4·8 g) in ethanol (25 ml) was hydrogenated at 140°/100 atm over copper chromite catalyst (0·4 g). Uptake of hydrogen (2 moles) was complete in 30 min. Removal of the catalyst followed by chilling of the ethanolic liquor afforded pale yellow crystalline material (2·77 g), m.p. 94–102°. Fractional crystallization from dioxan–cyclohexane gave 2,3-cis-*flavan*-3,4-cis-*diol* (1·21 g, 25%) as fine needles, m.p. 111–113°. (Found: C, 74·3; H, 5·8. $C_{15}H_{14}O_3$ requires: C, 74·4; H, 5·8%). The O,O-*isopropylidene derivative*, prepared in 60% yield from acetone–HCl, separated from ethanol in leaflets, m.p. 137–138°. (Found: C, 76·4; H, 6·5. $C_{18}H_{18}O_3$ requires: C, 76·6; H, 6·4%). The isopropylidene derivative (0·2 g) heated with acetic acid (8 ml) and water (2 ml) for 0·5 hr at 100° gave, after isolation, 2,3-*cis*-flavan-3,4-*cis*-diol (0·15 g), m.p. 111–113°. The *carbonate* (from carbonyl chloride) crystallized from ligroin in colourless plates m.p. 161–162°. (Found: C, 71·7; H, 4·7. $C_{16}H_{12}O_4$ requires: C, 71·6; H, 4·6%). The *diacetate* (from acetic anhydride–pyridine) separated from light petroleum (b.p. 60–80°) in needles, m.p. 114–115°. (Found: C, 70·0; H, 5·6. $C_{19}H_{18}O_6$ requires: C, 69·9; H, 5·5%). 2,3-*trans*-Flavan-3,4-*trans*-diol (0·48 g, 10%), m.p. 145–146° (mixed m.p. authentication) was also isolated from the product of hydrogenation of flavonol.

Oxidation of the cis-cis-*diol*. 2,3-*cis*-Flavan-3,4-*cis*-diol (0·10 g) in glacial acetic acid (20 ml) was added slowly to a cold, stirred solution of CrO_3 (0·05 g) in water (2 ml) and acetic acid (5 ml). Stirring was continued for 3 hr, water was added, and the crude product was isolated by extraction with chloroform. Crystallization from ethanol gave *trans*-3-hydroxy-flavanone (0·07 g), colourless needles, m.p. 182–184° (mixed m.p. authentication).

3-Bromoflavanones (V)

(a) An ice-cooled, stirred solution of flavanone (20 g) in CS_2 (150 ml) was treated with a solution of Br_2 (14·3 g) in CS_2 (150 ml) in the manner described by Oyamada.[12] Removal of solvent and crystallization of the crude product from methanol gave 3-bromoflavanone (13·2 g, 48%) in colourless prisms, m.p. 109–110° (lit.,[12] m.p. 110°; lit.,[10] m.p. 107–108°). (Found: C, 58·9; H, 3·8; Br, 25·9. Calc. for $C_{15}H_{11}BrO_2$: C, 59·4; H, 3·6; Br, 26·4%). Concentration of the mother liquors afforded

[12] T. Oyamada, *J. Chem. Soc. Japan* **64**, 864 (1943).

the isomer (1·65 g, 6%), colourless spars, m.p. 93–94° (lit.,[10] m.p. 93·5–94·5°). (Found: C, 59·0; H, 3·9; Br, 26·0%).

(b) A mixture of flavanone (2·24 g) and $CuBr_2$ (4·48 g) in methanol (150 ml) was stirred and refluxed for 75 min in an adaptation of Glazier's procedure[13] for the bromination of steroidal ketones. The mixture was filtered and the pale yellow filtrate was diluted with water before being extracted with chloroform. Removal of the solvent left a residue which was separated by crystallization from methanol into 3-bromoflavanone (0·42 g, 14%), m.p. 109–110°, and its isomer (0·45 g, 15%), m.p. 93–94°.

3-*Bromoflavan*-4-*ols* (VI)

(a) Sodium borohydride (0·4 g) was added to a solution of 3-bromoflavanone (1·0 g), m.p. 109–110°, in ethanol (120 ml) at 20°. After 2 hr the solution was acidified with acetic acid and the solvent was then removed under red. press. Crystallization of the residue from aqueous acetic acid gave 3-*bromoflavan*-4-*ol* (0·6 g, 60%) as fine colourless needles, m.p. 140–141°. (Found: C, 59·1; H, 4·5; Br, 25·7. $C_{15}H_{13}BrO_2$ requires: C, 59·0; H, 4·3; Br, 26·2%). Reduction of the bromoflavanone (1·00 g) in ether (50 ml) with $LiAlH_4$ (0·25 g) also gave the bromoflavanol (0·88 g, 88%), m.p. 140–141°.

(b) 3-Bromoflavanone (1·00 g), m.p. 93–94°, in ether (50 ml) was added slowly to a stirred, ice-cooled suspension of $LiAlH_4$ (0·25 g) in ether (50 ml). After the addition the mixture was stirred for 30 min at 20° and was then acidified with 10% H_2SO_4 before extraction with ether. The ethereal extract was dried (Na_2SO_4) and removal of the solvent left a residue which after crystallization from benzene gave the isomeric 3-*bromoflavan*-4-*ol* (0·71 g, 71%) as short colourless needles, m.p. 195° (dec). (Found: C, 59·4; H, 4·4; Br, 25·7%).

3,4-trans-*Diacetoxy*-2,3-cis-*flavan* (IV; R = Ac). 3-Bromoflavan-4-ol (0·10 g), m.p. 195° (dec), potassium acetate (2 g), acetic anhydride (5 ml), and acetic acid (20 ml) were gently refluxed together for 96 hr. The solution was cooled and poured on to ice and the resulting mixture was extracted with ether. The ethereal extract was washed (Na_2CO_3), and dried (Na_2SO_4), and the solvent was removed. Crystallization of the residue from methanol gave 3,4-trans-*diacetoxy*-2,3-cis-*flavan* (0·05 g, 67%) as colourless leaflets m.p. 169–170°. (Found: C, 69·6; H, 5·4. $C_{19}H_{18}O_5$ requires: C, 69·9; H, 5·5%).

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[13] E. R. Glazier, *J. Org. Chem.* **27**, 4397 (1962).