759. *Flavan Derivatives. Part V.*[1] *Synthesis of the Four Racemates of 3′,4′-Dimethoxy-6-methylflavan-3,4-diol Diacetate.*

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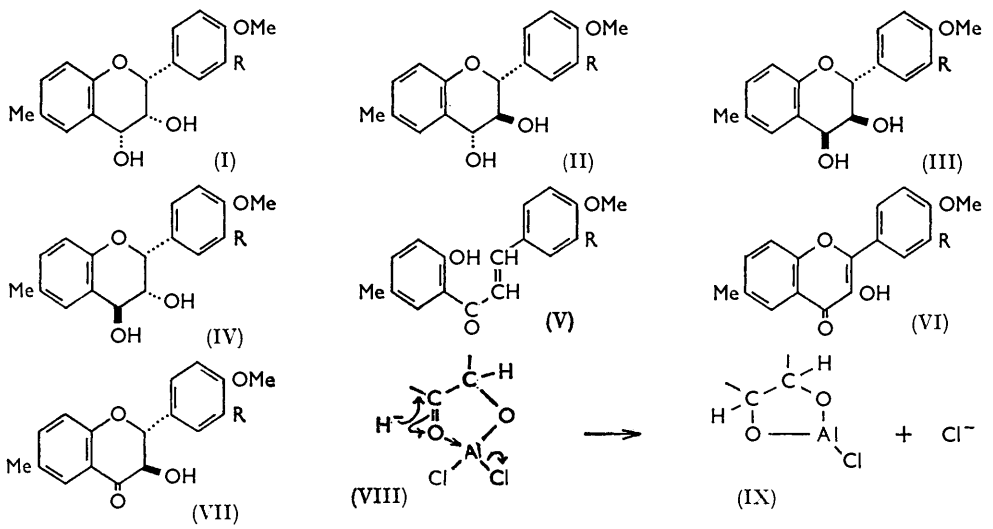
All four racemates of 3′,4′-dimethoxy-6-methylflavan-3,4-diol diacetate have been prepared and examined by nuclear magnetic resonance. The results permit an unequivocal assignment of geometrical configurations and illustrate the power of the method for elucidating the stereochemistry of flavan derivatives.

Proton magnetic resonance studies of flavanoids have shown the value of this technique for determining the geometrical configurations of flavan derivatives.[2,3] Measurements on some fifty-five flavanoid compounds, briefly summarised in a preliminary communication,[2] indicated the need for complete sets of the four racemates (*e.g.*, I—IV) * possible for each flavan-3,4-diol. The first complete set of racemates (I—IV; R = H) was

* All compounds described in this paper are racemic although only the 2*R*-enantiomer of each racemate is shown in structural formulæ.

[1] Part IV, Clark-Lewis, Katekar, and Mortimer, *J.*, 1961, 499.
[2] Clark-Lewis and Jackman, *Proc. Chem. Soc.*, 1961, 165.
[3] Corey, Philbin, and Wheeler, *Tetrahedron Letters*, 1961, 429.

obtained by Kulkarni and his co-workers,[4,5] although the configurations they assigned to the 2,3-*trans*-pair (II and III; R = H) have recently been interchanged.[6] The present communication describes preparation of a second set of four racemates [acetates of the diols (I—IV; R = OMe)] and reports nuclear magnetic resonance data for a complete set of flavan-3,4-diol racemates for the first time. The diacetates of the diols (I—IV; R = H) have also been prepared. Spin–spin coupling constants (J) for the 2-, 3-, and 4-protons confirm the configurations (I—IV) and are discussed briefly below.

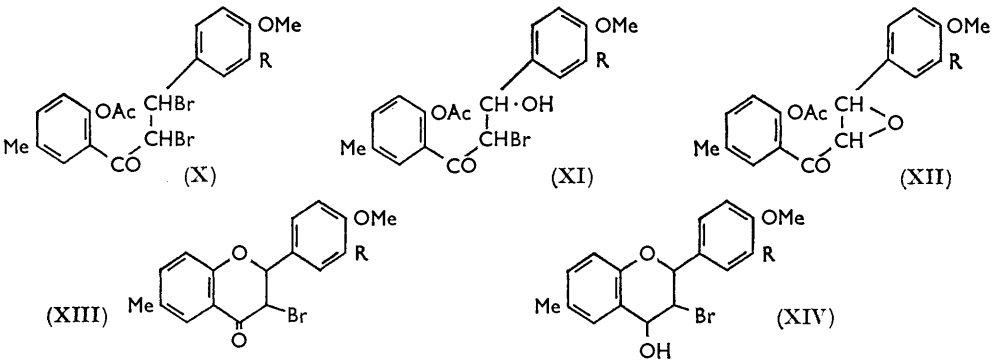


The chalcone (V; R = H), prepared by the method of Auwers and Anschütz,[7] was converted into the flavonol (VI; R = H) with alkaline hydrogen peroxide. The dimethoxychalcone (V; R = OMe) was similarly prepared from 2-hydroxy-5-methylacetophenone and veratraldehyde, and then converted into the flavonol (VI; R = OMe). Hydrogenation of the flavonols gave the *cis-cis*-racemates (I; R = H, OMe), and 3′,4′-dimethoxy-6-methyl-2,3-*cis*-flavan-3,4-*cis*-diol (I; R = OMe) was thus obtained in better yield (36%) than the 4′-methoxy-analogue (I; R = H) (16%). Losses are probably due to hydrogenolysis of the 1,2-bond in the flavandiols, and the yields are consistent with the expected retardation of hydrogenolysis by the 3,4-dimethoxyphenyl compared with the *p*-methoxyphenyl group. Hydrogenation of flavonols is the only route so far developed for synthesis of *cis-cis*-flavandiols.[1,8]

The pairs of 2,3-*trans*-flavan-3,4-diols (II and III; R = H or OMe) were obtained from the racemic *trans*-dihydroflavonols (VII; R = H or OMe) by methods similar to those recently discussed by Brown and his co-workers [6] in correcting the configurations of the diols (II and III; R = H). 4′-Methoxy-6-methyl-2,3-*trans*-flavan-3,4-*trans*-diol (II; R = H) was obtained by hydrogenation of the dihydroflavonol (VII; R = H) in acetic acid over platinum–charcoal, and by its reduction with sodium borohydride or with lithium aluminium hydride; the latter reagent was used to convert the dihydroflavonol (VII; R = OMe) into the new *trans-trans*-diol (II; R = OMe). 4′-Methoxy-6-methyl-2,3-*trans*-flavan-3,4-*cis*-diol (III; R = H) was obtained initially as a by-product in the reduction of the dihydroflavonol (VII; R = H) with sodium borohydride, but was more

[4] Joshi and Kulkarni, *Chem. and Ind.*, 1954, 1421; *J. Sci. Ind. Res., India*, 1957, **16**, *B*, 307, 355.
[5] Kulkarni and Joshi, *Chem. and Ind.*, 1956, 124; *J. Indian Chem. Soc.*, 1957, **34**, 753; see also Kashikar and Kulkarni, *Chem. and Ind.*, 1958, 1084; *J. Sci. Ind. Res., India*, 1959, **18**, *B*, 413.
[6] Bokadia, Brown, Kolker, Love, Newbould, Somerfield, and Wood, *J.*, 1961, 4663.
[7] Auwers and Anschütz, *Ber.*, 1921, **54**, 1543.
[8] King and Clark-Lewis, *Chem. and Ind.*, 1954, 757; *J.*, 1955, 3384.

conveniently prepared by reduction with lithium aluminium hydride–aluminium chloride, as described recently by Brown and his co-workers [6] except that reduction was effected at 0°. 3′,4′-Dimethoxy-6-methyl-2,3-*trans*-flavan-3,4-*cis*-diol (III; R = OMe) was



similarly obtained from the dihydroflavonol (VII; R = OMe), but in much higher yield. Co-ordination of aluminium with the keto-alcohol system provides a possible explanation for the formation of *cis*-diols with lithium aluminium hydride–aluminium chloride, as hydride ion attack on the keto-alcohol complex (*e.g.*, VIII) should lead to the *cis*-glycol complex (*e.g.*, IX). Aluminium chloride was found to have no influence on the reduction of 4′-methoxy-6-methylflavanone or the 3-bromoflavanones discussed below. The dihydroflavonols (VII; R = H or OMe) required for the above-mentioned syntheses were obtained by boiling the acetoxychalcone dibromides (X; R = H or OMe) briefly with aqueous acetone and then with aqueous sodium carbonate, as described by Kulkarni and Joshi; [9] cyclisation is thought to proceed *via* the bromohydrin (XI) and the epoxide (XII; R = H or OMe).[10]

2,3-*cis*-Flavan-3,4-*trans*-diols (IV) are the least accessible of the four racemic forms of these leucoanthocyanidins, and the diacetate of the diol (IV; R = H) was obtained from the 3-bromoflavanone (XIII; R = H) *via* the 3-bromoflavan-4-ol (XIV; R = H) as described by Kulkarni and Joshi.[5,11] Reduction of 3-bromo-3′,4′-dimethoxy-6-methylflavanone (XIII; R = OMe) with lithium aluminium hydride, alone or in the presence of aluminium chloride, similarly gave the 3-bromoflavan-4-ol (XIV; R = OMe) which was converted with potassium acetate and acetic anhydride into *trans*-3,4-diacetoxy-3′,4′-dimethoxy-6-methyl-2,3-*cis*-flavan (diacetate of IV; R = OMe).

Nuclear magnetic resonance results (Table 1) for the diacetates of the flavan-3,4-diols (I—IV; R = OMe) confirm the configurations shown and indicate that the heterocyclic ring adopts a conformation close to a half-chair, with the 2-aryl group equatorial in each case. The *cis*- and the *trans*-stereochemistry at the 2,3-positions is very clearly indicated by the low spin–spin coupling constants ($J_{2,3}$ = 0·9, 1·0 c./sec.) for the 2,3-*cis*-compounds and the much larger value for the 2,3-*trans*-compounds ($J_{2,3}$ = 10, 9·5 c./sec); the latter values slightly extend the range previously recorded by us [2] from 7·1—8·5 to 7·1—10 (Table 2). Corey, Philbin, and Wheeler [3] record $J_{2,3}$ = 10 c./sec. for 2,3-*trans*-flavan-3,4-*cis*-diol dibenzoate. There is similarly a clear distinction between the 3,4-*cis*-($J_{3,4}$ = 4·3 c./sec.) and 3,4-*trans*-($J_{3,4}$ = *ca.* 1 c./sec.) pair of 2,3-*cis*-flavan-3,4-diols (I and IV; R = OMe), and between the 3,4-*cis*-($J_{3,4}$ = 3·3 c./sec.) and 3,4-*trans*-($J_{3,4}$ = 7·5 c./sec.) pair of 2,3-*trans*-flavan-3,4-diols (II and III; R = OMe). Determination of spin–spin coupling constants for the 2-, 3-, and 4-protons by nuclear magnetic resonance

[9] Kulkarni and Joshi, *J. Indian Chem. Soc.*, 1957, **34**, 217.
[10] Bhide and Limaye, *Rasayanam*, 1955, **2**, 55.
[11] Kashikar and Kulkarni, *J. Sci. Ind. Res., India*, 1959, **18**, *B*, 418.

thus provides a convenient and clear means for determining the stereochemistry of flavan-3,4-diols, illustrated here for the first time with a complete set of the four possible racemates.

It has been suggested [6] that the acetate τ values of 2,3-*trans*-flavan-3,4-diol diacetates indicate the equatorial or axial conformation of the acetoxyl groups and hence provide information on the configurations. 3,4-*cis*-Diacetoxy-3′,4′-dimethoxy-6-methyl-2,3-*trans*-flavan [diacetate of (III; R = OMe)] gave τ values (8·14, 7·84) identical with those

TABLE 1.

τ Values for 3,4-diacetoxy-3′,4′-dimethoxy-6-methylflavans [diacetates of diols (I—IV; R = OMe)].

	Acetyl Me	Aryl Me	*O*-Me	2H	3H	4H
2,3-*cis*-3,4-*cis*	8·08, 7·86	7·69	6·12	4·72	4·36	3·69
2,3-*cis*-3,4-*trans*	8·11, 7·86	7·70	6·12	~4·80	~4·80	4·16
2,3-*trans*-3,4-*cis*	8·14, 7·84	7·73	6·12	4·79	4·50	3·84
2,3-*trans*-3,4-*trans*	8·16, 7·92	7·71	6·12	5·01	4·45	3·79

TABLE 2.

Spin–spin coupling constants for 2H, 3H, and 4H in flavan-3,4-diols and their esters.

	$J_{2,3}$		$J_{3,4}$			
	2,3-*cis* 2(*ax*), 3(*eq*)	2,3-*trans* 2(*ax*), 3(*ax*)	3,4-*trans* 3(*ax*), 4(*ax*)	3,4-*cis* 3(*ax*), 4(*eq*)	3,4-*cis* 3(*eq*), 4(*ax*)	3,4-*trans* 3(*eq*), 4(*eq*)
I; R = OMe	0·9				4·3	
IV; R = OMe	1·0					*ca.* 1·0
II; R = OMe		9·5	7·5			
III; R = OMe		10·0		3·3		
Range for flavan-3,4-diols and esters ...	0—1·0	7·1—10 [a]	5·8 [b]—7·5 [c]	3·3—3·5 [d]	3·9—4·3	0—1·0

[a] Previously recorded,[2] 7·1—8·5 c./sec. [b] Corey, Philbin, and Wheeler [3] report $J_{3,4}$ = 5·8 c./sec. for 2,3-*trans*-flavan-3,4-*trans*-diol dibenzoate. [c] Previously recorded, 6·5—6·7 c./sec. [incorrectly shown [2] in the 3(*ax*), 4(*eq*) column]. [d] Corey, Philbin, and Wheeler [3] report $J_{3,4}$ = 3·5 c./sec. for 2,3-*trans*-flavan-3,4-*cis*-diol dibenzoate.

reported for 3,4-*cis*-diacetoxy-4′-methoxy-6-methyl-2,3-*trans*-flavan and close to those for 3,4-*cis*-diacetoxy-2,3-*trans*-flavan (8·16, 7·87), the peaks due to equatorial acetoxyl occurring at higher field than those of the axial acetoxyl groups.[6] Similarly, our results for the *trans-trans*-diacetate [diacetate of (II; R = OMe); τ 8·16, 7·92] are close to the values recorded [6] for the *trans-trans*-isomers of flavan-3,4-diol diacetate (8·16, 8·02) and 4′-methoxy-6-methylflavan-3,4-diol diacetate (8·17, 7·97). Values for 3,4-*cis*-diacetoxy-3′,4′-dimethoxy-6-methyl-2,3-*cis*-flavan [diacetate of (I; R = OMe); τ 8·08, 7·86] and unpublished values for other *cis-cis*-flavandiol diacetates are also consistent with this view, but 3,4-*trans*-diacetoxy-3′,4′-dimethoxy-6-methyl-2,3-*cis*-flavan [diacetate of (IV; R = OMe); τ 8·11, 7·86] constitutes an apparent exception to this simple interpretation.

EXPERIMENTAL

Nuclear magnetic resonance measurements for the 3,4-diacetoxy-3′,4′-dimethoxy-6-methylflavans [diacetates of diols (I—IV; R = OMe)] dissolved in deuterochloroform were recorded at 60 Mc./sec. with tetramethylsilane as internal standard. Carbonates were prepared from the diols and ethyl chloroformate as described for (±)-melacacidin tetramethyl ether carbonate.[8]

2′-Hydroxy-3,4-dimethoxy-5′-methylchalcone (V; R = OMe).—2-Hydroxy-5-methylacetophenone [12] (10 g.) and veratraldehyde (9 g.) were condensed with the aid of sodium hydroxide, as described by Auwers and Anschütz [7] for the monomethoxy-compound (V; R = H). The sodium salt was collected and added to dilute hydrochloric acid; the precipitated *2′-hydroxy-3,4-dimethoxy-5′-methylchalcone* crystallised from ethanol in orange plates (11·6 g., 58%),

[12] Rosemund and Schnurr, *Annalen*, 1928, **460**, 83.

m. p. 142—143° (Found: C, 72·3; H, 6·2. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·1%). The *acetate* (80%) crystallised from methanol in yellow needles, m. p. 102—103° (Found: C, 70·5; H, 6·0. $C_{20}H_{20}O_5$ requires C, 70·6; H, 5·9%).

3′,4′-Dimethoxy-6-methylflavonol (VI; R = OMe).—The foregoing chalcone (10 g.) was converted into the flavonol (6 g., 57%) with alkaline peroxide as described by King and Bottomley [13] for 7,8,3′,4′-tetramethoxyflavonol; the flavonol crystallised from acetic acid in needles, m. p. 198—199° (lit.,[14] 200°,[15] 198°) (Found: C, 69·2; H, 5·2. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·2%).

3′,4′-Dimethoxy-6-methyl-2,3-cis-flavan-3,4-cis-diol (I; R = OMe).—The foregoing flavonol (2 g.) in ethanol (100 c.c.) was hydrogenated for 14 hr. at 90°/100 atm. over aged Raney nickel (W6; *ca.* 2 g.). The catalyst was removed by filtration through kieselguhr and the filtrate was evaporated under reduced pressure; crystallisation of the residue from benzene gave *3′,4′-dimethoxy-6-methyl-2,3-cis-flavan-3,4-cis-diol* (0·56 g., 28%) in needles, m. p. 162—163° (Found: C, 68·5; H, 6·7; O, 26·0. $C_{18}H_{20}O_5$ requires C, 68·3; H, 6·4; O, 25·3%). A further quantity (0·16 g., 8%) was recovered from the residues by chromatography on alumina. The *diacetate* crystallised from ethanol in needles, m. p. 159—160° (Found: C, 65·6; H, 6·1. $C_{22}H_{24}O_7$ requires C, 66·0; H, 6·0%). The *carbonate* crystallised from ethanol in needles, m. p. 141—142° (Found: C, 66·2; H, 5·5. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%).

4′-Methoxy-6-methyl-2,3-cis-flavan-3,4-cis-diol (I; R = H) (0·32 g., 16%) was prepared by hydrogenation of 4′-methoxy-6-methylflavonol (2·0 g.) as described above for the dimethoxy-analogue, and isolated after chromatography on alumina; it crystallised from ethanol in needles, m. p. 160—161° (lit.,[5] m. p. 162°).

2′-Acetoxy-3,4-dimethoxy-5′-methylchalcone Dibromide (X; R = OMe).—Bromine (2·5 g.) in carbon tetrachloride (10 c.c.) was added slowly to a solution of 2′-acetoxy-3,4-dimethoxy-5′-methylchalcone (5 g.) in carbon tetrachloride (100 c.c.), and after 2 hr. the solution was evaporated under reduced pressure. Crystallisation of the residue from benzene–light petroleum (b. p. 40—60°) gave *2′-acetoxy-3,4-dimethoxy-5′-methylchalcone dibromide* (6·2 g., 84%) in needles, m. p. 146—147° (Found: C, 48·1; H, 4·0; Br, 32·6. $C_{20}H_{20}Br_2O_5$ requires C, 48·0; H, 4·0; Br, 32·0%).

trans-*Dihydro-3′,4′-dimethoxy-6-methylflavonol* (VII; R = OMe).—2′-Acetoxy-3,4-dimethoxy-5′-methylchalcone (6 g.) was converted into the dibromide as described above and the residue, obtained by evaporating the carbon tetrachloride, was boiled with 1 : 4 aqueous acetone (100 c.c.) for 15 min. and then for a further 3 min. after the addition of aqueous 10% sodium carbonate (70 c.c.). Dilution of the cooled solution with water precipitated an oil, which solidified, and crystallisation of the solid from ethanol gave 3,4-trans-*dihydro-3′,4′-dimethoxy-6-methylflavonol* (2·5 g., 40%) in pale yellow needles, m. p. 160—161° (Found: C, 68·7; H, 5·7; O, 25·5. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·8; O, 25·5%).

3,4-trans-*Dihydro-4′-methoxy-6-methylflavonol* (VII; R = H) (50%), m. p. 159—160° (lit.,[9] m. p. 160°), was similarly prepared from 2′-acetoxy-4-methoxy-5′-methylchalcone *via* the dibromide, m. p. 132—133° (lit.,[7] m. p. 126—127°).

3′,4′-Dimethoxy-6-methyl-2,3-trans-flavan-3,4-trans-diol (II; R = OMe).—*trans*-Dihydro-3′,4′-dimethoxy-6-methylflavonol (4 g.) in tetrahydrofuran (30 c.c.) was added dropwise to a stirred mixture of lithium aluminium hydride (0·63 g.) and tetrahydrofuran (100 c.c.) at 0°. After 1 hr. the excess of reagent was decomposed with water, the mixture was poured into cold 3N-hydrochloric acid (30 c.c.), and the solution was extracted with ether and with chloroform. The residue remaining after evaporation of the extract crystallised from benzene and gave *3′,4′-dimethoxy-6-methyl-2,3-trans-flavan-3,4-trans-diol* in needles (2·3 g., 58%), m. p. 185—186° (Found: C, 68·1; H, 6·5. $C_{18}H_{20}O_5$ requires C, 68·3; H, 6·4%). The *diacetate* crystallised from ethanol in colourless needles, m. p. 141—142° (Found: C, 65·6; H, 6·1. $C_{22}H_{24}O_7$ requires C, 66·0; H, 6·0%). The *carbonate* (41%) crystallised from ethanol in needles, m. p. 163—164° (Found: C, 66·9; H, 5·4. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%).

4′-Methoxy-6-methyl-2,3-trans-flavan-3,4-trans-diol (II; R = H).—(*a*) The flavandiol (0·95 g., 32%) was obtained in needles, m. p. 172—173° (lit.,[4] 169° and [6] 172—173°), by reduction of the dihydro-4′-methoxy-6-methylflavonol (3 g.) with lithium aluminium hydride in tetrahydrofuran as described above for the dimethoxy-analogue. The diacetate crystallised from

[13] King and Bottomley, *J.*, 1954, 1399.
[14] Gowan, Hayden, and Wheeler, *J.*, 1955, 862.
[15] Marathe, *Science and Culture*, 1956, **22**, 175; *Chem. Abs.*, 1957, **51**, 5760.

ethanol in needles, m. p. 121—122·5° (lit.,[4] 123° and [6] 121—123°). The carbonate crystallised from ethanol in needles, m. p. 134—136° (lit.,[6] m. p. 136—137·5°).

(*b*) Catalytic hydrogenation [4] of the dihydroflavonol (1 g.) in 85% acetic acid (80 c.c.) at room temperature and pressure over platinum (5%) on carbon similarly gave the flavandiol (0·65 g., 65%), needles, m. p. 171—172°.

(*c*) Sodium borohydride (1·5 g.) was slowly added to a solution of *trans*-dihydro-4′-methoxy-6-methylflavonol (4 g.) in methanol (600 c.c.) at 0°, and after 24 hr. at room temperature the solution was acidified with acetic acid and evaporated under reduced pressure. The residue was kept *in vacuo* over potassium hydroxide for 24 hr., washed with water, and dried; crystallisation from methanol gave the *trans-trans*-diol (2·0 g., 50%), m. p. 171—172°. The residue obtained by evaporation of the methanolic filtrate was chromatographed on alumina (50 g.) deactivated with water (5 g.) and elution with benzene–ether gave a mixture of *cis*- and *trans*-diols from which 4′-methoxy-6-methyl-2,3-*trans*-flavan-3,4-*cis*-diol (0·6 g., 15%) was obtained by crystallisation from ethanol in colourless prisms, m. p. 191—192° alone and when mixed with that described below.

3′,4′-*Dimethoxy*-6-*methyl*-2,3-trans-*flavan*-3,4-cis-*diol* (III; R = OMe).—3,4-Dihydro-3′,4′-dimethoxy-6-methylflavonol (5 g.) in tetrahydrofuran (100 c.c.) was added slowly to a stirred mixture of lithium aluminium hydride (1·5 g.) and aluminium chloride (10·5 g.) in tetrahydrofuran (200 c.c.) at 0°. After 1 hr. the excess of lithium aluminium hydride was decomposed with water (40 c.c.) and 1·5N-hydrochloric acid (40 c.c.), and the mixture was extracted with ether. Removal of the solvent left a residue which gave 3′,4′-*dimethoxy*-6-*methyl*-2,3-trans-*flavan*-3,4-cis-*diol* in needles (4·3 g., 86%), m. p. 201—202°, from ethanol (Found: C, 67·8; H, 6·5. $C_{18}H_{20}O_5$ requires C, 68·3; H, 6·4%). The *diacetate* crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 93—94° (Found: C, 65·9; H, 6·1. $C_{22}H_{24}O_7$ requires C, 66·0; H, 6·0%). The *carbonate* crystallised from ethanol in needles, m. p. 168—169° (Found: C, 66·4; H, 5·4. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%).

4′-*Methoxy*-6-*methyl*-2,3-trans-*flavan*-3,4-cis-*diol* (III; R = H) (0·6 g., 30%) was similarly obtained by reduction of 3,4-dihydro-4′-methoxy-6-methylflavonol (2 g.) with lithium aluminium hydride–aluminium chloride; it crystallised from ethanol in needles, m. p. 192—193° (lit.,[4,5,16] 193° and [6] 192·5—194°). The diacetate crystallised from ethanol in needles, m. p. 96—97° (lit.,[4] m. p. 98°). The carbonate crystallised from ethanol in needles, m. p. 167—168° (lit.,[6] m. p. 167—168°).

3′,4′-*Dimethoxy*-6-*methylflavanone*.—2′-Hydroxy-3,4-dimethoxy-5′-methylchalcone (5 g.) was dissolved in ethanol (400 c.c.), and concentrated hydrochloric acid (130 c.c.) and water (400 c.c.) were added. The mixture was boiled for 4 hr. and then extracted with ether; the extract was washed with aqueous sodium hydroxide before evaporation under reduced pressure. The residual 3′,4′-*dimethoxy*-6-*methylflavanone* crystallised from ethanol in plates (2·6 g., 52%), m. p. 108—109° (Found: C, 72·7; H, 6·0. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·1%).

3-*Bromo*-4′-*methoxy*-6-*methylflavanones* (XIII; R = H).—(*a*) 4′-Methoxy-6-methylflavanone, m. p. 109—110° (lit.,[5] 110°), was prepared as described above for the dimethoxyflavanone. A 25% w/v solution (5·2 c.c.) of bromine in acetic acid was added to a boiling solution of the flavanone (2 g.) in acetic acid (4 c.c.). Next day the crystalline product (*A*) was collected and repeated crystallisation from acetic acid gave 3-bromo-4′-methoxy-6-methylflavanone (1·13 g., 44%) in pale yellow plates, m. p. 157—158° (lit.,[9] m. p. 152°). The filtrate from *A* was diluted with a large volume of water before extraction with ether, and evaporation of the extract left a mixture (0·31 g., 12%), m. p. 120—121°, from which the isomer, m. p. 137—138°, was obtained by recrystallisations from ethanol.

(*b*) 2′-Acetoxy-4-methoxy-5′-methylchalcone dibromide [7] (5 g.), m. p. 132—133° (lit.,[7] 126—127°), was boiled with acetic acid (10 c.c.) for 30 min. and the solution was then evaporated under reduced pressure. Several crystallisations from ethanol gave the 3-bromoflavanone (1·2 g., 33%), m. p. 154—156°, and a mixture of isomers (1·5 g., 41%), m. p. 120—121°. In a second experiment the acetic acid solution was diluted with water and extracted with ether. Evaporation of the ether left a residue which was separated by crystallisation from ethanol into the 3-bromoflavanone (2 g., 55%), m. p. 158—159°, and a mixture (0·6 g., 15%), m. p. 120—121°.

(*c*) 2′-Acetoxy-4-methoxy-5′-methylchalcone dibromide [7] (5 g.) was dissolved in warm 85%

[16] Bognár, Rákosi, Fletcher, Philbin, and Wheeler, *Tetrahedron Letters*, 1959, No. 19, 4.

acetic acid (20 c.c.) and kept at room temperature. The crystalline product was collected after 2 days, and recrystallisation from ethanol gave the bromoflavanone (1·5 g., 41%) in needles, m. p. 137—138° (lit.,[9] 138°).

3-*Bromo*-4′-*methoxy*-6-*methylflavan*-4-*ols* (XIV; R = H).—(*a*) Sodium borohydride (0·7 g.) was added slowly to an ice-cold solution of 3-bromo-4′-methoxy-6-methylflavanone (2 g.), m. p. 158—159°, in methanol (300 c.c.). After 2 days at 0° the solution was acidified with acetic acid and evaporated under reduced pressure, and the residue was chromatographed on alumina (100 g.) deactivated with water (10 g.). Elution with benzene gave the 3-bromoflavan-4-ol (1·3 g., 65%) in needles, m. p. 175—176° (lit.,[5] 175°). The bromoflavanol (0·3 g., 30%), m. p. 175—176°, was also obtained by reduction of the bromoflavanone (1 g.) in tetrahydrofuran (100 c.c.) with lithium aluminium hydride (0·5 g.) and aluminium chloride (3·5 g.).

(*b*) 3-Bromo-4′-methoxy-6-methylflavanone (3 g.), m. p. 137—138°, in tetrahydrofuran (100 c.c.) was added dropwise to a stirred slurry of lithium aluminium hydride (1·5 g.) in tetrahydrofuran (60 c.c.) at 0°. After 1 hr. the excess of reagent was decomposed with water and the yellow solution was then acidified with 1·5N-hydrochloric acid (30 c.c.) before being extracted with ether. The ethereal extract was dried ($MgSO_4$) and evaporation left a residue of the bromoflavanol, which crystallised from ethanol in needles (1·56 g., 52%), m. p. 201—202° (lit.,[5] 200°).

3-*Bromo*-3′,4′-*dimethoxy*-6-*methylflavanone* (XIII; R = OMe).—The crude chalcone dibromide, obtained as an oil by addition of bromine to 2′-acetoxy-3,4-dimethoxy-5′-methylchalcone (24 g.), was dissolved in warm 85% acetic acid 100 c.c.). Next day the solution was diluted with water and cooled, and the semi-solid precipitate crystallised from ethanol in needles (11·5 g., 43%), m. p. 142—143°, consisting of 3-*bromo*-3′,4′-*dimethoxy*-6-*methylflavanone* (Found: C, 57·4; H, 4·7; Br, 21·8. $C_{18}H_{17}BrO_4$ requires C, 57·3; H, 4·5; Br, 21·2%).

3-*Bromo*-3′,4′-*dimethoxy*-6-*methylflavan*-4-*ol* (XIV; R = OMe).—Reduction of 3-bromo-3′,4′-dimethoxy-6-methylflavanone (5 g.), m. p. 142—143°, as described above for the 4′-methoxy-analogue, with lithium aluminium hydride alone or mixed with aluminium chloride, gave 3-*bromo*-3′,4′-*dimethoxy*-6-*methylflavan*-4-*ol* which crystallised from ethanol in needles (2·4 g., 48%), m. p. 179—181° (Found: C, 57·6; H, 5·5; Br, 21·4. $C_{18}H_{19}BrO_4$ requires C, 57·0; H, 5·0; Br, 21·1%).

3,4-trans-*Diacetoxy*-4′-*methoxy*-6-*methyl*-2,3-cis-*flavan* [*Diacetate of* (IV; R = H)].—The 3-bromo-4′-methoxy-6-methylflavan-4-ol (0·3 g.), m. p. 201—202°, was converted into the diol with ethanolic potassium acetate as described by Joshi and Kulkarni.[5] The diol remained as an oil, and acetylation gave the diacetate (0·17 g., 54%) which crystallised from ethanol in needles, m. p. 148—149° unchanged by recrystallisation (lit.,[5] m. p. 150°).

3,4-trans-*Diacetoxy*-3′,4′-*dimethoxy*-6-*methyl*-2,3-cis-*flavan* [*Diacetate of* (IV; R = OMe)].—The 3-bromo-3′,4′-dimethoxy-6-methylflavan-4-ol (0·5 g.), m. p. 179—181°, was boiled for 70 hr. with acetic anhydride (5 c.c.), acetic acid (20 c.c.), and potassium acetate (2 g.), and the solution was then diluted with ice–water (200 c.c.). The precipitated solid crystallised from ethanol in needles (0·34 g., 64%), m. p. 179—180°, consisting of 3,4-trans-*diacetoxy*-3′,4′-*dimethoxy*-6-*methyl*-2,3-cis-*flavan* (Found: C, 65·7; H, 5·6. $C_{22}H_{24}O_7$ requires C, 66·0; H, 6·0%). The bromoflavanol gave an oil when treated with ethanolic potassium acetate as described above for the 4′-methoxy-analogue.

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