Epimerisation of 4-Acetoxyflavans and of Flavan-4-ols

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5,7,3′,4′-Tetramethoxyflavan-4β-ol reacts at 0 °C with pyridine, acetic anhydride, and a trace of acetic acid to give the 4β-acetoxy derivative but at 90 °C the 4α-acetoxyflavan is formed. Either acetate when equilibrated with this acetylating agent yields a mixture of the 4α- and the 4β-acetoxy compounds containing 5—10% of the 4β-isomer, from which we conclude that the 4α-acetate is of greater thermodynamic stability than its 4β-epimer. For the epimerisation we favour an S_N1 mechanism through a 4-carbocation. Substitution of methoxy groups at the 5- and 7-positions controls the ease of the epimerisation, the order of decreasing reactivity being 5,7,3′,4′-tetramethoxy ≈ 5,7-dimethoxy > 7,3′,4′-trimethoxy ≈ 3-acetoxy-5,7,3′,4′-tetramethoxy > 5,3′,4′-trimethoxy ≫ 3′,4′-dimethoxy. Flavan-4β-ols unsubstituted in ring A give the corresponding 4α-acetoxyflavans when heated with glacial acetic acid and a small amount of toluene-*p*-sulphonic acid, again indicating the greater stability of the 4α-compounds. Flavan-4β-ols can be epimerised to 4α-ols in acidified solvents, the ease of the epimerisation being greatly increased by 5- and 7-methoxy substituents.

There are several examples of the epimerisation of 4-substituted flavans. Some 3,4-*cis*- and 3,4-*trans*-diols give the same 3,4-*cis*-isopropylidene derivative with acetone and a Lewis acid [1,2] and certain 3,4-diols epimerise at C-4 when they form 4-ethoxy derivatives in ethanol and hydrochloric acid.[3] Also, acetylation of 2,3-*trans*-3,4-*trans*-5,7,3′,4′-tetramethoxyflavan-3,4-diol gives the 3,4-*cis*-diacetate [4] whereas 2,3-*trans*-3,4-*cis*-6-methyl-3′,4′-dimethoxyflavan-3,4-diol gives the 3,4-*trans*-diacetate.[5] In addition, Krishnamurthy *et al.*[6] report that 5,7,3′,4′-tetramethoxy- and 5,7,4′-trimethoxyflavan-4β-ols do not form acetates on treatment with acetic anhydride and pyridine but that the products are the corresponding flavan-4α-ols.† Two further puzzling reports concerning stereochemistry and reactivity at C-4 are that flavan-4β-ols react with phosphorus tribromide to give 4-bromides assumed to be 4β-compounds and these are said to react with alcoholic potassium hydroxide to yield flavan-4α-ols [7] and that 4′-methoxyflavan-4β-ol with thiophenol gives the corresponding 4α-thio compound but that flavan-4β-ol does not react under the same conditions.[8]

We have made a systematic study of the epimerisation of 4-acetoxyflavans and of flavan-4-ols with a view to explaining these observations and in order to establish any relationship which might exist between the methoxy substitution pattern and the ease of epimerisation at the 4-position.

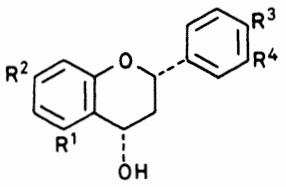
A series of 4β-acetates have been prepared by treating flavan-4β-ols with acetic anhydride and pyridine at room temperature. To avoid formation of the 4-carbocation from the more highly substituted flavan acetates, water was avoided in the work-up; instead, the reagents were removed under reduced pressure and the residues then recrystallised. The 4β-acetates (8), (10), and (11), were successfully prepared in this way and the acetate (12) which Krishnamurthy *et al.*[6] had been unable to prepare, was obtained in good yield by acetylation of the corresponding 4β-ol (7) at 0 °C. However, when this acetylation was carried out at 90 °C, the epimeric 4α-acetoxy-5,7,3′,4′-tetramethoxyflavan (19) was obtained in 64% yield. 5,7-Dimethoxyflavan-4β-acetate (9) was also obtained by acetylation of the 4β-ol (4) at 0 °C. The n.m.r. peaks at *ca.* τ 8 confirmed that in each case acetylation had occurred and the stereochemistry, 4α (2,4-*trans*) or 4β (2,4-*cis*), was inferred from $\Sigma J_{3,4}$.[9]

The formation of two epimeric acetates from 5,7,3′,4′-tetramethoxyflavan-4β-ol (7) suggests that the 4β-acetate (12) formed at low temperature, results from kinetic control and the 4α-acetate (19), formed at high temperature, from thermodynamic control. To test this hypothesis, samples of the pure acetates were heated with pyridine, acetic anhydride, and a trace of acetic acid. Volatile matter was removed and n.m.r. spectra showed that both samples were now identical and consisted of a mixture of the 4β- and 4α-acetate which contained 5—10% of the 4β-isomer. This proportion, having been obtained starting from either pure isomer, must indicate the composition of an equilibrium mixture and enables the conclusion to be drawn that the 4α-acetate is of greater thermodynamic stability than its 4β-epimer.

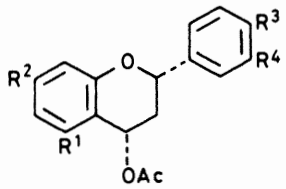
Three feasible mechanisms can be suggested for the epimerisation of the 4β-acetate and of these that involving elimination and re-addition of acetic acid was ruled out by the observation that the postulated intermediate, the flav-3-ene, is inert under the conditions of the reaction.[3] Another possibility is an S_N2 mechanism involving acetate ion or acetic acid. Against this however is the reaction of both 4α- and 4β-acetoxy-5,7,3′,4′-tetramethoxyflavans (19) and (12) with potassium hydroxide in methanol which results partly in cleavage of the esters by the normal acyl–oxygen fission to give the alcohol of unchanged stereochemistry and partly in cleavage by alkyl-oxygen fission to give from each ester 4α,5,7,3′,4′-pentamethoxyflavan. 4β,5,7,3′,4′-Pentamethoxyflavan was shown to be inert to methanolic potassium hydroxide and would therefore have been detected had it been formed by S_N2 attack on the 4α-acetate (19). Other reactions of both 4α- and 4β-acetates with nucleophiles in which the products invariably have 4α-stereochemistry will be discussed in later papers. We therefore believe that the most likely route for equilibration of the two acetates is by an S_N1 mechanism resulting in a 4-carbocation (27) which recombines with acetic acid. Since 4β-acetoxytetramethoxyflavan (12) was found to be stable in hot pyridine, it seems probable that the initial loss of acetate is catalysed by the inevitable traces of acetic acid in the acetic anhydride.

We next considered whether the other available 4β-acetoxyflavans would epimerise and since the epimerisation is thought to be acid catalysed, we used acetic anhydride which contained 25 mol percent of acetic acid (monitored by n.m.r.) for many of our subsequent investigations. 4β-Acetoxy-5,7-dimethoxyflavan (9) was found to have similar reactivity to that of its 4β-acetoxy-5,7,3′,4′-tetramethoxy analogue (12) in that from each, the corresponding 4α-acetoxyflavan (16) or (19) was

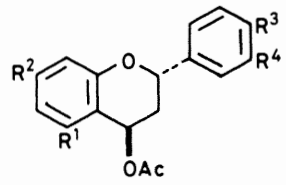
† The convention in flavonoid chemistry is that α = 2,4-*trans* and β = 2,4-*cis*.



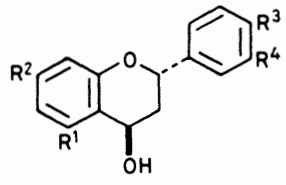
(1) $R^1 = R^2 = R^3 = R^4 = H$
(2) $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
(3) $R^1 = R^2 = H$, $R^3 = R^4 = OMe$
(4) $R^1 = R^2 = OMe$, $R^3 = R^4 = H$
(5) $R^1 = H$, $R^2 = R^3 = R^4 = OMe$
(6) $R^2 = H$, $R^1 = R^3 = R^4 = OMe$
(7) $R^1 = R^2 = R^3 = R^4 = OMe$



(8) $R^1 = R^2 = H$, $R^3 = R^4 = OMe$
(9) $R^1 = R^2 = OMe$, $R^3 = R^4 = H$
(10) $R^1 = H$, $R^2 = R^3 = R^4 = OMe$
(11) $R^2 = H$, $R^1 = R^3 = R^4 = OMe$
(12) $R^1 = R^2 = R^3 = R^4 = OMe$



(13) $R^1 = R^2 = R^3 = R^4 = H$
(14) $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
(15) $R^1 = R^2 = H$, $R^3 = R^4 = OMe$
(16) $R^1 = R^2 = OMe$, $R^3 = R^4 = H$
(17) $R^1 = H$, $R^2 = R^3 = R^4 = OMe$
(18) $R^2 = H$, $R^1 = R^3 = R^4 = OMe$
(19) $R^1 = R^2 = R^3 = R^4 = OMe$



(20) $R^1 = R^2 = R^3 = R^4 = H$
(21) $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
(22) $R^1 = R^2 = H$, $R^3 = R^4 = OMe$
(23) $R^1 = R^2 = OMe$, $R^3 = R^4 = H$
(24) $R^1 = H$, $R^2 = R^3 = R^4 = OMe$
(25) $R^2 = H$, $R^1 = R^3 = R^4 = OMe$
(26) $R^1 = R^2 = R^3 = R^4 = OMe$

All compounds are racemic. Relative stereochemistry is indicated

obtained in *ca.* 60% yield after treatment at 80 °C with pyridine and the acetic anhydride–acetic acid mixture. On the other hand, 4β-acetoxy-7,3′,4′-trimethoxyflavan (10) was inert to the pyridine–acetic anhydride–acetic acid mixture but treatment of it with acetic anhydride–acetic acid without pyridine at 60 °C readily gave 4α-acetoxy-7,3′,4′-trimethoxyflavan (17). 4β-Acetoxy-5,3′,4′-trimethoxyflavan (11) required more vigorous heating (90 °C) with acetic anhydride–acetic acid before conversion into 4α-acetoxy-5,3′,4′-trimethoxyflavan (18) occurred, while 4β-acetoxy-3′,4′-dimethoxyflavan (8) was unaffected even under these vigorous conditions (see Table).

Assuming that the transition state for formation of the 4-carbocation (27) resembles that ion in structure and hence in energy, the observed order of reactivity is just what would be expected for an S_N1 mechanism since the stability of the carbocation (27) is increased by methoxy substitution in the 5- and 7-positions. The greater reactivity of 7,3′,4′- (10) compared with 5,3′,4′-trimethoxy-4β-acetoxyflavan (11) is analogous to the greater reactivity of anisole towards electrophiles at the *para* compared with the *ortho* position [40] and perhaps represents the difference in energy between the *ortho* (for the 5,3′,4′-compound) and the *para* (for the 7,3′,4′-compound) quinonoid canonicals of the 4-carbocations (28) and (29) respectively.

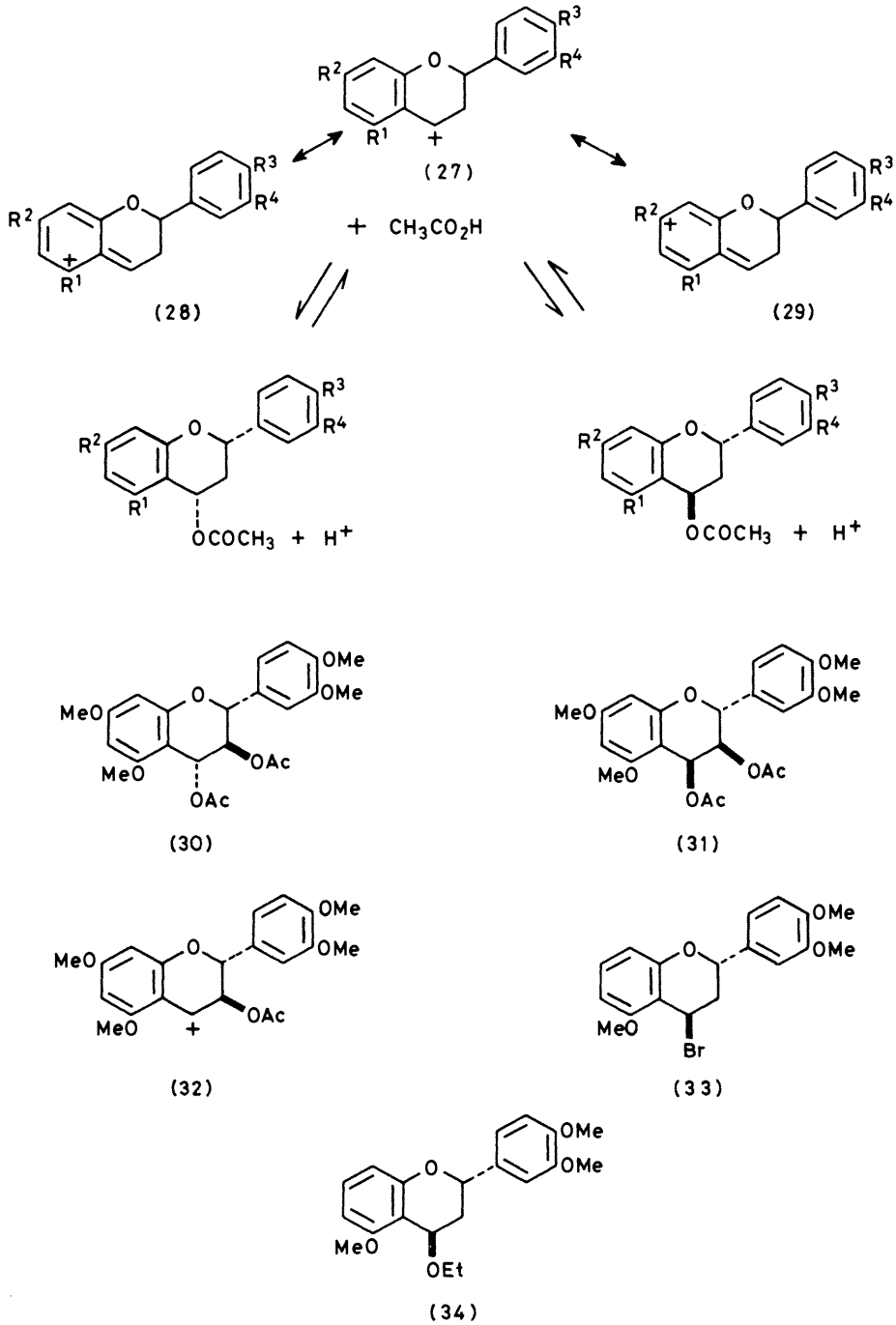
For flavanoids without methoxy substituents in ring A, we have found it possible to cause epimerisation at the 4-position by treating the flavan-4β-ols (1), (2) and (3) with glacial acetic acid and a small amount of toluene-*p*-sulphonic acid at 80 °C. The products, isolated in high yield, were the 4α-acetates (13), (14), and (15) which can be hydrolysed to the 4α-ols (20), (21), and (22). This is a further indication that 4α-substituted (2,4-*trans*) compounds are thermodynamically more stable than the corresponding 4β-(2,4-*cis*) compounds and it is understandable that without assistance from methoxy groups suitably placed (5 or 7) in the A ring, more forcing conditions, *i.e.* glacial acetic acid and toluene-*p*-sulphonic acid, are necessary to effect the 4β to 4α-conversion.

Table. The epimerisation of 4β-acetoxyflavans by various reagents

Methoxylation pattern	Compound	% of 4α-Acetate isolated with Reagent: * i	ii	iii
3′,4′	(8)	0	0	0 †
5,3′,4′	(11)	0 †	0 †	59
7,3′,4′	(10)	0 †	34	
5,7,3′,4′	(12)	60		
5,7	(9)	57		

* *Reagents:* i, pyridine–acetic anhydride–acetic acid at 80 °C; ii, acetic anhydride–acetic acid at 60 °C; iii, acetic anhydride–acetic acid at 90 °C. † 4β-Acetate recovered.

We have investigated the epimerisation of 2,3-*trans*-3,4-*trans*-diacetoxy-5,7,3′,4′-tetramethoxyflavan (30) and its 2,3-*trans*-3,4-*cis*-isomer (31).[2] The *trans*-*trans*-compound (30) was unaffected by the pyridine–acetic anhydride–acetic acid mixture at 80 °C but the acetic anhydride–acetic acid mixture at 60 °C converted it into the thermodynamically more stable *trans*,*cis*-compound (31) in 70% isolated yield. Equilibration of either diacetate in the acetic anhydride–acetic acid mixture gave 14—18% of the *trans*,*trans*-isomer (30) and 82—86% of the *trans*,*cis*-isomer (31). Thus, in reactivity, the *trans*,*trans*-diacetate (30) resembles 4β-acetoxy-7,3′,4′-trimethoxyflavan



(10) (see Table), the presence of the 3-acetoxy group decreasing the reactivity at the 4-position, presumably because the inductive effect of the 3-acetoxy group destabilises the 4-carbocation (32).

Treatment of flavan-4β-ol (1) with boiling aqueous acidic dioxane gave flavan-4α-ol (20) (50%) and with increased methoxy substitution in ring A the epimerisation was effected by aqueous acid in a suitable solvent at room temperature. In this way the 4β-ols (5), (6), and (7) were converted into the corresponding 4α-ols (24), (25), and (26) in yields of 47, 30, and 62% respectively, thus furnishing an adequate general synthesis of flavan-4α-ols and providing evidence that a 4α-ol is thermodynamically more stable than a 4β-ol.

We find that 5,3′,4′-trimethoxyflavan-4α-ol (25) melts at 121—123 °C whereas Kamat *et al.*[7] record m.p. 86—88 °C for the compound they obtained *via* the 4-bromoflavan. We repeated the procedure of these authors and by treating 5,3′,4′-trimethoxyflavan-4β-ol (6) with phosphorus tribromide, isolating the 4α-bromoflavan (33), and treating this with ethanolic potassium hydroxide, obtained the compound of m.p. 86—88 °C which we identified (n.m.r. and elemental analysis) as 4α-ethoxy-5,3′,4′-trimethoxyflavan (34). From our own results [11] we know that 4-bromoflavans prepared in this way have 4α-stereochemistry and the S_N1 reaction with ethanolic potassium hydroxide follows the established pattern through the 4-carbocation (27) which reacts irreversibly (being in alkaline conditions) with the most abundant nucleophile, ethanol, to give the 4α-ethoxyflavan (34). In confirm-

ation of this mechanism we obtained 5,3′,4′-trimethoxyflavan-4α-ol (25) (74%) by treating the 4α-bromoflavan (33) with aqueous alkaline dioxane and forcing the carbocation (27) to react with the hydroxide ion or with water.

It seems likely that Kamat *et al.*[7] also obtained 4α-ethoxy-5,4′-dimethoxyflavan instead of 5,4′-dimethoxyflavan-4α-ol from 4-bromo-5,4′-dimethoxyflavan with ethanolic potassium hydroxide. On the other hand 4-bromo-5,7,3′,4′-tetramethoxyflavan (which Kamat *et al.*[7] did not isolate) may already have reacted with water before ethanolic alkali was added, giving 5,7,3′,4′-tetramethoxyflavan-4α-ol as claimed.

The 5,7,3′,4′-tetramethoxyflavan-4α-ol (26) which we obtained from the 4β-ol (7) had a wide m.p. range (80—90 °C) not greatly changed by recrystallisation. A sample prepared by reduction of 4α-acetoxy-5,7,3′,4′-tetramethoxyflavan (19) with lithium aluminium hydride had m.p. 126.5—127.5 °C and the two samples had identical n.m.r. spectra. Krishnamurthy *et al.*[6] record m.p. 89 °C and it may be that the samples of low melting point are contaminated with polymeric flavanoids which are not removed by recrystallisation. The 4α-ol probably arose in the attempted acetylation by Krishnamurthy *et al.*[6] by cleavage of the flavanyl acetate in the aqueous and polar medium of the isolation procedure, the resulting 4-carbocation then reacting with water to give the flavan-4α-ol (26).

Since we find that 5,7-dimethoxy substitution of ring A has a marked effect on reactivity at the flavanoid 4-position but that 3′,4′-substitution of ring B has little effect, we reinvestigated the reaction of thiophenol with flavan-4β-ol and with 4′-methoxyflavan-4β-ol.[8] Treatment of both 4β-ols with thiophenol in 1 : 1 dioxane–0.5M HCl gave comparable yields (*ca.* 60%) of the corresponding flavan-4α-yl phenyl sulphides together with *ca.* 15% of the corresponding flavan-4α-ols which probably result from reaction of the 4-carbocation intermediates with water in the reaction mixture. Thus, contrary to the earlier statement,[8] methoxy substitution at the 4′-position of ring B had no effect on this reaction.

Experimental

M.p.s were determined on a Kofler block and are corrected. ^{1}H N.m.r. spectra were determined at 90 or 100 MHz; coupling constants are quoted in Hz. Dichloromethane was washed with sulphuric acid and aqueous sodium hydroxide, distilled from calcium hydride, and stored over molecular sieve. Organic extracts were dried over magnesium sulphate. Petroleum refers to redistilled light petroleum, b.p. 60—80 °C.

3′,4′-*Dimethoxyflavan*-4β-*ol* (3).—3′,4′-Dimethoxyflavanone (10.0 g) in chloroform (100 ml) and methanol (150 ml) was treated with sodium borohydride (3.5 g) at −10 °C for 3 h. Water (700 ml) was added, the mixture separated, and the aqueous phase extracted with chloroform (3 × 100 ml). The combined organic extracts were washed with water (2 × 100 ml), dried, and evaporated. Crystallisation of the residue from ethanol–water furnished 3′,4′-*dimethoxyflavan*-4β-*ol* (3) (9.2 g) as rods, m.p. 157.5—158.5 °C (Found: C, 71.3; H, 6.25. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.3), $\nu_{max.}$ (Nujol) 3 500 cm^{-1} (OH).

7,3′,4′-*Trimethoxyflavan*-4β-*ol* (5).—7,3′,4′-Trimethoxyflavanone [12] (2.0 g) in chloroform (25 ml) and methanol (50 ml) at 0 °C was reduced overnight with sodium borohydride (0.7 g). After dilution with water and chloroform, extraction with ether afforded 7,3′,4′-*trimethoxyflavan*-4β-*ol* (5) (1.85 g), m.p. 139—140 °C (from methanol) (Found: C, 68.5; H, 6.45. $C_{18}H_{20}O_5$ requires C, 68.35; H, 6.35%), τ ($CDCl_3$) 2.64 (1 H, d, 5-H), 2.98—3.12 (3 H, m, B ring), 3.40—3.60 (2 H, m, 6-H and 8-H), 4.94 (1 H, dd, 2-H), 5.02 (1 H, dd, 4-H), 6.12 (6 H, s, 2 × OMe), 6.26 (3 H, s, OMe), 7.56 (1 H, ddd, 3-H), 7.88 (1 H, m, 3-H), and 7.82 (1 H, s, OH, exchangeable), Σ $J_{2,3}$ 13.6, Σ $J_{3,4}$ 16.4.

5,7,3′,4′-*Tetramethoxyflavan*-4β-*ol* (7).—5,7,3′,4′-Tetramethoxyflavanone [13] (5.1 g) in chloroform (100 ml) and methanol (100 ml) was reduced at 0 °C with sodium borohydride (1.5 g). After 2 h, the mixture was diluted with water and extracted with ether. The dried organic extracts furnished 5,7,3′,4′-tetramethoxyflavan-4β-ol (7) (4.1 g), m.p. 113—116 °C (from ethanol containing a trace of potassium hydroxide) (lit.,[14] m.p. 116—117 °C).

Preparation of 4β-*Acetoxyflavans* (8), (9), (10), (11), *and* (12).—The appropriate flavan-4β-ol was allowed to react in dry pyridine (4 ml for 1 g of flavanol) with acetic anhydride (4 ml for 1 g of flavanol). Evaporation at 30 °C and recrystallisation from dichloromethane–petroleum gave the corresponding 4β-acetates.

By this method 3′,4′-dimethoxyflavan-4β-ol (3) (1.0 g) after 22 h at 20 °C gave 4β-*acetoxy*-3′,4′-*dimethoxyflavan* (8) as needles, m.p. 116—118 °C (Found: C, 69.4; H, 6.25. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.15%). 5,7-Dimethoxyflavan-4β-ol [7] (4) (240 mg) after 48 h at 0 °C gave prisms of 4β-*acetoxy*-5,7-*dimethoxyflavan* (9) (172 mg), m.p. 96—98 °C (Found: C, 69.6; H, 6.25. $C_{17}H_{20}O_5$ requires C, 69.5; 6.15%), τ ($CDCl_3$) 2.66 (5 H, bs, B-ring), 3.74—3.94 (3 H, m, 4-H and A-ring), 4.78 (1 H, dd, 2-H), 6.22 (3 H, s, OMe), 6.26 (3 H, s, OMe), 7.28—8.00 (2 H, m, 3-H's), 8.24 (3 H, s, $ClCH_3$), Σ $J_{2,3}$ = 12.4, Σ $J_{3,4}$ = 13.0.

5,3′,4′-Trimethoxyflavan-4β-ol [7] (6) (0.50 g) after 42 h at 20 °C gave 4β-*acetoxy*-5,3′,4′-*trimethoxyflavan* (11) (0.49 g) as needles, m.p. 137—139 °C (Found: C, 67.2; H, 6.0. $C_{20}H_{22}O_6$ requires C, 67.0; H, 6.2%), τ ($CDCl_3$) 2.80 (1 H, t, 7-H), 3.00—3.12 (3 H, m, B-ring), 3.38 and 3.52 (2 H, 2 bd, A-ring), 3.68 (1 H, t, 4-H), 4.88 (1 H, dd, 2-H), 6.10 (6 H, bs, 2 × OMe), 6.20 (3 H, s, OMe), 7.22—7.90 (2 H, m, 3-H's), and 8.08 (3 H, s, $COCH_3$), Σ $J_{2,3}$ 12.6, Σ $J_{3,4}$ 14.4.

7,3′,4′-Trimethoxyflavan-4β-ol (5) (0.40 g) after 20 h at 20 °C gave 4β-*acetoxy*-7,3′,4′-*trimethoxyflavan* (10) (0.43 g) as prisms, m.p. 101—103 °C (Found: C, 67.1; H, 6.15. $C_{20}H_{22}O_6$ requires C, 67.0; H, 6.2%), τ ($CDCl_3$) 2.80—3.52 (6 H, m, aromatics), 3.82 (1 H, bdd, 4-H), 4.86 (1 H, dd, 2-H), 6.10 (6 H, s, 2 × OMe), 6.20 (3 H, s, OMe), 7.24—7.90 (2 H, m, 3-H's), and 7.88 (3 H, s, $COCH_3$), Σ $J_{2,3}$ 13.4, Σ $J_{3,4}$ 16.6.

5,7,3′,4′-Tetramethoxyflavan-4β-ol (7) (3.0 g) after 3 days at 0 °C gave needles of 4β-*acetoxy*-5,7,3′,4′-*tetramethoxyflavan* (12) (2.6 g), m.p. 125—127 °C (Found: C, 64.95; H, 6.3. $C_{21}H_{24}O_7$ requires C, 64.95; H, 6.25%), τ ($CDCl_3$) 2.98—3.10 (3 H, m, B-ring), 3.74 (1 H, t, 4-H), 3.82 and 3.90 (2 H, 2d, A-ring), 4.90 (1 H, dd, 2-H), 6.10 and 6.12 (6 H, 2s, 2 × OMe), 6.22 (6 H, s, 2 × OMe), 7.24—7.90 (2 H, m, 3-H's), and 8.10 (3 H, s, $COCH_3$), Σ $J_{2,3}$ 12.4, Σ $J_{3,4}$ 14.8.

4α-*Acetoxy*-5,7,3′,4′-*tetramethoxyflavan* (19).—5,7,3′,4′-Tetramethoxyflavan-4β-ol (7) (0.50 g) in dry pyridine (1 ml) and acetic anhydride (1 ml) was heated to 90 °C for 1 h. Evaporation and recrystallisation from dichloromethane–petroleum gave 4α-*acetoxy*-5,7,3′,4′-*tetramethoxyflavan* (19) (0.36 g) as needles, m.p. 124—126.5 °C (Found: C, 65.0; H, 6.35. $C_{21}H_{24}O_7$ requires C, 64.95; H, 6.25%), τ ($CDCl_3$) 2.96—3.08 (3 H, m, B-ring), 3.78—3.92 (3 H, m, 4-H and A-ring), 4.90 (1 H, dd, 2-H), 6.08, 6.10, 6.20, and 6.22 (12 H, 4s, 4 × OMe), 7.70—7.90 (2 H, m, 3-H's), and 7.90 (3 H, s, $COCH_3$), Σ $J_{2,3}$ 14.2, Σ $J_{3,4}$ < 11.

Equilibration of 4β- *and* 4α-*Acetoxy*-5,7,3′,4′-*tetramethoxyflavans* (12) *and* (19).—Separate samples (65 mg each) of 4α- and 4β-acetoxy-5,7,3′,4′-tetramethoxyflavan in dry pyridine (0.5 ml), acetic anhydride (0.5 ml), and acetic acid (1 drop) were heated to 90 °C for 2 h. The solvent was removed on a rotary oil pump at 80 °C and the residue dried *in vacuo* over potassium hydroxide. The n.m.r. spectrum of each sample resembled that of 4α-acetoxy-5,7,3′,4′-tetramethoxyflavan with an extra peak at τ 8.10 due to the 4β-isomer. Comparison of the integrated intensity of this peak with the corresponding (acetyl) peak of the 4α-isomer or with the signal due to 2-H (τ 4.90), showed that in each sample the proportion of the 4β-isomer was 5—10%.

The Effect of Hot Acetic Anhydride–Acetic Acid–Pyridine on 5,7,3′,4′-*Tetramethoxyflav*-3-*ene*.—5,7,3′,4′-Tetramethoxyflav-3-ene [15] (100 mg) in dry pyridine (0.5 ml), acetic anhydride (0.5 ml), and acetic acid (1 drop) was heated to 90 °C for 3 h. After evaporation, starting material (80 mg) separated from ether, m.p. and mixed m.p. 121—122 °C.

Reaction of 4α- (19) *and* 4β-*Acetoxy*-5,7,3′,4′-*tetramethoxyflavan* (12) *with Methanolic Potassium Hydroxide*.—(*a*) 4β-Acetoxy-5,7,3′,4′-tetramethoxyflavan (12) (125 mg) was added to a boiling solution of potassium hydroxide (80 mg) in methanol (5 ml). After a few minutes, the mixture was allowed to cool, diluted with ether (50 ml), washed with water (10 ml) and brine, and dried. Removal of the solvent left an oil which was chromatographed on 2 × 20 cm p.l.c. plates (coating, Merck $PF_{254 + 366}$silica; eluant, ether).

The faster running band (60 mg) separated from methanol as needles of 4α,5,7,3′,4′-*pentamethoxyflavan*, m.p. 98.5—100 °C (Found: C, 66.6; H, 6.9. $C_{20}H_{24}O_6$ requires C, 66.65; H, 6.7%), τ ($CDCl_3$) 2.92—3.16 (3 H, m, B-ring), 3.88 (2 H, s, 6-H and 8-H), 4.76 (1 H, dd, 2-H), 5.42 (1 H, t, 4-H), 6.08, 6.10, 6.12, and 6.22 (12 H, 4s, 4 × OMe), 6.50 (3 H, s, 4-OMe), 7.68 (1 H, dt, 3-H), and 8.10 (1 H, 8 lines, 3-H), Σ $J_{2,3}$ 14.6, Σ $J_{3,4}$ 5.2.

The slower band (27 mg) separated from methanol as prisms of 5,7,3′,4′-tetramethoxyflavan-4β-ol, m.p. 111—118 °C, n.m.r. identical with that of an authentic sample.

(*b*) 4α-Acetoxy-5,7,3′,4′-tetramethoxyflavan (19) (120 mg) treated as in (*a*) also yielded two products. The faster running band (48 mg) separated from methanol as needles of 4α,5,7,3′,-4′-pentamethoxyflavan, m.p. and mixed m.p. 97—99 °C.

The slower band (35 mg) separated from methanol as prisms of 5,7,3′,4′-tetramethoxyflavan-4α-ol (26), m.p. 82—87 °C, identified by n.m.r. spectroscopy (see below).

4β,5,7,3′,4′-*Pentamethoxyflavan*.—5,7,3′,4′-Tetramethoxyflavan-4β-ol (7) (0.34 g) in dry dimethylformamide (10 ml) was treated with sodium hydride (50% dispersion; 0.25 g) and then methyl iodide (0.5 ml). After 6 h, ether (150 ml) was added and the mixture was washed twice with water, dried, and evaporated. Crystallisation from methanol gave 4β,5,7,3′,-4′-*pentamethoxyflavan* (0.21 g), m.p. 110—112 °C (Found: C, 66.55; H, 6.7. $C_{20}H_{24}O_6$ requires C, 66.65; H, 6.7%), τ ($CDCl_3$) 3.00—3.20 (3 H, m, B-ring), 3.90 (2 H, s, 6-H and 8-H), 5.02 (1 H, dd, 2-H), 5.22 (1 H, t, 4-H), 6.10, 6.12, 6.18, 6.24, and 6.68 (15 H, 5 s, 5 × OMe), and 7.38—7.82 (2 H, m, 3-H's), Σ $J_{2,3}$ 12.8, Σ $J_{3,4}$ 14.8.

A sample crystallised unchanged after treatment for several minutes with boiling methanolic potassium hydroxide.

The Action of Heat on 4β-*Acetoxy*-5,7,3′,4′-*tetramethoxyflavan in Pyridine*.—4β-Acetoxy-5,7,3′,4′-tetramethoxyflavan (100 mg) in dry pyridine (1 ml) was heated to 80 °C for 2 h. Evaporation of the solvent left a gum which separated from dichloromethane–light petroleum (b.p. 60—80 °C) as needles of 4β-acetoxy-5,7,3′,4′-tetramethoxyflavan (81 mg), m.p. and mixed m.p. 125—127 °C.

The Relative Reactivities of Variously Substituted 4β-*Acetoxyflavans*.—The 4β-acetoxyflavans were treated with one or more of the following reagents (acetic anhydride mixture = acetic anhydride containing 25 mol percent of acetic acid): i, 1 : 1 acetic anhydride mixture–pyridine at 65 °C; ii, 1 : 1 acetic anhydride mixture–pyridine at 80 °C or 90 °C (temperature specified in text); iii, acetic anhydride mixture at 60 °C; and iv, acetic anhydride mixture at 90 °C. The reaction mixtures were worked up by evaporation of volatile matter at 0.2 Torr and the residues were either examined immediately by n.m.r. spectroscopy or the products isolated by crystallisation from dichloromethane–light petroleum (b.p. 60—80 °C) and identified.

(*a*) 4β-*Acetoxy*-5,7,3′,4′-*tetramethoxyflavan* (12). The 4β-acetoxyflavan (50 mg) treated with reagent i (1 ml) for 1 h gave a 1 : 1 mixture of 4α- and 4β-acetoxy-5,7,3′,4′-tetramethoxyflavan, identified by n.m.r. spectroscopy.

Treatment of the 4β-acetoxyflavan (103 mg) with reagent ii (1 ml) at 80 °C for 2 h, yielded 4α-acetoxy-5,7,3′,4′-tetramethoxyflavan (62 mg), m.p. and mixed m.p. 124.5—126.5 °C (depressed on admixture with 4β-isomer).

(*b*) 4β-*Acetoxy*-5,7-*dimethoxyflavan* (9). Treatment of the 4β-acetoxyflavan (30 mg) with reagent i (1 ml) for 1 h gave a 1 : 1 mixture of 4α- and 4β-acetoxy-5,7-dimethoxyflavan, identified by n.m.r. spectroscopy.

The 4β-acetoxyflavan (106 mg) with reagent ii (1 ml) at 80 °C for 2 h furnished 4α-*acetoxy*-5,7-*dimethoxyflavan* (16) (60 mg) as rods, m.p. 123—125 °C (Found: C, 69.4; H, 6.25. $C_{17}H_{20}O_5$ requires C, 69.5; H, 6.15%), τ ($CDCl_3$) 2.58 (5 H, bs, B-ring), 3.78—3.90 (3 H, m, A-ring and 4-H), 4.84 (1 H, dd, 2-H), 6.20 (6 H, bs, 2 × OMe), 7.70—7.92 and 7.90 (5 H, m and s, 3-H's and $COCH_3$), Σ $J_{2,3}$ 15.0, Σ $J_{3,4}$ < 11.

(*c*) 4β-*Acetoxy*-7,3′,4′-*trimethoxyflavan* (10). The 4β-acetoxyflavan (115 mg) was heated to 90 °C with reagent ii (1 ml) for 2 h. The standard work-up furnished prisms of the starting material (105 mg), m.p. 100—103 °C, identified by its n.m.r. spectrum.

Treatment of the 4β-acetoxyflavan (76 mg) with reagent iii (1 ml) for 2 h afforded 4α-*acetoxy*-7,3′,4′-*trimethoxyflavan* (17) (26 mg) as prisms, m.p. 119—121 °C (Found: C, 67.25; H, 6.15. $C_{20}H_{22}O_6$ requires C, 67.0; H, 6.15%), τ ($CDCl_3$) 2.70 (1 H, d, 5-H), 2.90—3.08 (3 H, m, B-ring), 3.36—3.54 (2 H, d, and bs, A-ring), 4.02 (1 H, t, 4-H), 4.82 (1 H, t, 2-H), 6.08 and 6.10 (6 H, 2s, 2 × OMe), 6.22 (3 H, s, OMe), 7.64—7.80 (2 H, m, 3-H's), and 7.90 (3 H, s, $COCH_3$), Σ $J_{2,3}$ 14.4, Σ $J_{3,4}$ 6.0.

(*d*) 4β-*Acetoxy*-5,3′,4′-*trimethoxyflavan* (11). The 4β-acetoxyflavan (74 mg) treated with reagent ii (1 ml) at 80 °C for 2 h was recovered unchanged (69 mg), m.p. and mixed m.p. 138—139 °C.

Treatment of the 4β-acetoxyflavan (70 mg) with reagent iii (1 ml) for 2 h also yielded recovered starting material (62 mg), m.p. and mixed m.p. 137—139 °C.

Treatment of the 4β-acetoxyflavan (79 mg) with reagent iv for 2 h afforded 4α-*acetoxy*-5,3′,4′-*trimethoxyflavan* (18) (46 mg) as needles, m.p. 138—140 °C (mixed m.p. with starting material 115—135 °C) (Found: C, 67.25; H, 5.94. $C_{20}H_{22}O_6$ requires C, 67.0, H, 6.2%), τ ($CDCl_3$) 2.78 (1 H, t, 7-H), 3.00—3.18 (3 H, m, B-ring), 3.42 and 3.56 (2 H, 2bd, A-ring), 3.78 (1 H, t, 4-H), 4.92 (1 H, dd, 2-H), 6.08 and 6.10 (6 H, 2 s, 2 × OMe), 6.18 (3 H, s, -OMe), and 7.70—7.96 and 7.90 (5 H, m overlapping s, 3-H's and $COCH_3$), Σ $J_{2,3}$ 14.2, Σ $J_{3,4}$ 6.0.

(*e*) 4β-*Acetoxy*-3′,4′-*dimethoxyflavan* (8). The 4β-acetoxyflavan (96 mg) treated with reagent iv (1.0 ml) for 2 h was

recovered unchanged (83 mg), m.p. and mixed m.p. 116—118 °C.

4α-*Acetoxyflavan* (13).—Flavan-4β-ol (5.86 g) and toluene-*p*-sulphonic acid (110 mg) were heated in glacial acetic acid (100 ml) at 80 °C for 1 h. The mixture was poured into water (1 l), neutralised with powdered sodium carbonate, and extracted with ether. Evaporation of the ether and crystallisation of the residue from ethanol gave 4α-acetoxyflavan (4.98 g), m.p. and mixed m.p. 84—85 °C.

4α-*Acetoxy*-4′-*methoxyflavan* (14).—4′-Methoxyflavan-4β-ol (1.6 g), treated as above, gave 4α-acetoxy-4′-methoxyflavan (1.7 g) which separated from light petroleum (b.p. 40—60 °C) as rods, m.p. 77—79 °C (lit.,[16] m.p. 71 °C).

Hydrolysis of the acetate with ethanolic potassium hydroxide gave 4′-methoxyflavan-4α-ol which crystallised from aqueous ethanol as needles, m.p. 130—131 °C (lit.,[16] m.p. 131—132 °C).

3′,4′-*Dimethoxyflavan*-4α-*ol* (22).—3′,4′-Dimethoxyflavan-4β-ol (900 mg) and toluene-*p*-sulphonic acid (37 mg) were heated at 80 °C for 1 h in glacial acetic acid (30 ml). The 4α-acetoxy compound, was obtained as above and hydrolysed without isolation to give 3′,4′-*dimethoxyflavan*-4α-*ol* as needles from benzene–light petroleum (b.p. 40—60 °C), m.p. 123—124 °C (Found: C, 71.3; H, 6.3. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.3%).

Epimerisation of 2,3-trans,3,4-trans-*Diacetoxy*-5,7,3′,4′-*tetramethoxyflavan* (30).—2,3-*trans*,3,4-*trans*-Diacetoxy-5,7,-3′,4′-tetramethoxyflavan [2] (100 mg) was recovered unchanged after 2 h in pyridine (1 ml), acetic anhydride (0.75 ml), and acetic acid (0.25 ml) at 80 °C. Evaporation and crystallisation from ether gave starting material (81 mg), m.p. and mixed m.p. 133—136 °C.

A sample of the diacetate (30) (129 mg) heated in acetic anhydride–acetic acid (3 : 1, v/v) to 60 °C for 2 h and worked up in the same way, yielded 2,3-*trans*,3,4-*cis*-diacetoxy-5,7,3′,-4′-tetramethoxyflavan (31) (90 mg), m.p. and mixed m.p. with an authentic sample,[2] 158.5—160 °C.

Samples of the diacetates (30) and (31) heated separately in acetic anhydride–acetic acid to 70 °C for 2.5 h, each yielded on evaporation a mixture of the two isomers containing 14—18% of the *trans*,*trans*-isomer (30) (n.m.r. evidence).

Flavan-4α-*ol* (20).—Flavan-4β-ol (500 mg), dioxane (50 ml), and concentrated hydrochloric acid (1 ml) were kept over magnesium sulphate for 1 h and then boiled for 2 h. Dilution with water, isolation with ether, and crystallisation from ether–light petroleum (b.p. 40—60 °C), gave flavan-4α-ol (255 mg) as needles m.p. and mixed m.p. 117—118.5 °C.

5,3′,4′-*Trimethoxyflavan*-4α-*ol* (25).—5,3′,4′-Trimethoxyflavan-4β-ol (6) (0.32 g) was stirred in acetonitrile (10 ml) and 0.1M-hydrochloric acid (20 ml) for 24 h. The mixture was poured into ethyl acetate (50 ml), washed with 2M aqueous sodium hydroxide, water and brine, and dried and evaporated. Crystallisation from benzene and then aqueous methanol gave 5,3′,4′-*trimethoxyflavan*-4α-*ol* (25) (150 mg) as prisms, m.p. 121—123 °C (Found: C, 68.55; H, 6.55. $C_{18}H_{20}O_5$ requires C, 68.35; H, 6.35%), τ ($CDCl_3$) 2.72—3.20 (4 H, m, 7-H and B-ring), 3.38 and 3.54 (2 H, 2d, A-ring), 4.82—5.00 (2 H, dd, + t, 2-H and 4-H), 6.12 (9 H, bs, 3 × OMe), 7.26 (1 H, bs, OH, exchangeable), and 7.60—8.00 (2 H, m, 3-H's), Σ $J_{2,3}$ 14.0, Σ $J_{3,4}$ < 10.

7,3′,4′-*Trimethoxyflavan*-4α-*ol* (24).—7,3′,4′-Trimethoxyflavan-4β-ol (5) (0.51 g) was stirred in water (40 ml), acetonitrile (40 ml), and 2M-hydrochloric acid (1.5 ml) until the solid dissolved. Water (300 ml) was added gradually during 24 h and the precipitate at 0 °C was collected. Several recrystallisations from benzene afforded 7,3′,4′-*trimethoxyflavan*-4α-*ol* (24) (155 mg), m.p. 128—130 °C (Found: C, 68.3; H, 6.25. $C_{18}H_{20}O_5$ requires C, 68.35; H, 6.35%), τ ($CDCl_3$) 2.66—3.20 (4 H, m, 5-H and B-ring), 3.42—3.52 (2 H, m, 6-H and 8-H), 4.82 (1 H, dd, 2-H), 5.24 (1 H, t, 4-H), 6.12 (6 H, s, 2 × OMe), 6.26 (3 H, s, OMe), and 7.80—7.96 (3 H, m, 3-H's and HO, exchangeable), Σ $J_{2,3}$ 14.0, Σ $J_{3,4}$ 6.0.

5,7,3′,4′-*Tetramethoxyflavan*-4α-*ol* (26).—(*a*) 5,7,3′,4′-Tetramethoxyflavan-4β-ol (7) (1.00 g) in benzene (30 ml) and ether (100 ml) was stirred for 28 h with 0.1M-hydrochloric acid (20 ml). The mixture was diluted with ether (100 ml) and the organic phase was washed with aqueous sodium carbonate and dried. Removal of the solvent and crystallisation from ethanol gave 5,7,3′,4′-tetramethoxyflavan-4α-ol (26) (0.62 g), m.p. 80—90 °C, n.m.r. identical with that of a pure sample prepared as in (*b*).

(*b*) To a solution of 4α-acetoxy-5,7,3′,4′-tetramethoxyflavan (19) (145 mg) in dry ether (25 ml) and dry tetrahydrofuran (7 ml) at 0 °C was added lithium aluminium hydride (70 mg) with stirring. After 5 h at room temperature, wet ether was added and then 2M-aqueous sodium hydroxide (0.3 ml). Evaporation of the organic phase and crystallisation from ether afforded 5,7,3′,4′-*tetramethoxyflavan*-4α-*ol* (26) (62 mg) as needles, m.p. 126.5—128.5 °C (Found: C, 65.7; H, 6.4. $C_{19}H_{22}O_6$ requires C, 65.9; H, 6.4%), τ ($CDCl_3$) 2.90—3.20 (3 H, m, B-ring), 3.86 and 3.92 (2 H, 2 d, A-ring), 4.88 and 4.98 (2 H, dd and t, 2-H and 4-H), 6.10 (6 H, s, 2 × OMe), 6.14 (3 H, s, OMe), 6.22 (3 H, s, OMe), 7.40 (1 H, bs, HO, exchangeable), and 7.62—8.26 (2 H, m, 3-H's), Σ $J_{2,3}$ 13.4, Σ $J_{3,4}$ 4.0.

Reaction of 5,3′,4′-*Trimethoxyflavan*-4β-*ol* (6) *with Phosphorus Tribromide and Potassium Hydroxide in Ethanol or Aqueous Dioxane.*—(*a*) The method of Kamat *et al.*[7] applied to 5,3′,4′-trimethoxyflavan-4β-ol (6) (1.0 g) yielded 4α-*ethoxy*-5,3′,4′-*trimethoxyflavan* (34) (0.57 g) which separated from ethanol as needles, m.p. 86—88 °C (Found: C, 69.55; H, 6.85. $C_{20}H_{24}O_5$ requires C, 69.75; H, 7.0%), τ ($CDCl_3$) 2.78—3.20 (4 H, m, 7-H and B-ring), 3.44 and 3.54 (2 H, 2 d, A-ring), 4.76 (1 H, dd, 2-H), 5.30 (1 H, t, 4-H), 6.10, 6.12, and 6.14 (9 H, 3 S, 3 × OMe), 6.26 (2 H, bq, OEt), 7.70 (1 H, dt, 3-H), 8.08 (1 H, ddd, 3-H), and 8.72 (3 H, t, OEt), Σ $J_{2,3}$ 14.4, Σ $J_{3,4}$ 5.6.

(*b*) The method used in (*a*) was modified by replacing ethanolic potassium hydroxide with a solution of potassium hydroxide (0.35 g) in water (40 ml) and dioxane (40 ml). After 2 h at the boiling point, dilution with water and cooling furnished 5,3′,4′-trimethoxyflavan-4α-ol (25) (0.74 g), m.p. and mixed m.p. 121—123 °C after crystallisation from methanol.

Reactivity of Flavan-4β-*ol and* 4′-*Methoxyflavan*-4β-*ol towards Thiophenol.*—Samples of flavan-4β-ol (0.23 g) and 4′-methoxyflavan-4β-ol (0.25 g) were separately heated under reflux in dioxane (12 ml), hydrochloric acid (0.5M; 12 ml), and thiophenol (1.0 ml). T.l.c. [silica plates; eluant, ether–light petroleum (b.p. 40—60 °C), 1 : 1 (v/v)] indicated formation of 4α-phenylthioflavan and 4′-methoxy-4α-phenylthioflavan at roughly the same rate. After 75 min, each mixture was diluted with ether and washed with 2M-aqueous sodium hydroxide. The organic extracts were dried, evaporated, and the residues crystallised from ethanol. The mother liquors were evaporated and the residues were crystallised from ether–petroleum.

Flavan-4β-ol yielded 4α-phenylthio-4′-methoxyflavan (194

mg), m.p. 124—125 °C (lit.,[8] m.p. 127—128 °C), n.m.r. identical with that of an authentic sample; and flavan-4α-ol (38 mg), m.p. and mixed m.p. 117—119 °C (lit.,[17] 119 °C).

4′-Methoxyflavan-4β-ol yielded 4α-phenylthio-4′-methoxyflavan (219 mg), m.p. 103—105 °C (lit.,[8] 104—105 °C); and 4′-methoxyflavan-4α-ol (24 mg), m.p. and mixed m.p. 130—132 °C.[16]

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