Synthesis and Reactions of 4-Aryloxyflavans

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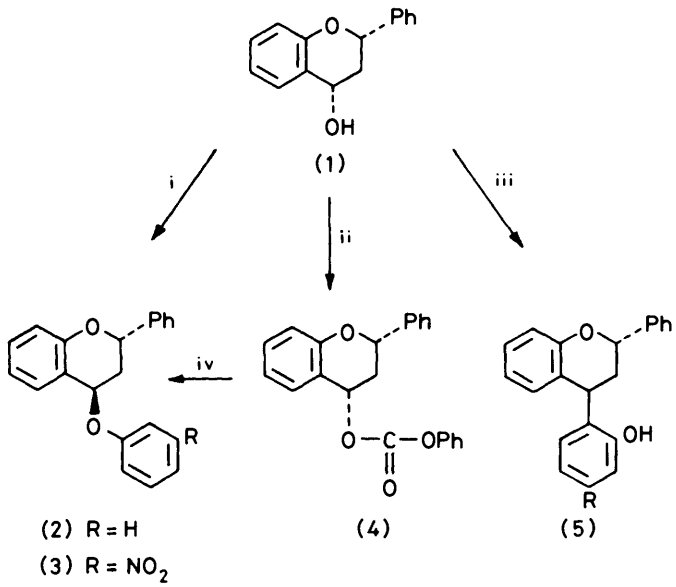
4α-Aryloxyflavans unsubstituted in ring A have been synthesised by the reaction of phenols with flavan-4β-ols in the presence of boron trifluoride in ether. If reaction times are prolonged beyond disappearance of the starting 4β-ols, thermodynamic control leads to 4-arylflavans and the yields of 4-aryloxyflavans are negligible. 4-Arylflavans are the sole products when the catalyst is toluene-*p*-sulphonic acid. Thermal decomposition of flavan-4β-yl phenol carbonate in the presence of phenols affords a synthesis of 4α-aryloxyflavans free from 4-arylflavans. Syntheses of 7-methoxy-4α-aryloxyflavans have not been successful, nor can 4-aryloxyflavan-3-ols be obtained from 3,4-diols by these methods. The 4-aryloxyflavans react rapidly with acids to yield 4-carbocations which can be trapped by a variety of nucleophiles yielding 4α-ols with water, 4α-alkoxyflavans with alcohols, 4α-arylflavans with phenols, and 4α-sulphides with thiols.

2,3-*cis*-Flav-3-ene epoxide reacts with phenols to give 2,3-*cis*-3,4-*cis*-4-aryloxyflavan-3-ols and with sodium salts of phenols to give 2,3-*cis*-3,4-*trans*-4-aryloxyflavan-3-ols. The 2,3-*trans*-epoxide similarly gives the 2,3-*trans*-4-aryloxyflavan-3-ols. A biflavonoid containing a 4-aryloxy link has been synthesised from the 2,3-*trans*-epoxide and 7-hydroxyflavan-4-one. A series of 2,3-*trans*-4'-methoxy-4-aryloxyflavan-3-ols has been synthesised from crude 2,3-*trans*-4'-methoxyflav-3-ene epoxide. The substitution of a methoxy group into position 7 of the flavonoid A-ring prevented the preparation of the epoxides, but the action of *N*-bromosuccinimide and sodium acetate in acetic anhydride and acetic acid on 7,4'-dimethoxyflav-3-ene gave 2,3-*cis*- and 2,3-*trans*-4-acetoxy-3-bromo-7,4'-dimethoxyflavans, the latter of which was converted by the action of sodium salts of phenols into the expected 4-aryloxyflavan-3-ols. 5,7,3',4'-Tetramethoxyflav-3-ene gave nuclear brominated products even with *N*-bromosuccinimide; thus the synthesis of 5,7,3',4'-tetramethoxy-4-aryloxyflavan-3-ols has not been possible by this method.

4-Aryloxyflavonoid structures are known to occur in some natural products,[1] though 4-arylflavonoids are more prevalent in the polymers which have been isolated and investigated.[2] Bond-energy summations show that 4-aryloxyflavans are expected to be thermodynamically less stable than 4-arylflavans and their hydrolysis to require *ca.* 45 kJ less energy. Since, therefore, if kinetic factors are favourable, 4-aryloxyflavans should be convertible into 4-arylflavans by hydrolysis and recombination of the products *in vivo* or during isolation, we have developed syntheses of 4-aryloxyflavans,[3,4] structures hitherto unknown by synthesis, in order that we may study their properties. We have already described the synthesis of 4β-aryloxyflavans [5] and here we discuss the synthesis of the 4α-isomers and of 4-aryloxyflavan-3-ols.

Earlier [6] we have made use of the reaction between phenols and flavan-4-ols (1) in alcoholic hydrogen chloride for the synthesis of 4-arylflavans (5). The use of a catalytic amount of toluene-*p*-sulphonic acid similarly yields 4-arylflavans and we have been unable to detect any 4-aryloxyflavans in either of these reactions. However, the use of boron trifluoride as catalyst in ether or in dioxane affords a satisfactory synthesis of 4a-aryloxyflavans from flavan-4β-ols and phenols, provided reaction times of less than 6 h at room temperature are used to minimise the production of the thermodynamically more stable 4-arylflavans which, nevertheless, accompany the 4-aryloxyflavans and make a separation by crystallisation or on a preparative plate necessary. Prolonged reaction times lead to the exclusive production of the carbon–carbon linked 4-arylflavans. The 4α-aryloxyflavans listed in Table 1 have been obtained in acceptable yields by limiting the reaction time to the minimum required for disappearance of the flavan-4β-ol as indicated by t.l.c. 4α-*m*-Nitrophenyloxyflavan (3), obtained in this way, was reduced with hydrazine to yield 4α-*m*-aminophenyloxyflavan which with acetic anhydride in pyridine gave 4α-*m*-acetamidophenoxyflavan.



All compounds are racemic. Relative stereochemistry is indicated. *Reagents:* i, RC_6H_4OH-*m*, BF_3, ether; ii, PhOCOCl; iii, RC_6H_4OH-*m* and HCl, EtOH or *p*-TsOH, $CHCl_3$; iv, RC_6H_4OH-*m*, heat

The 4α-aryloxyflavans listed in Table 2 have been synthesised by thermal decomposition [7] in the presence of phenols of flavan-4β-yl phenyl carbonate (4), obtained from flavan-4β-ol (1) and phenyl chloroformate in pyridine. By this method of synthesis, the resulting 4α-aryloxyflavans are free of 4-arylflavans, presumably because they are formed in the absence of an acid catalyst and under kinetic, not thermodynamic control.

Table 1. 4α-Aryloxyflavans from flavan-4β-ols

Flavan	M.p. (°C)	Yield (%)	$\Sigma J_{3,4}$	Found (%) C	H	Requires (%) C	H
4α-Phenoxy-	164—165	70	6.0 [a]	83.7	5.9	83.4	6.0
4α-*m*-Methoxycarbonylphenoxy-	95—96	32	5.8 [b]	76.4	5.6	76.6	5.6
4α-*m*-Ethoxycarbonylphenoxy-	84—85	43	5.4 [b]	77.0	5.9	77.0	5.9
4α-*m*-Nitrophenoxy-	109—110	30	5.6 [a]	72.9	5.0	72.6	4.9
				N, 3.9		N, 4.0	
4α-*p*-Tolyloxy-	87—92	40	6.0 [a]	83.6	6.4	83.5	6.3
4α-(2,4,6-Trimethylphenoxy)-	85—86	75	5.6 [a]	83.7	6.9	83.7	7.0
4′-Methoxy-4α-phenoxy-	145—146	37	6.0 [b]	79.6	6.2	79.5	6.0
4′-Methoxy-4α-*p*-tolyloxy-	131—132	20	5.6 [b]	79.55	6.45	79.75	6.4
4′-Methoxy-4α-(2,4,6-trimethylphenoxy)-	112—113	20		80.2	7.0	80.45	7.0
4′-Methoxy-4α-phenoxy-	105—106	49	5.6 [b]	83.5	6.1	83.5	6.3
4′-Chloro-4α-phenoxy-	125—126	35		74.6	5.2	74.9	5.1
				Cl, 10.3		Cl, 10.5	
3′,4′-Dimethoxy-4α-phenoxy-	95—96	26	5.8 [b]	75.9	6.0	76.2	6.1

[a] In CCl_4. [b] In benzene.

Table 2. 4α-Aryloxyflavans from flavan-4β-yl phenyl carbonate (4)

Flavan	M.p. (°C)	Yield (%)	$\Sigma J_{3,4}$ ($CDCl_3$)	Found (%) C	H	Requires (%) C	H
4α-Phenoxy-	164—165 (and mixed)	72		See Table 1			
4α-*p*-Tolyloxy-	87—92 (and mixed)	66		See Table 1			
4α-(2,6-Dimethylphenoxy)-	87—88	40	5.2	83.75	6.7	83.65	6.7
4α-(2-Naphthyloxy)-	39—40	26	5.4	85.4	5.9	85.2	5.7
4α-*p*-Nitrophenoxy-	148—149	19	5.8	72.35	4.75	72.6	4.95
				N, 3.85		N, 4.0	
4β-*p*-Nitrophenoxy-	119—120	3.5	15.9	72.45	5.15		
				N, 3.85			

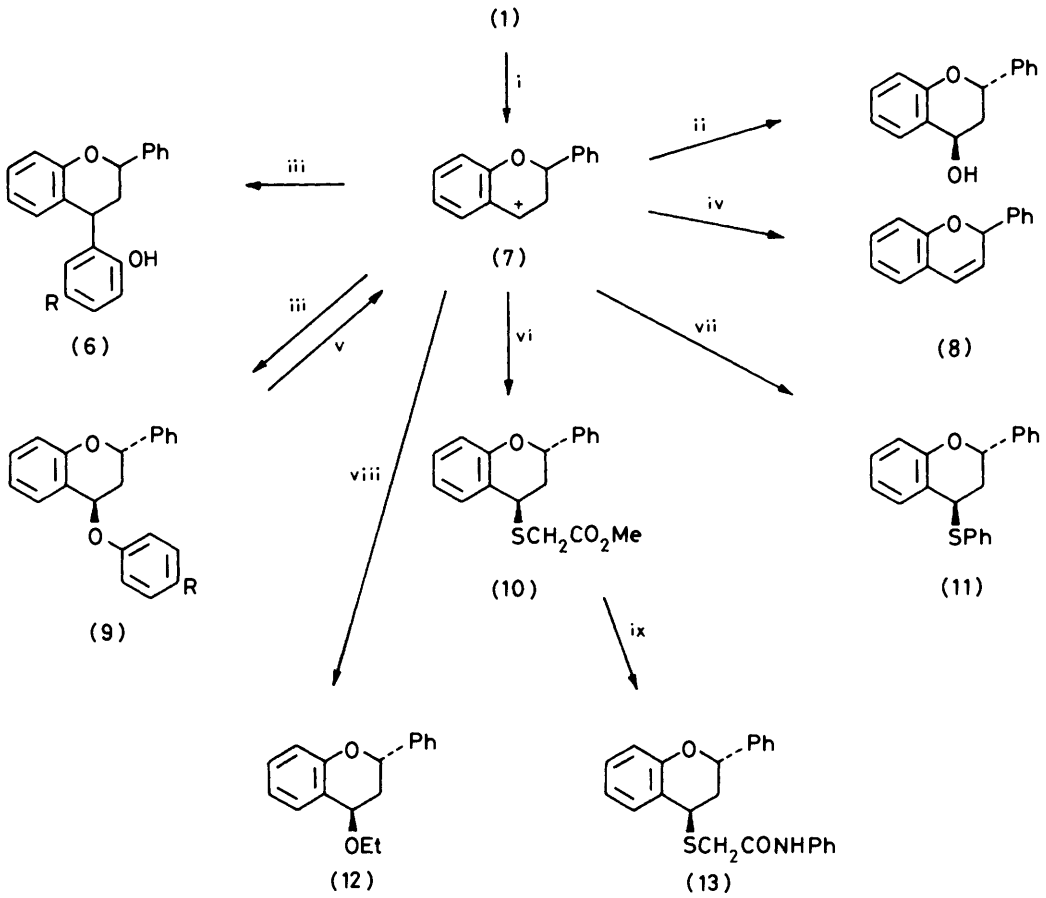
Table 3. Acid-catalysed hydrolysis of 4′-methoxy-4α-phenoxyflavan

Compound	Approx. time of appearance. 20 °C	40 °C	R_F * ($CHCl_3$)	Spray * $FeCl_3$–$K_3Fe(CN)_6$	Isovanillin *
4′-Methoxy-4α-phenoxyflavan	0—48 h	0—20 h	0.71		Yellow
4′-Methoxyflavan-4α-ol	1 min	1 min	0.20		Pale yellow
Phenol	1 min	1 min	0.20	Blue–green	
4′-Methoxyflav-3-ene	4 h	1 h	0.57		Yellow
4β-*o*-Hydroxyphenyl-4′-methoxyflavan	48 h	20 h	0.33		Orange

* Authentic samples had the same R_F values and colour reactions.

We believe that in the synthesis first described, the formation of a 4α-aryloxyflavan (9) from a flavan-4β-ol (1) occurs through a 4-carbocation (7) which can be regenerated from the 4-aryloxyflavan (9) by boron trifluoride, thus eventually leading to the thermodynamically more stable 4-arylflavan (6) as the 4-carbocation (7) is captured by the phenol acting as a carbon nucleophile. Similarly, the acid-catalysed hydrolysis of 4′-methoxy-4α-phenoxyflavan (see Table 3) which yields phenol, the 4α-ol, and the flav-3-ene together with the 4-arylflavan, can be interpreted as proceeding through a 4-carbocation and the treatment of 4α-*p*-tolyloxyflavan with toluene-*p*-sulphonic acid in ether gave flavan-4α-ol and 4α-(2-hydroxy-5-methylphenyl)flavan (6; R = Me). In ethanol, 4α-*p*-tolyloxyflavan and toluene-*p*-sulphonic acid gave 4α-ethoxyflavan (12). 4α-(2,4,6-Trimethylphenoxy)flavan with toluene-*p*-sulphonic acid in the presence of *p*-cresol yielded flav-3-ene (8) and a small amount of 4α-*p*-tolyloxyflavan as well as flavan-4α-ol and 4α-(2-hydroxy-5-methylphenyl)flavan (6; R = Me), the last three compounds arising from the interaction of the 4-carbocation (7) with various nucleophiles. Sulphur nucleophiles likewise can trap the 4-carbocation: mercaptoacetic acid reacted quickly with 4α-(2,4,6-trimethylphenoxy)flavan to yield, after methylation, methyl (flavan-4α-ylthio)acetate (10) which was converted into its crystalline acetanilide (13), and thiophenol reacted with 4α-*p*-tolyloxyflavan giving 63% of 4α-phenylthioflavan (11).

Both of the syntheses of 4α-aryloxyflavans described above are of limited scope. The boron trifluoride method suffers from the concomitant production of 4-arylflavans which have to be separated from the 4-arylflavans. A greater disadvantage, however, is that the method fails when the flavan-4β-ol used as starting material contains a 7-methoxy group and when a 3-hydroxy group is present, as in the flavan-3,4-diols which readily undergo self-condensation in the presence of Lewis



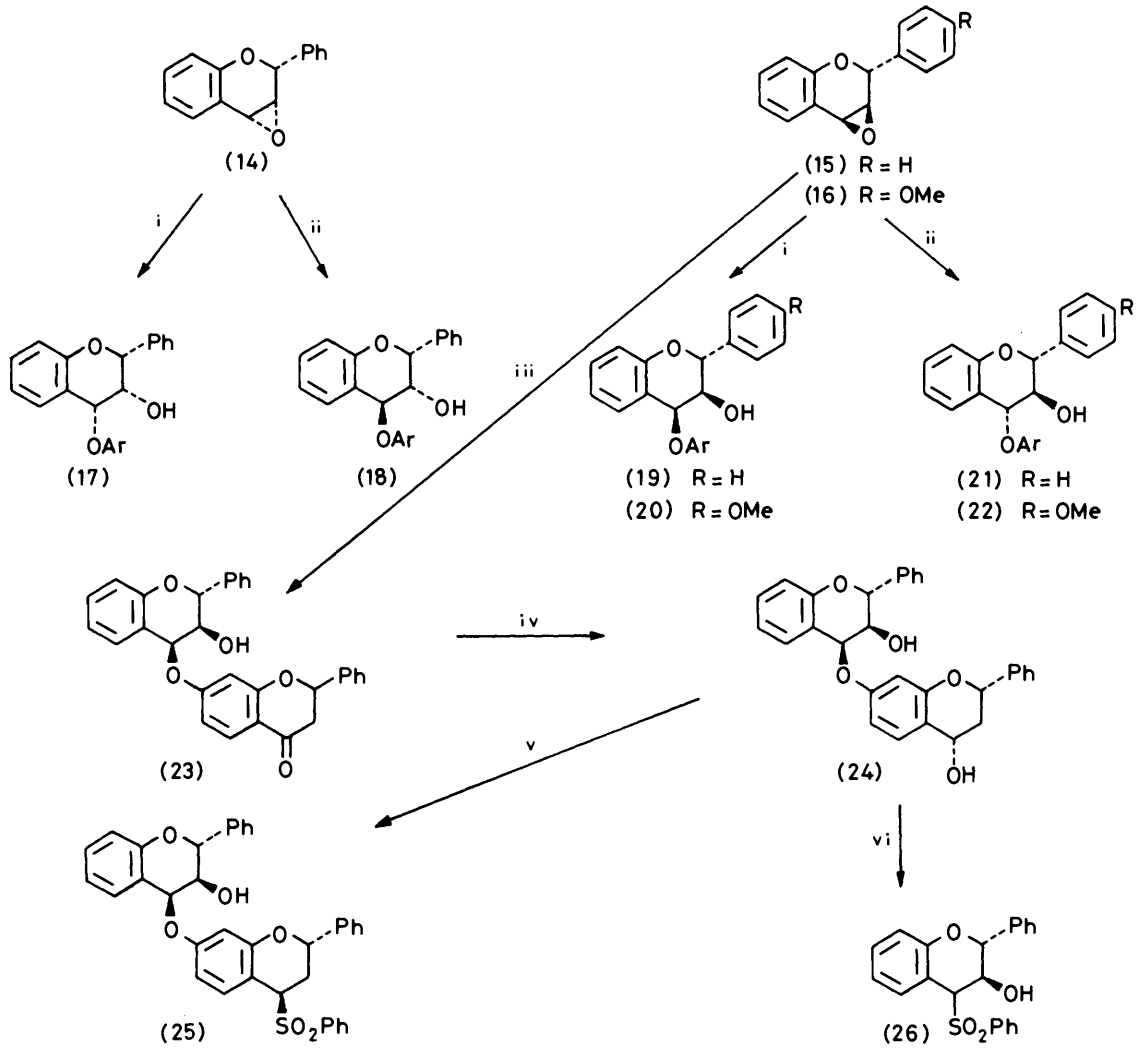
Reagents: i, BF_3; ii, H_2O; iii, RC_6H_4OH-*p*; iv, $-H^+$; v, Lewis or proton acid; vi, $HSCH_2CO_2H$ then CH_2N_2; vii, PhSH, H_3O^+; viii, *p*-TsOH, EtOH; ix, PhNHMgBr

acids yielding biflavonoids containing dioxane linkages.[8] The phenyl carbonate method is better in that no 4-arylflavans are produced, thus making the purification of the 4-aryloxyflavans easier. However, the reaction of flavan-4α-yl phenyl carbonate with *p*-nitrophenol gave low yields of 4α-*p*-nitrophenoxyflavan and its 4β-isomer which necessitated separation by p.l.c. Substitution of a methoxy group at the 7-position of the flavan-4β-yl phenyl carbonate renders the method unsatisfactory: we were unable to isolate 7-methoxyflavan-4β-yl phenyl carbonate since the starting material, 7-methoxyflavan-4β-ol, easily polymerises and the product, 7-methoxyflavan-4β-yl phenyl carbonate, readily decomposes. Treatment of the crude reaction product from 7-methoxyflavan-4β-ol and phenyl chloroformate with phenol gave a 3% yield of 7-methoxy-4α-phenoxyflavan.

Neither of the two syntheses so far described is easily adaptable to the synthesis of 4-aryloxyflavan-3-ols and for these we have utilised reactions between flav-3-ene epoxides (14), (15), and (16) and phenols or phenolate anions.[4] 2,3-*cis*-Flav-3-ene epoxide (14) and 2,3-*trans*-flav-3-ene epoxide (15) react analogously (i) with phenols to yield 2,3-*cis*-3,4-*cis*-4-aryloxyflavan-3-ols (17) and 2,3-*trans*-3,4-*cis*-4-aryloxyflavan-3-ols (19) respectively and (ii) with phenolate anions in an S_N2 reaction to yield 2,3-*cis*-3,4-*trans*-4-aryloxyflavan-3-ols (18) and 2,3-*trans*-3,4-*trans*-4-aryloxyflavan-3-ols (21) (see Table 4). We believe that the *cis*-opening of the epoxide ring by phenol occurs by the ion-pair mechanism proposed by Brewster,[9] since this explains the exclusive 3,4-*cis*-stereochemistry of the products from the flav-3-ene epoxides. Participation of the aromatic B-ring by π-electron stabilisation of a carbonium ion (S_N1 mechanism) would lead to 3,4-*trans*-stereochemistry.

The method is general for phenols and phenolate anions of varied structures and the yields are acceptable, but those from the reaction with phenolate anions are generally the lower, being very dependent upon the purity and dryness of the sodium salts of the phenols used. The 4-aryloxyflavan-3-ols react with thiophenol to yield 3-hydroxyflavan-4-yl phenyl sulphides, as do flavan-3,4-diols and some naturally occurring poly flavonoids.[10] The reaction of 2,3-*trans*-flav-3-ene epoxide (15) with 7-hydroxyflavan-4-one in chloroform gave the biflavonoid (23) which on reduction with sodium borohydride yielded 7-(2,3-*trans*-3,4-*cis*-3-hydroxyflavan-4-yloxy)flavan-4β-ol (24). This biflavanoid behaved towards sulphur nucleophiles as predicted from our earlier studies [10] in that treatment with benzenesulphinic acid in 20% aqueous ethanolic acetic acid caused the selective replacement of the 4-hydroxy group (which is activated by the oxygen substituent at the 7-position) but left intact the unactivated ether link between the flavonoid units, resulting in a biflavanyl phenyl sulphone (25). Treatment of the biflavonoid (24) with benzenesulphinic acid under strongly acidic conditions (in 90% formic acid) caused, as expected,[10] rupture of the 4-ether link and the monomeric phenyl sulphones (26) resulted; the other primary product, 7-hydroxyflavan-4β-ol, is expected to undergo rapid polymerisation in strongly acidic media [11] and could not be isolated.

We prepared 2,3-*cis*-3,4-*trans*-4-acetoxy-3-bromo-4′-methoxyflavan (28) [12] by two methods: (*a*) that used for the



Reagents: i, ArOH; ii, ArO^- Na^+; iii, 7-hydroxyflavan-4-one, $CHCl_3$; iv, $NaBH_4$, MeOH–$CHCl_3$; v, $PhSO_2H$, 20% HOAc in aq. EtOH; vi, $PhSO_2H$, 90% HCO_2H

Table 4. 4-Aryloxyflavan-3-ols (17), (18), (19), and (21) from 2,3-*cis*- (14) and 2,3-*trans*-flav-3-ene epoxides (15)

Flavan-3-ol	2,3-Stereochem. of epoxide	Reactant	M.p. (°C)	Yield (%)
2,3-*cis*-3,4-*cis*-4-Phenoxy-(17; Ar = Ph)	*cis*	PhOH	125—126	73
2,3-*cis*-3,4-*trans*-4-Phenoxy-(18; Ar = Ph)	*cis*	PhO^-	130—131	19
2,3-*trans*-3,4-*cis*-4-Phenoxy-(19; Ar = Ph)	*trans*	PhOH	105—106	77
2,3-*trans*-3,4-*trans*-4-Phenoxy-(21; Ar = Ph)	*trans*	PhO^-	145—147	73
2,3-*trans*-3,4-*cis*-4-*p*-Tolyloxy-(19; Ar = *p*-MeC_6H_4)	*trans*	*p*-MeC_6H_4OH	106—107	78
2,3-*trans*-3,4-*trans*-4-*p*-Tolyloxy-(21; Ar = *p*-MeC_6H_4)	*trans*	*p*-$MeC_6H_4O^-$	95—96	17
2,3-*trans*-3,4-*cis*-4-*p*-Methoxyphenoxy-(19; Ar = *p*-$MeOC_6H_4$)	*trans*	*p*-$MeOC_6H_4OH$	114—115	32
2,3-*trans*-3,4-*trans*-4-*p*-Methoxyphenoxy-(21; Ar = *p*-$MeOC_6H_4$)	*trans*	*p*-$MeOC_6H_4O^-$	128—129	19

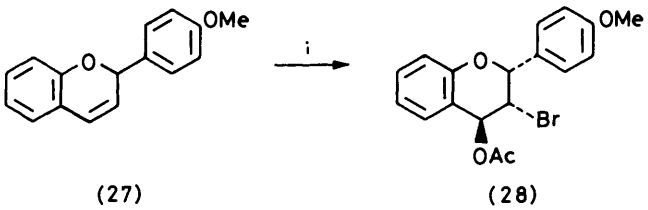
Flavan-3-ol	$J_{2,3}$	$J_{3,4}$	Found (%) C	Found (%) H	Requires (%) C	Requires (%) H
2,3-*cis*-3,4-*cis*-4-Phenoxy-(17; Ar = Ph)		4.4	79.0	5.8		
2,3-*cis*-3,4-*trans*-4-Phenoxy-(18; Ar = Ph)		2.4	78.9	5.8	79.2	5.7
2,3-*trans*-3,4-*cis*-4-Phenoxy-(19; Ar = Ph)	8.4		79.0	5.8		
2,3-*trans*-3,4-*trans*-4-Phenoxy-(21; Ar = Ph)	9.9	8.0	79.0	5.8		
2,3-*trans*-3,4-*cis*-4-*p*-Tolyloxy-(19; Ar = *p*-MeC_6H_4)	8.4	3.6	79.75	6.2	79.5	6.05
2,3-*trans*-3,4-*trans*-4-*p*-Tolyloxy-(21; Ar = *p*-MeC_6H_4)	8.0	9.4	79.4	6.15		
2,3-*trans*-3,4-*cis*-4-*p*-Methoxyphenoxy-(19; Ar = *p*-$MeOC_6H_4$)	8.8	3.6	76.0	5.85	75.85	5.8
2,3-*trans*-3,4-*trans*-4-*p*-Methoxyphenoxy-(21; Ar = *p*-$MeOC_6H_4$)	8.0	9.6	75.3	6.05		

Table 5. 2,3-*trans*-4′-Methoxy-4-aryloxyflavan-3-ols (20) and (22) from 2,3-*trans*-4′-methoxyflav-3-ene epoxide (16)

2,3-*trans*-4′-Methoxyflavan-3-ol	M.p. (°C)	Yield (%)	$J_{2,3}$	$J_{3,4}$	Found (%) C	Found (%) H	Requires (%) C	Requires (%) H
3,4-*cis*-4-Phenoxy-(20; Ar = Ph)	133—134	54	8.4	4.4	76.1	6.0	75.8	5.8
3,4-*trans*-4-Phenoxy-(22; Ar = Ph)	105—106	36	10.0	8.0	75.9	6.0		
3,4-*cis*-4-*p*-Tolyloxy-(20; Ar = *p*-MeC_6H_4)	128—129	49	8.8	3.0	75.9	6.3	76.2	6.1
3,4-*trans*-4-*p*-Tolyloxy-(22; Ar = *p*-MeC_6H_4)	134—135	31	10.0	8.0	76.0	6.0		
3,4-*cis*-4-*p*-Methoxyphenoxy-(20; Ar = *p*-$MeOC_6H_4$)	112—113	35	9.2	3.6	73.1	5.9	73.0	5.9
3,4-*trans*-4-*p*-Methoxyphenoxy-(22; Ar = *p*-$MeOC_6H_4$)	104—105	15	9.6	8.0	72.7	5.9		

Table 6. 2,3-*cis*-3,4-*trans*-7,4′-Dimethoxy-4-arylflavan-3-ols (33) from 2,3-*trans*-3,4-*trans*-4-acetoxy-3-bromoflavan (31) and phenolate ions

Flavan-3-ol	M.p. (°C)	Yield (%)	$J_{3,4}$	Found (%) C	Found (%) H	Requires (%) C	Requires (%) H
2,3-*cis*-3,4-*trans*-7,4′-Dimethoxy-4-phenoxy-(33; Ar = Ph)	109—110	64	2.6	72.7	5.9	73.0	5.9
2,3-*cis*-3,4-*trans*-7,4′-Dimethoxy-4-*p*-tolyloxy-(33; Ar = *p*-MeC_6H_4)	104—105	71	2.6	73.3	6.3	73.5	6.2
2,3-*cis*-3,4-*trans*-7,4′-Dimethoxy-4-*p*-methoxyphenoxy-(33; Ar = *p*-$MeOC_6H_4$)	132—133	70	2.6	70.4	5.9	70.6	5.9

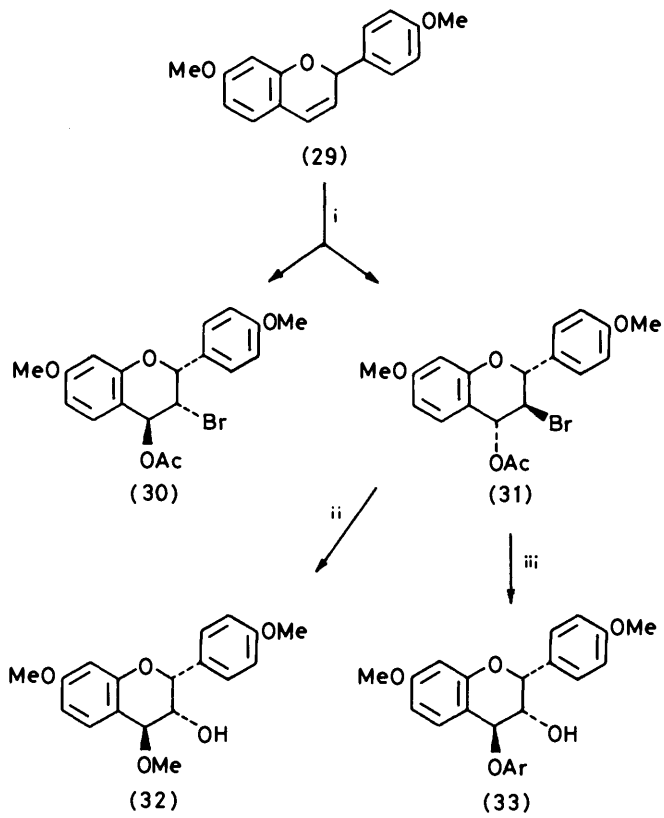


(27) (28)

Reagent: i, Br_2, NaOAc, Ac_2O, HOAc

unsubstituted compound [13,*] and (*b*) by the action of bromine, sodium acetate, acetic anhydride, and acetic acid on 4′-methoxyflav-3-ene (27), a method we first used with success on flav-2-enes.[14] We did not purify the epoxide (16) [12] but found it advantageous to use it directly as obtained from the 4-acetoxy-3-bromoflavan (28) and treatment of it with phenols and phenolate anions gave the 2,3-*trans*-3,4-*cis*- (20) and 2,3-*trans*-3,4-*trans*-4-aryloxy-4′-methoxyflavan-3-ols (22) as described above for the unsubstituted compounds (Table 5).

Further substitution with methoxy groups necessitated a modification of our experimental procedures. Treatment of 7,4′-dimethoxyflav-3-ene (29) with bromine gave 3-bromo-7,4′-dimethoxyflav-3-ene and 3,3-dibromo-7,4′-dimethoxyflavan-4α- and -4β-ols with none of the 3,4-dibromoflavan which would be required [13] for synthesis of the 3,4-epoxide. Treatment of 7,4′-dimethoxyflav-3-ene with bromine, acetic acid, acetic anhydride, and sodium acetate resulted in the production of a 4-acetoxy-3-bromo-compound having a brominated A-ring, *viz.* 2,3-*trans*-3,4-*trans*-4-acetoxy-3,6-dibromo-7,4′-dimethoxyflavan. Substitution of *N*-bromosuccinimide for bromine in the above acetic mixture enabled 2,3-*cis*-3,4-*trans*- (30) (15%) and 2,3-*trans*-3,4-*trans*-4-acetoxy-3-bromo-7,4′-dimethoxyflavans (31) (52%) to be prepared; separation of the isomers on a silica column proved easy. An attempt to prepare the 3,4-epoxide from the 2,3-*trans*-acetoxybromoflavan (31) by the action of methanolic potassium hydroxide yielded instead 2,3-*cis*-3,4-*trans*-4,7,4′-trimethoxyflavan-3-ol (32) presumably by attack of methanol



Reagents: i, NBS, NaOAc, Ac_2O, HOAc; ii, KOH, MeOH; iii, $ArO^-\ Na^+$

on the first formed epoxide. In view of this, the 2,3-*trans*-3,4-*trans*-4-acetoxy-3-bromoflavan (31) was treated directly with phenolate anions and gave the expected 2,3-*cis*-3,4-*trans*-7,4′-dimethoxy-4-aryloxyflavan-3-ols (33) in satisfactory yield (Table 6).

We have not been successful, by the method described, in synthesising 4-aryloxyflavan-3-ols with a 5,7,3′,4′-tetramethoxy substitution pattern: treatment of 5,7,3′,4′-tetramethoxyflav-3-ene with *N*-bromosuccinimide and the acetic

* We thank Professor Philbin for kindly making available to us unpublished experimental details for the preparation of 2,3-*cis*-flav-3-ene epoxide.

Table 7. 4-Arylflavans

Product	M.p. (°C)	$\Sigma J_{3,4}$ (CCl_4)	Found (%) C	Found (%) H	Requires (%) C	Requires (%) H
4α-*o*-Hydroxyphenylflavan [a]	134—134.5	9.0	83.4	5.9	83.4	6.0
4α-*o*-Methoxyphenylflavan [b]	193—195	8.0 [g]	83.4	6.4	83.5	6.3
4β-*o*-Methoxyphenylflavan [c]	97—98.5	17.5	83.5	6.3		
4α-*p*-Hydroxyphenylflavan [e]	148—149	8.8	83.0	6.0	83.4	6.0
4α-*p*-Methoxyphenylflavan [d]	100—101	8.8	83.5	6.2	83.5	6.3
4β-*p*-Hydroxyphenylflavan [a]	170—171	18.0	83.2	6.2	83.4	6.0
4β-*p*-Methoxyphenylflavan [b,d]	135—136	18.5	83.6	6.2	83.5	6.3
4α-(2-Hydroxy-5-methylphenyl)flavan [e]	64—65	9.0	82.3	6.3	82.4	6.4
4α-(2-Methoxy-5-methylphenyl)flavan [b]	152—153	7.6	83.4	6.5	83.6	6.7
4α-(2-Acetoxy-5-methylphenyl)flavan [b]	130—131	10.0	80.3	6.0	80.4	6.1
4β-(4-Acetoxy-3,5-dimethylphenyl)flavan [f]	192—194	18.0	80.7	6.5	80.7	6.5
4′-Methoxy-4α-(2-hydroxy-5-methylphenyl)flavan [e]	173—175	8.6 [g]	79.5	6.5	79.7	6.4

[a] From flavan-4β-ol and phenol with toluene-*p*-sulphonic acid as catalyst. See Experimental section. [b] From the preceding phenol by methylation or acetylation. [c] By the Grignard synthesis (32%).[6] [d] From flavan-β-ol, anisole, and BF_3. See Experimental section. [e] From BF_3 syntheses of 4α-aryloxyflavans (Table 1). [f] Isolated in small yield by acetylation and fractional crystallisation of the products obtained from flavan-4β-ol, 2,6-dimethoxyphenol, and BF_3. [g] N.m.r. in $CDCl_3$.

mixture caused nuclear bromination and we were able to isolate only 2,3-*trans*-3,4-*cis*-4-acetoxy-3,6(or 8)-dibromo-5,7,3′,4′-tetramethoxyflavan in low yield; we are uncertain whether the nuclear bromine has entered the 6- or the 8-position.

In Table 7 are collected the 4-arylflavans obtained from various reactions. Those from the reactions of flavan-4β-ols with phenols and boron trifluoride and which had been allowed to proceed longer than 6 h, were isolated by preparative layer chromatography. We have not recorded yields because these reactions were of an exploratory nature, done to ascertain the conditions leading to maximum yields of 4-aryloxyflavans. Good yields of mixtures of *o*- and *p*-hydroxy- and 4α- and 4β-arylflavans can be obtained from 4β-ols and phenols with toluene-*p*-sulphonic acid as catalyst.

Assignment of 4α(2,4-*trans*) or 4β(2,4-*cis*) stereochemistry to the 4-substituted flavans synthesised is most simply made from the coupling constants ($\Sigma J_{3,4}$) in the n.m.r. spectra which are listed in the tables. For 4-*O*-substituted flavans a value of 5—6 Hz is indicative of 4α-stereochemistry and one of 15—17 Hz indicates 4β-stereochemistry.[15] The corresponding values for 4-arylflavans are 4α: $\Sigma J_{3,4}$ = 7.5—10 and 4β: $\Sigma J_{3,4}$ = 17—19 Hz. The stereochemistry of the 3,4-substituted flavans has been assigned from the values of $J_{2,3}$ and $J_{3,4}$.[15]

Experimental

N.m.r. spectra were recorded on a Perkin-Elmer R14 100 MHz instrument and coupling constants (*J*) are quoted in Hz. T.l.c. plates were coated with Merck Kieselgel HF_{254} and p.l.c. plates with Merck Kieselgel PF_{254}. Molecular sieve was Linde 3A in powder form. Silica for columns was Sorbsil M 60, supplied by Harrington Bros. Ltd. Ether refers to diethyl ether.

4′-Methylflavan-4-one.—(a) 2′-Hydroxy-4-methylchalcone (5 g) in ethanol (130 ml) and 6M-hydrochloric acid (60 ml) was boiled under reflux for 42 h. The mixture was poured onto ice (400 mg) and the precipitated solid was recrystallised from light petroleum (b.p. 30—40 °C), to give *4′-methylflavan-4-one* (1.65 g) as prisms, m.p. 69—71 °C (Found: C, 80.4; H, 5.9. $C_{16}H_{14}O_2$ requires C, 80.6; H, 5.9), *m/z* 238 (*M*, 63%) and 118 (100%); τ($CDCl_3$) 2.05—3.10 (8 H, m, ArH), 4.45—4.71 (1 H, q, 2-H), 6.75—7.30 (2 H, 2 × q, 3-H's), and 7.62 (3 H, s, CH_3), $\Sigma J_{2,3}$ = 16.0, $J_{3,3}$ = 17.1.

(b) 2′-Hydroxy-4-methylchalcone (3.0 g) in hot ethanol (45 ml) was treated with aqueous 1.5% sodium hydroxide (210 ml) during 45 min with stirring. The reaction mixture was kept at 0 °C for 3 days and the crystals which had separated were recrystallised from light petroleum (b.p. 30—40 °C), to give the flavanone (0.4 g), m.p. and mixed m.p. 69—71 °C. The filtrate was poured into water to yield a yellow solid which was mainly chalcone.

4′-Methylflavan-4β-ol.—4′-Methylflavan-4-one (8.7 g) in ethanol (300 ml) was reduced at 5 °C with sodium borohydride (3.7 g) and then kept at 0 °C overnight. Acetic acid (5 ml) was added to the mixture, followed by water (700 ml). The precipitated solid was recrystallised from ethanol to yield *4′-methylflavan-4β-ol* (5.5 g) as plates, m.p. 109—110 °C (Found: C, 79.9; H, 6.8. $C_{16}H_{16}O_2$ requires C, 80.0; H, 6.7%), *m/z* 240 (M^+, 10%) and 118 (100%); τ($CDCl_3$) 2.50—3.21 (8 H, m, ArH), 4.85—5.11 (2 H, 2 × q, 2-H and 4-H), 7.30—8.45 (3 H, m, 3-H's and OH, exchanges with D_2O), $\Sigma J_{2,3}$ = 13.3, $\Sigma J_{3,4}$ = 16.9.

4′-Chloroflavan-4β-ol.—Reduction of 4′-chloroflavan-4-one (3.0 g) at 10 °C as above gave *4′-chloroflavan-4β-ol* (2.0 g) which separated from methanol as needles, m.p. 160—161 °C (Found: C, 69.0; H, 5.1; Cl, 13.8. $C_{15}H_{13}ClO_2$ requires C, 69.1; H, 5.0; Cl, 13.6%), *m/z* 260 (M^+, 10%) and 121 (100%); τ($CDCl_3$) 2.32—3.20 (8 H, m, ArH), 4.83—5.08 (2 H, 2 × q, 2-H and 4-H), 7.43—8.15 (2 H, m, 3-H's), 8.12—8.21 (1 H, d, OH, exchanges with D_2O), $\Sigma J_{2,3}$ = 13.5.

4α-Phenoxyflavan (2).—The following are typical details for the synthesis of 4-aryloxyflavans by catalysis with boron trifluoride (Table 1).

(a) Flavan-4β-ol (1.0 g), phenol (1.75 g), molecular sieve (5 g), and boron trifluoride–ether (6 ml) were stirred in ether (80 ml) for 6 h. The reaction mixture was shaken with ether (175 ml) and 0.2M-NaOH (200 ml) and the ether layer was then extracted with 2M-NaOH (6 × 100 ml). Removal of ether and crystallisation of the residue from methanol–acetone gave *4α-phenoxyflavan* (0.82 g) as needles, m.p. 164—165 °C, see Table 1 for analysis; τ($CDCl_3$) 2.45—2.85 (10 H, m, ArH, B- and D-ring), 2.85—3.2 (4 H, m, A-ring ArH), 4.64 (1 H, t, 4-H), 4.66 (1 H, q, 2-H), 7.48 (1 H, 2 × t, 3-H), and 7.83 (1 H, 2 × q, 3-H); *m/z* 302 (M^+, 1.1%) and 209 (100%).

(b) Flavan-4β-ol (200 mg), phenol (500 mg), and boron trifluoride–ether (0.5 ml) were kept in ether (15 ml) at 20 °C for 2 days. The mixture was diluted with ether (60 ml) and

washed several times with 2M-NaOH (60 ml). The washed and dried ethereal layer was evaporated and the residue put onto a silica column (40 g) and eluted with 20% ether in light petroleum (b.p. 40—60 °C). The first fraction gave 4α-phenoxyflavan (65 mg), m.p. and mixed m.p. 164—165 °C.

The second fraction contained several products which were separated by p.l.c. into two sharp bands, the first of which gave 4α-(*o*-hydroxyphenyl)flavan (50 mg), m.p. and mixed m.p. 134—134.5 °C. The second band (75 mg) was identified (n.m.r.) as containing a 3 : 1 mixture of 4α- and 4β-(*p*-hydroxyphenyl)flavan and repeated crystallisation of the mixture from benzene–light petroleum gave 4α-(p-*hydroxyphenyl*)*flavan* (7 mg) as prisms, m.p. 148—150 °C; see Table 7 for analysis; τ(CCl_4) 2.4—3.4 (13 H, m, aromatics), 4.6br (1 H, OH, exchanges with D_2O), 5.00 (1 H, q, 2-H), 5.90 (1 H, t, 4-H), and 7.5—8.0 (2 H, m, 3-H's); *m/z* 302 (M^+, 68%) and 197 (100%).

4α-m-*Aminophenoxyflavan*.—4α-*m*-Nitrophenoxyflavan (500 mg), hydrazine hydrate (5 ml), and 10% Pd–C (250 mg) were boiled in ethanol (200 ml) for 20 min. Filtration, removal of solvent, and crystallisation of the residue from ethanol gave 4α-*aminophenoxyflavan* (370 mg) as needles, m.p. 175—176 °C (Found: C, 79.2; H, 6.2; N, 4.2. $C_{21}H_{19}NO_2$ requires C, 79.5; H, 6.0; N, 4.4%), τ($CDCl_3$) 2.1—3.8 (13 H, m, ArH), 4.6—4.9 (2 H, overlapping t and q, 4-H and 2-H), 6.2—6.6br (2 H, s, NH_2), and 7.3—8.0 (2 H, 2 × t overlapping 2 × q, 3-H's), $\Sigma J_{2,3} = 14.2$, $\Sigma J_{3,4} = 5.8$.

4α-m-*Acetamidophenoxyflavan* (84%) was obtained from the above amino compound by acetylation with acetic anhydride–pyridine and crystallised from ethanol as prisms, m.p. 222—223 °C (Found: C, 76.6; H, 5.9; N, 3.8. $C_{23}H_{21}NO_3$ requires C, 76.9; H, 5.85; N, 3.9%), τ[$(CD_3)_2SO$] 0.1—0.2 (1 H, s, NHAc), 2.5—3.3 (13 H, m, ArH), 4.5—5.0 (2 H, t and q, 2-H and 4-H), 7.5—7.9 (2 H, m, 3-H), and 7.9—8.1 (3 H, s, $COCH_3$), $\Sigma J_{2,3} = 15.2$, $\Sigma J_{3,4} = 4.8$.

Flavan-4β-yl Phenyl Carbonate (4).—Flavan-4β-ol (2.26 g) in pyridine (30 ml) was stirred at 0 °C and phenyl chloroformate (2.50 g) was added dropwise. Stirring was continued at 20 °C for 3 h and then dichloromethane (250 ml) was added and the organic solution washed successively with 2M-HCl (twice), 2M-NaOH, and water. Evaporation gave a solid which separated from methanol to give *flavan-4β-yl phenyl carbonate* (2.46 g) as needles, m.p. 96—110 °C (decomp.) (Found: C, 76.3; H, 5.3. $C_{22}H_{18}O_4$ requires C, 76.3; H, 5.2%), τ(CCl_4) 2.5—3.2 (14 H, m, ArH), 3.94 (1 H, q, 4-H), 4.81 (1 H, q, 2-H), 7.25 (1 H, 2 × q, 3-H), and 7.73 (1 H, 8 line m, 3-H), $\Sigma J_{2,3} = 14.0$, $\Sigma J_{3,4} = 17.0$, $J_{3,3} = 13.0$.

The following are typical details for the synthesis of 4-aryloxyflavans from flavan-4β-yl phenyl carbonate (Table 2).

4α-p-*Tolyloxyflavan* (9; R = Me).—The carbonate (40 mg) was heated with *p*-cresol (200 mg) at 80 °C for 30 min. The mixture was taken up into ether (20 ml) and washed with 2M-NaOH (×6). Evaporation of the dry organic layer and crystallisation of the residue from methanol gave 4α-*p*-tolyloxyflavan (30 mg) as prisms, m.p. and mixed m.p. 87—92 °C.

Acid-catalysed Hydrolysis of 4′-Methoxy-4α-phenoxyflavan.—0.5M-Hydrochloric acid (2 ml) was added to 4′-methoxy-4α-phenoxyflavan (10 mg) in ethanol (8 ml) and stirred (i) at 20 °C and (ii) at 40 °C. The progress of both reactions was followed by t.l.c. and the results are summarised in Table 3. Flavonoids appeared as yellow spots when the plates were sprayed with isovanillin (1% in conc. H_2SO_4) and then heated for a few minutes in a hot oven. An aqueous 1 : 1 (v/v) mixture of 0.067M-$FeCl_3$ and 0.067M-$K_3Fe(CN)_6$ was sprayed to identify the phenols.

Reaction of 4α-p-Tolyloxyflavan with Toluene-p-sulphonic Acid.—(a) *In ether*. 4α-*p*-Tolyloxyflavan (35 mg), ether (1 ml), and toluene-*p*-sulphonic acid (11 mg) were kept at room temperature for 65 days. Work-up and separation by p.l.c. gave 4α-*p*-tolyloxyflavan (1 mg), 4α-(2-hydroxy-5-methylphenyl)flavan (3 mg), and flavan-4α-ol (8 mg), all identified by m.p., mixed m.p. and comparison of i.r. and n.m.r. spectra.

(b) *In ethanol*. 4α-*p*-Tolyloxyflavan (8 mg), ethanol (0.5 ml), and toluene-*p*-sulphonic acid were kept at room temperature for 45 days. Work-up and p.l.c. gave 4α-ethoxyflavan (4 mg) as an oil, which was identified by comparison of its i.r. and n.m.r. spectra with those of an authentic sample prepared from flavan-4β-ol.[15,16]

Reaction of 4α-(2,4,6-Trimethylphenoxy)flavan with p-Cresol catalysed by Toluene-p-sulphonic Acid.—4α-(2,4,6-Trimethylphenoxy)flavan (70 mg), *p*-cresol (220 mg), and toluene-*p*-sulphonic acid (190 mg) in dioxane (5 ml) were kept at room temperature for 42 h. More toluene-*p*-sulphonic acid (190 mg) was added and after a further 4 days, work-up and p.l.c. gave flav-3-ene (3 mg), 4α-*p*-tolyloxyflavan (4 mg), 4α-(2-hydroxy-5-methylphenyl)flavan (14 mg), and flavan-4α-ol (20 mg), all identified by m.p., i.r., and n.m.r. comparisons.

Methyl (Flavan-4α-ylthio)acetate (10).—Flavan-4β-ol (2.8 g), dioxane (250 ml), mercaptoacetic acid (12 g), and 2M-hydrochloric acid (250 ml) were heated under reflux for 3 h; an excess of saturated aqueous sodium carbonate was then added and the whole extracted with ether (3 × 150 ml). After acidification with 2M-hydrochloric acid, the mixture was re-extracted with ether (2 × 100 ml) and the dried extracts methylated with an excess of diazomethane. Removal of the solvent and methyl (methylthio)acetate under reduced pressure, yielded an oil (5.0 g) which was chromatographed on a column of silica (500 g), made up in light petroleum (b.p. 40—60 °C). Gradient elution up to 75% ether in light petroleum gave *methyl (flavan-4α-yl)thioacetate* as prisms which separated from methanol as needles (2.3 g), m.p. 84—85 °C (Found: C, 68.7; H, 5.75; S, 10.2. $C_{18}H_{18}O_3S$ requires C, 68.8; H, 5.75; S, 10.2%), $\nu_{max.}$ (CCl_4) 1 738, 1 490, 1 246, and 1 124 cm^{-1}; τ(CCl_4) 2.5—3.3 (9 H, m, ArH), 4.6 (1 H, m, 2-H), 5.8 (1 H, t, 4-H), 6.3 (3 H, s, OCH_3), 6.6—6.95 (2 H, q, SCH_2), 7.7—7.8 (2 H, m, 3-H's), $\Sigma J_{2,3} = 13.8$, $\Sigma J_{3,4} = 6.2$; *m/z* 314 (M^+) and 209 (100%).

Reaction of 4α-(2,4,6-Trimethylphenoxy)flavan with Mercaptoacetic Acid.—4α-(2,4,6-Trimethylphenoxy)flavan (700 mg), dioxane (21 ml), mercaptoacetic acid (2.0 g), and 2M-hydrochloric acid (25 ml) were kept at 60 °C for 4 h and then poured into an excess of saturated aqueous sodium hydrogen carbonate. The mixture was washed with ether (250 ml), acidified with 2M-hydrochloric acid, and extracted with ether (3 × 100 ml). The dried extracts were methylated with an excess of diazomethane. Removal of solvent and methyl (methylthio)acetate under reduced pressure yielded a yellow oil (500 mg) and a sublimate of 2,4,6-trimethylphenol (200 mg) (m.p. and mixed m.p.). P.l.c. of the oil and isolation of the major component (slowest band of three) gave methyl (flavan-4α-ylthio)acetate (210 mg), m.p. and mixed m.p. 84—85 °C.

Flavan-4α-ylthioacetanilide (13).—Methyl flavan-4α-ylthioacetate (40 mg) in 1,2-dimethoxyethane (2.5 ml) was added to a solution of anilinomagnesium bromide from magnesium (0.16 g), ether (3 ml), ethyl bromide (0.6 ml), and aniline

(0.52 g) in tetrahydrofuran (4 ml). After a few minutes 2M-hydrochloric acid (50 ml) was added and the resulting mixture was extracted with ether (200 ml). Evaporation of the washed (water) and dried extract gave an oil which was purified by p.l.c. to give *flavan-4α-ylthioacetanilide* (32 mg) which separated from methanol as prisms, m.p. 161—162 °C (Found: C, 73.3; H, 5.8; N, 3.8. $C_{23}H_{21}NO_2S$ requires C, 73.6; H, 5.6; N, 3.7%), $\nu_{max.}$ ($CHCl_3$) 3 340, 1 690, 1 600, 1 530, 1 485, 1 440, 1 315, 1 250, 1 115, 905, 705, and 700 cm^{-1}; τ($CDCl_3$) 1.5br (1 H, s, NH, exchanges with D_2O), 2.3—3.2 (14 H, m, ArH), 4.55 (1 H, q, 2-H), 5.75 (1 H, t, 4-H), 6.48, 6.60 (2 H, q, SCH_2), and 7.55—7.75 (2 H, m, 3-H's), Σ $J_{2,3}$ = 14.0, Σ $J_{3,4}$ = 6.0; *m/z* 375 (M^+, 11%) and 135 (100%).

Reaction of 4α-p-*Tolyloxyflavan with Thiophenol.*—4α-*p*-Tolyloxyflavan (50 mg), dioxane (2.5 ml), thiophenol (0.2 ml), and 2M-hydrochloric acid (2.5 ml) were boiled for 5 h. Work-up [10] gave 4α-phenylthioflavan (31 mg), m.p. and mixed m.p. 126—127 °C,[10] n.m.r. spectrum identical with that of an authentic sample.

7-*Methoxy*-4α-*phenoxyflavan.*—7-Methoxyflavan-4β-ol (310 mg) in pyridine (3.5 ml) was stirred at 0 °C and phenyl chloroformate (450 mg) was added during 20 min. After a further 2.5 h at 0 °C, dichloromethane (50 ml) was added. The mixture was well washed with water, dried, and the solvent evaporated to yield an oil which was heated with phenol (1.50 g) at 80 °C for 20 min. The mixture was extracted with ether (50 ml) and the extract well washed with 2M-sodium hydroxide and then with water, dried, and the ether evaporated to give a mixture of flavonoids. Separation by p.l.c. gave 7-*methoxy*-4α-*phenoxyflavan* (15 mg) which separated from methanol as needles, m.p. 90—91 °C (Found: C, 79.3; H, 6.0. $C_{22}H_{20}O_3$ requires C, 79.5; H, 6.0%), τ($CDCl_3$) 2.45—3.10 (11 H, m, ArH), 3.35—3.55 (2 H, m, ArH), 4.55—4.75 (2 H, m, 2-H and 4-H), 6.30 (3 H, s, OCH_3), 7.40—7.60 (1 H, 2 × t, 3-H), and 7.65—8.0 (1 H, m, 3-H), Σ $J_{2,3}$ = 15.5, Σ $J_{3,4}$ = 6.2; *m/z* 239 (100%), 240 (18%), 115 (17%), and 91 (15%).

The following are typical details of the reaction between flav-3-ene epoxides and phenols which yield, stereospecifically, either 2,3-*cis*-(from the *cis*-epoxides) or 2,3-*trans*-(from the *trans*-epoxide) 3,4-*cis*-aryloxyflavan-4-ols (Table 4).

2,3-cis-3,4-cis-4-*Phenoxyflavan*-3-*ol* (17).—2,3-*cis*-Flav-3-ene epoxide [13] (99 mg) and phenol (2.0 g) were heated at 100 °C for 30 min. Ether (150 ml) was added and the solution was washed with 2M-sodium hydroxide (4 × 150 ml) and dried. Removal of ether gave an oil and crystallisation from light petroleum (b.p. 60—80 °C) gave 2,3-cis-3,4-cis-4-*phenoxyflavan*-3-*ol* (102 mg) as needles, m.p. 125—126 °C; see Table 4 for analysis; τ($CDCl_3$) 2.54—3.15 (14 H, m, ArH), 4.42 (1 H, d, 4-H), 4.90 (1 H, s, 2-H), 5.71 (1 H, m, 3-H), 7.85 (1 H, d, HO, exchanges with D_2O), $J_{3,4}$ = 4.4, $J_{3,OH}$ = 3.0; *m/z* 318 (M^+ 3%) and 107 (100%).

The following are typical details of the reaction between flav-3-ene epoxides and phenolate ions which yield, stereospecifically, 2,3-*cis*-(from the *cis*-epoxide) or 2,3-*trans*-(from the *trans*-epoxide) 3,4-*trans*-aryloxyflavan-3-ols (Table 4).

2,3-cis-3,4-trans-4-*Phenoxyflavan*-3-*ol* (18).—2,3-*cis*-Flav-3-ene epoxide (87 mg) and sodium phenolate (170 mg) were heated at 100 °C in anhydrous dimethylformamide (5 ml) for 2 h. Work-up as above gave an oil (83 mg) which on p.l.c. with ether–light petroleum (b.p. 40—60 °C) (1 : 1, v/v) as eluant gave an oil. Crystallisation from light petroleum (b.p. 60—80 °C) gave crystalline 2,3-cis-3,4-trans-4-*phenoxyflavan*-3-*ol* (23 mg), m.p. 130—131 °C; for analysis see Table 4; τ($CDCl_3$) 2.60—3.16 (14 H, m, ArH), 4.70 (1 H, s, 2-H), 4.80 (1 H, d, 4-H), 5.81 (1 H, m, 3-H), and 8.16br (1 H, s, HO, exchanges with D_2O), $J_{3,4}$ = 2.4; *m/z* 318 (M^+, 1%), 107 (100%).

Reaction of 2,3-cis-3,4-cis-4-*Phenoxyflavan*-3-*ol* (17) *with Thiophenol.*—The phenoxyflavan-3-ol (105 mg) was boiled with thiophenol (1.5 ml) in dioxane (12 ml) and 5M-hydrochloric acid (12 ml) for 3 h. Ether (150 ml) was added and the mixture was washed with water (100 ml) and 2M-NaOH (4 × 100 ml). Evaporation and crystallisation of the residue from light petroleum (b.p. 60—80 °C) gave needles (64 mg) of 2,3-*cis*-3,4-*trans*-3-hydroxy-4-phenylthioflavan, m.p. and mixed m.p. 159—160 °C.[10]

7-(2,3-trans-3,4-cis-3-*Hydroxyflavan*-4-*yloxy*)*flavanone* (23).—2,3-*trans*-Flav-3-ene epoxide (399 mg) and 7-hydroxyflavanone (1.23 g) were boiled for 6 h in ethanol-free chloroform (60 ml). The chloroform was evaporated, the residue taken up in ether (150 ml) and the solution washed with 2M-NaOH (4 × 150 ml) and dried. Removal of ether and recrystallisation of the crystalline residue from light petroleum (b.p. 60—80 °C) gave needles (487 mg) of 7-(2,3-trans-3,4-cis-3-*hydroxyflavan*-4-*yloxy*)*flavanone*, m.p. 191—192 °C (Found: C, 77.4; H, 5.2. $C_{30}H_{24}O_5$ requires C, 77.6; H, 5.2%), τ($CDCl_3$)* 2.58—3.27 (17 H, m, ArH), 4.64 (3 H, m, 2-H, 2-*H*, and 4-*H*), 5.71 (1 H, octet, collapses to q on addition of D_2O, 3-*H*), 7.01—7.30 (2 H, m, 3-H), and 7.78 (1 H, d, OH, exchanges with D_2O), $J_{2,3}$ = 9.2, $J_{3,4}$ = 3.4, $J_{3,OH}$ = 6.0; *m/z*: M^+ not observed, 120 (100%); $\nu_{max.}$ ($CHCl_3$) 3 585 (OH) and 1 681 cm^{-1} (C=O).

7-(2,3-trans-3,4-cis-3-*Hydroxyflavan*-4-*yloxy*)-2,4-cis-*flavan*-4-*ol* (24).—Sodium borohydride (300 mg) was added during 30 min to a stirred solution of 7-(2,3-*trans*-3,4-*cis*-3-hydroxyflavan-4-yloxy)flavanone (989 mg) in methanol (50 ml) and chloroform (50 ml) at 5 °C. More borohydride (150 mg) was added and after 15 h acetic acid (0.5 ml) was added and the mixture was poured into water (200 ml) and extracted with chloroform (3 × 200 ml). Evaporation of chloroform from the dried extract gave 7-(2,3-trans-3,4-cis-3-*hydroxyflavan*-4-*yloxy*)-2,4-cis-*flavan*-4-*ol* which separated from light petroleum (b.p. 60—80 °C) as needles (888 mg), m.p. 167—168 °C (Found: C, 77.1; H, 5.7. $C_{30}H_{26}O_5$ requires C, 77.2; H, 5.6%); τ($CDCl_3$) 2.58—3.41 (17 H, m, ArH), 4.68—5.10 (4 H, m, 2-H, 2-*H* and 4-*H*), 5.74 (1 H, octet, collapses to q on addition of D_2O, 3-*H*), 7.50—8.21 (4 H, m, 2 × OH, exchange with D_2O and 2 × 3-H), $J_{2,3}$ = 9.0, $J_{3,4}$ = 3.5; *m/z* M^+ not observed, 224 (100%); $\nu_{max.}$ ($CHCl_3$) 3 575 (OH) and 3 390 cm^{-1} (OH).

7-(2,3-trans-3,4-cis-3-*Hydroxyflavan*-4-*yloxy*)-2,4-trans-*flavan*-4-*yl Phenyl Sulphone* (25).—7-(2,3-*trans*-3,4-*cis*-3-Hydroxyflavan-4-yloxy)-2,4-*cis*-flavan-4-ol (156 mg) and sodium benzenesulphinate (0.9 g) were boiled in 50% aqueous ethanol (30 ml) and acetic acid (6 ml) for 4 h. Ether was added and the mixture was washed with water (3 × 200 ml) and then with saturated sodium hydrogen carbonate (3 × 200 ml) and dried. Evaporation of ether and crystallisation of the residue from light petroleum (b.p. 60—80 °C) gave 7-(2,3-trans-3,4-cis-3-*hydroxyflavan*-4-*yloxy*)-2,4-trans-*flavan*-4-*yl phenyl sulphone* (159 mg) as prisms, m.p. 88—90 °C (Found: C, 73.5; H, 5.0; S, 5.1. $C_{36}H_{30}O_6S$ requires C, 73.2; H, 5.1; S, 5.4%), τ($CDCl_3$) 2.41—3.32 (22 H, m, ArH), 4.71 (3 H, m, 2-H, 2-*H* and 4-*H*), 5.72 (2 H, m, 3-*H* and 4-*H*), 7.70—7.83 (3 H, m,

* Hydrogen atoms designated 2-*H* (*i.e.* italicised) refer to those in the 'upper half' of the molecule as written in formulae (23), (24), and (25).

OH, exchanges with D_2O and 2 × 3-H), $J_{2,3}$ = 8.4, $J_{3,4}$ = 3.2; *m/z*: M^+ not observed, 448 (1%) and 224 (100%).

2,3-trans-3-*Hydroxyflavan*-4-*yl Phenyl Sulphones* (26).—7-(2,3-*trans*-3,4-*cis*-3-Hydroxyflavan-4-yloxy)-2,4-*cis*-flavan-4-ol (426 mg) and sodium benzenesulphinate (5.0 g) were boiled in formic acid (40 ml) and water (4 ml) for 4 h. Ether (200 ml) was added and the mixture was washed with water (2 × 150 ml) and 2M-NaOH (3 × 200 ml). The ether was removed from the dried extract and the residue was eluted from a silica column (170 g) with ether–light petroleum (b.p. 40—60 °C) mixtures of progressively increasing polarity. Fractions of composition 2 : 3 (v/v) gave a solid which separated from light petroleum (b.p. 60—80 °C) as prisms (122 mg), m.p. and mixed m.p. 152—154 °C with 2,3-*trans*-3,4-*trans*-3-hydroxyflavan-4-yl phenyl sulphone.[10] Further elution of the column with solvent of composition 4 : 1 (v/v) gave a solid which separated from light petroleum (b.p. 60—80 °C) as needles (73 mg), m.p. and mixed m.p. 188—192 °C with 2,3-*trans*-3,4-*cis*-3-hydroxyflavan-4-yl phenyl sulphone.[10]

2,3-cis-3,4-trans-4-*Acetoxy*-3-*bromo*-4′-*methoxyflavan* (28).—4′-Methoxyflav-3-ene [17] (4.18 g), anhydrous sodium acetate (5 g), acetic anhydride (1.5 ml), and acetic acid (48.5 ml) were treated at 10 °C during 30 min with a solution of bromine (0.86 ml) in acetic anhydride (1.5 ml) and acetic acid, (48.5 ml). After a further 12 h, the precipitated solid was separated and recrystallised from chloroform to give crystals (1.78 g), m.p. and mixed m.p. 189—190 °C with 2,3-*cis*-3,4-*trans*-4-acetoxy-3-bromo-4′-methoxyflavan.[12] 2,3-*trans*-4′-Methoxyflav-3-ene epoxide (16) [12] was obtained as an oil (113 mg) by treating the above 4-acetoxy-3-bromoflavan (196 mg) with methanolic potassium hydroxide as described.[12]

The practical details for the conversion of the crude epoxide (16) into 4-aryloxyflavan-3-ols are as described above for the unsubstituted epoxides. The results are collected in Table 5.

Reaction of 4′,7-*Dimethoxyflav*-3-*ene with Bromine*.—(a) *In* CCl_4. Bromine (1.07 ml) in carbon tetrachloride (60 ml) was added during 90 min to a stirred solution of 4′,7-dimethoxyflav-3-ene [18] (5.60 g) in carbon tetrachloride (50 ml) at 5 °C. The mixture was kept at 5 °C for a further 6 h and allowed to warm to room temperature during 18 h. Removal of solvent and chromatography of the residue on a silica column (170 g) with ether–light petroleum (b.p. 40—60 °C), as eluant gave, from fractions of composition 1 : 9 (v/v), 3-*bromo*-4′,7-*dimethoxyflav*-3-*ene* (531 mg) which separated from light petroleum (b.p. 60—80 °C) as needles, m.p. 102—103 °C (Found: C, 58.5; H, 4.6; Br, 22.9. $C_{17}H_{15}BrO_3$ requires C, 58.8; H, 4.3; Br, 23.0%); τ($CDCl_3$) 2.58—3.61 (7 H, m, ArH), 3.66 (1 H, s, 4-H), 4.17 (1 H, s, 2-H), 6.20 (3 H, s, OCH_3), and 6.27 (3 H, s, OCH_3); *m/z* 347 (M^+, 8%) and 267 (100%).

Further elution with solvent of composition 4 : 1 (v/v) gave a mixture of 3,3-dibromo-4′,7-dimethoxyflavan-4α- and 4β-ols (3.63 g) as needles, m.p. 144—146 °C (Found: 45.9; H, 3.6; Br, 35.6. Calc. for $C_{17}H_{16}Br_2O_4$: C, 46.0; H, 3.6; Br, 35.9%); τ [$(CD_3)_2SO$] 2.44—3.45 (7 H, m, ArH), 3.81—4.06 (1 H, 2 × d, OH, exchanges with D_2O), 4.70—5.06 (1 H, 2 × q became 2 × d with D_2O, 4-H), 5.46—5.56 (1 H, 2 × d, 2-H), 6.20 (3 H, s, OCH_3), 6.22 (3 H, s, OCH_3), $J_{2,4}$ = 9.0, $J_{4\text{-OH}}$ = 7.2; *m/z* 444 (M^+, 6%) and 212 (100%). Attempts to separate the 4-ols by recrystallisation or by chromatography were not successful.

(b) *In* HOAc–Ac_2O. Bromine (0.87 ml) in acetic acid (97 ml) and acetic anhydride (3 ml) was added during 30 min at 10—15 °C to a stirred solution of 4′,7-dimethoxyflav-3-ene (4.50 g) in acetic acid (1.45 ml) and acetic anhydride (5 ml) containing anhydrous sodium acetate (12.4 g). After 12 h at room temperature the mixture was poured into water and extracted with chloroform (4 × 300 ml). The extract was washed with water (2 × 300 ml), then saturated aqueous sodium hydrogen carbonate (2 × 300 ml), and finally dried and evaporated. The resulting oil was dissolved in the minimum volume of ether and after 12 h at 0 °C the solid precipitate was recrystallised from methanol to give 2,3-*trans*-3,4-*trans*-4-acetoxy-3,6-dibromo-4′,7-dimethoxyflavan (1.39 g) as needles, m.p. 154—156 °C (lit.,[12] m.p. 154—155 °C).

4-*Acetoxy*-3-*bromo*-4′,7-*dimethoxyflavans* (30) *and* (31).—*N*-Bromosuccinimide (630 mg) in acetic acid (18 ml) and acetic anhydride (2 ml) was added during 30 min at 10—15 °C to a stirred solution of 4′,7-dimethoxyflav-3-ene (948 mg) in acetic acid (27 ml) and acetic anhydride (3 ml) containing anhydrous sodium acetate (2 g). After 24 h at 20 °C the mixture was poured into water (200 ml) and extracted with chloroform (2 × 100 ml). The extract was washed with water (2 × 200 ml) and saturated aqueous sodium hydrogen carbonate (2 × 200 ml), dried, and evaporated to yield an oil which was eluted from a silica column with ether–light petroleum (b.p. 40—60 °C) mixtures of progressively increasing polarity. Fractions of composition 2 : 3 (v/v) gave 2,3-trans-3,4-trans-4-*acetoxy*-3-*bromo*-4′,7-*dimethoxyflavan* (31) which separated from methanol as prisms (745 mg), m.p. 160—161 °C (Found: C, 56.2; H, 4.8; Br, 19.3. $C_{19}H_{19}BrO_5$ requires C, 56.0; H, 4.7; Br, 19.6%), τ($CDCl_3$) 2.63—3.56 (7 H, m, ArH), 3.62 (1 H, d, 4-H), 4.80 (1 H, d, 2-H), 5.48 (1 H, q, 3-H), 6.19 (3 H, s, OCH_3), 6.25 (3 H, s, OCH_3), 7.94 (3 H, s, $OCOCH_3$) $J_{2,3}$ = 10.0, $J_{3,4}$ = 8.0; *m/z* 407 (M^+, 1%) and 267 (100%); $\nu_{max.}$ ($CHCl_3$) 1 740 cm^{-1} (C=O).

Further elution with solvent of composition 3 : 2 (v/v) gave 2,3-cis-3,4-trans-4-*acetoxy*-3-*bromo*-4′,7-*dimethoxyflavan* (30) which separated from methanol as prisms (218 mg), m.p. 124—125 °C (Found: C, 56.2; H, 4.9; Br, 19.9. $C_{19}H_{19}BrO_5$ requires C, 56.0; H, 4.7, Br, 19.6%), τ($CDCl_3$) 2.53—3.43 (7 H, m, ArH), 3.90 (1 H, d, 4-H), 4.75 (1 H, d, 2-H), 5.68 (1 H, q, 3-H), 6.17 (3 H, s, OCH_3), 6.20 (3 H, s, OCH_3), and 7.88 (3 H, s, $OCOCH_3$) $J_{3,4}$ = 2.5; *m/z* 407 (M^+, 1%) and 267 (100%); $\nu_{max.}$ ($CHCl_3$) 1 735 cm^{-1} (C=O).

2,3-cis-3,4-trans-4,4′,7-*Trimethoxyflavan*-3-*ol* (32).—2,3-*trans*-3,4-*trans*-4-Acetoxy-3-bromo-4′,7-dimethoxyflavan (335 mg) and potassium hydroxide (3 g) were kept at 20 °C for 2 h in methanol (40 ml). The mixture was evaporated to *ca.* 5 ml, diluted with ether (200 ml), and the ether extract decanted and evaporated. Crystallisation of the residue from light petroleum (b.p. 60—80 °C), gave plates of 2,3-cis-3,4-trans-4,4′,7-*trimethoxyflavan*-3-*ol* (126 mg), m.p. 79—80 °C (Found: C, 68.4; H, 6.6. $C_{18}H_{20}O_5$ requires C, 68.3; H, 6.4%), τ($CDCl_3$) 2.49—3.44 (7 H, m, ArH), 4.79 (1 H, d, 2-H), 5.87 (1 H, d, 4-H), 5.95 (1 H, q, 3-H), 6.19 (3 H, s, OCH_3), 6.22 (3 H, s, OCH_3), 6.52 (3 H, s, OCH_3), and 8.22 (1 H, s, OH), $J_{3,4}$ = 2.6; *m/z* 316 (M^+, 7%) and 167 (100%). The following are typical practical details for the conversion of 2,3-*trans*-3,4-*trans*-4-acetoxy-3-bromo-4′,7-dimethoxyflavan into 4-aryloxyflavan-3-ols (Table 6).

2,3-cis-3,4-trans-4′,7-*Dimethoxy*-4-*phenoxyflavan*-3-*ol* (33; Ar = Ph).—2,3-*trans*-3,4-*trans*-4-Acetoxy-3-bromo-4′,7-dimethoxyflavan (506 mg) and sodium phenolate (1.9 g) were heated at 100 °C in dimethylformamide (30 ml) for 3 h. Water (300 ml) was added and the mixture was extracted with ether (2 × 100 ml). The extract was washed with 2M-NaOH (2 × 300 ml), dried, and evaporated to give an oil which crystallised from light petroleum (b.p. 60—80 °C), to give needles (302 mg) of 2,3-cis-3,4-trans-4′,7-*dimethoxy*-4-*phenoxyflavan*-3-*ol*, m.p. 109—110 °C; see Table 6 for analysis; τ($CDCl_3$) 2.63—3.57

(12 H, m, ArH), 4.83 (1 H, s, 2-H), 4.95 (1 H, d, 4-H), 5.97 (1 H, q, 3-H), 6.25 (6 H, s, 2 × OCH_3), 8.30 (1 H, s, OH, exchanges with D_2O); *m/z* (M^+ not observed) 121 (100%).

2,3-trans-3,4-cis-4-*Acetoxy*-3,6(or 8)-*dibromo*-5,7,3′,4′-*tetramethoxyflavan*.—*N*-Bromosuccinimide (333 mg) in acetic acid (18 ml) and acetic anhydride (2 ml) was added during 30 min at 10—15 °C to a stirred solution of 5,7,3′,4′-tetramethoxyflav-3-ene [19] (611 mg) in acetic acid (27 ml) and acetic anhydride (3 ml) containing anhydrous sodium acetate (2 g). After 1 day at 20 °C, the mixture was poured into water (200 ml) and extracted with chloroform. The extract was washed with water (2 × 200 ml) and saturated aqueous sodium hydrogen carbonate (2 × 200 ml), and then dried and evaporated to give an oil which separated from methanol giving needles (100 mg) of 2,3-trans-3,4-cis-4-*acetoxy*-3,6(or 8)-*dibromo*-5,7,3′,4′-*tetramethoxyflavan*, m.p. 203—205 °C (Found: C, 45.9; H, 3.8; Br, 29.6. $C_{21}H_{22}Br_2O_7$ requires C, 46.1; H, 4.0; Br, 29.3%), τ($CDCl_3$) 2.92—3.16 (3 H, m, B-ring), 3.43 (1 H, d, 4-H), 3.82 (1 H, s, 6-H or 8-H), 4.79 (1 H, d, 2-H), 5.64 (1 H, q, 3-H), 6.11 (9 H, s, 3 × OCH_3), 6.17 (3 H, s, OCH_3), and 7.88 (3 H, s, $OCOCH_3$), $J_{2,3}$ = 11.2, $J_{3,4}$ = 3.4; *m/z* 546 (M^+, 7%) and 405 (100%), $\nu_{max.}$ ($CHCl_3$) 1 750 cm^{-1} (C=O).

The following are practical details for the synthesis of 4-arylflavans by catalysis with toluene-*p*-sulphonic acid (Table 7).

4-*Hydroxyphenylflavans*.—Flavan-4β-ol (500 mg), phenol (20 g), and toluene-*p*-sulphonic acid (10 mg) were boiled in ethanol-free chloroform (150 ml) for 10 min. The phenol and acid were removed by washing with 2M-NaOH and the residue after removal of chloroform, was separated by p.l.c. on a silica plate in 10% ether–light petroleum (b.p. 40—60 °C) into two bands, the faster running of which gave material which was recystallised from aqueous ethanol to give 4α-o-*hydroxyphenylflavan* (180 mg) as prisms, m.p. 134—134.5 °C; see Table 7 for analysis; τ(CCl_4) 2.6—3.4 (13 H, m, ArH), 5.00 (1 H, t, 2-H), 5.4br (1 H, s, OH, undergoes D_2O exchange), 5.53 (1 H, t, 4-H), 7.6—7.8 (2 H, m, 3-H's), Σ $J_{2,3}$ = 13.0, Σ $J_{3,4}$ = 9.0; *m/z* 302 (M^+, 83%) 181 (100%).

The slower running band gave prisms (440 mg), m.p. 80—82 °C from aqueous methanol; from its n.m.r. spectrum it was identified as a 1.3 : 1.0 mixture of 4α-*p*-hydroxyphenylflavan and its 4β-isomer. Several recrystallisations from benzene–light petroleum (b.p. 60—80 °C), taking small crops, gave pure 4β-p-*hydroxyphenylflavan* as needles, m.p. 170—171 °C; see Table 7 for analysis; τ(CCl_4) 2.5—3.4 (13 H, m, ArH), 4.88 (1 H, q, 2-H), 4.80br (1 H, s, OH undergoes D_2O exchange), 5.80 (1 H, q, 4-H), 7.5—8.0 (2 H, m, 3-H's), Σ $J_{2,3}$ = 13.0, Σ $J_{3,4}$ = 18.0; *m/z* 302 (M^+, 51%) and 197 (100%).

4-p-*Methoxyphenylflavans*.—Flavan-4β-ol (250 mg), anisole (2 ml), and BF_3–ether (1 ml, 7.2 mol equiv.) were kept at −5 °C for 1 day. The mixture was poured into water and the products extracted into ether (150 ml). The extract was washed thoroughly with water, dried, and evaporated. P.l.c. of the residue removed traces of anisole and the resulting mixed isomers were fractionally crystallised from ethanol.

The first crop was recrystallised many times to give prisms of 4α-p-*methoxyphenylflavan* (10 mg), m.p. 100—101 °C; see Table 7 for analysis; τ(CCl_4) 2.6—3.4 (13 H, m, ArH), 5.03 (1 H, q, 2-H), 5.93 (1 H, t, 4-H), 6.26 (3 H, s, OCH_3), 7.5—8.0 (2 H, m, 3-H's), Σ $J_{2,3}$ = 12.6, Σ $J_{3,4}$ = 8.8; *m/z* 316 (M^+, 75%) and 181 (100%).

Several recrystallisations of the solid from the filtrate gave a 1 : 1.5 mixture of the 4α- and 4β-isomers (19 mg). Further recrystallisation gave needles of 4β-*p*-methoxyphenylflavan (6 mg), m.p. and mixed m.p. 135—136 °C.

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