Reactions of Flavanoids and Condensed Tannins with Sulphur Nucleophiles

By **Ben R. Brown** * and **Mark R. Shaw**, Dyson Perrins Laboratory, Oxford University, Oxford OX1 3QY

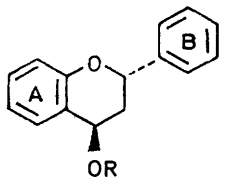
Reactions of benzenethiol and arenesulphinic acids with flavan-4-ols under acidic conditions are facilitated by 5-, 7-, and 4'-methoxy-groups, and 5,7-dimethoxyflavan-4β-ol (V) reacts quickly with benzenethiol in the absence of added acid. All products are 4α-thio-substituted flavans. 2,3-*trans*-Flavan-3,4-diols react less quickly than the corresponding 4-ols and the resulting 4-thio-substituted flavan-3-ols have mixed stereochemistry (3,4-*cis*- and *trans*-). Flavan-4-yl sulphones are less labile than 4-thioethers under acidic conditions but their lability is increased by a 7-methoxy-group: the products of the acid-catalysed exchange of thio-groups at C-4 have 4α-stereochemistry.

Calluna vulgaris tannin reacts with benzenethiol in the absence of acid to give, after methylation, (+)-2,3-*cis*-3,4-*trans*-3',4',5,7-tetramethoxy-4-phenylthioflavan-3-ol (XXVI). On the other hand, *Picea pungens* tannin gives the same product with benzenethiol only in the presence of acid, and (−)-tetra-*O*-methylcatechin (XXVII) is produced as well.

Our original application of mercaptoacetic acid as a reagent in the elucidation of the structure of *Calluna vulgaris* tannin [1] and its reaction with some monomeric flavanoids [2] was followed by studies of its reaction with naturally occurring flavan-3,4-diols,[3-5] dimeric procyanidins,[6] methylated *Tsuga heterophylla* tannin,[7] and suitably substituted 4-arylflavans.[8] Recently [9] toluene-α-thiol in acid solution has also been utilised for the structural investigation of some plant procyanidins. Systematic studies on the relationship between structure and reactivity towards various sulphur nucleophiles under differing conditions of acidity would be expected to lead both to the choice of the most convenient and efficient sulphur nucleophiles for tannin degradation and to a reliable diagnosis of differing types of linkage between the monomeric flavanoid units comprising condensed tannins. To our earlier study [2] of the action of mercaptoacetic acid on flavanoids, we have now added the reactions of benzenethiol and benzene- and toluene-*p*-sulphonic acids with flavan-4-ols and with flavan-3,4-diols having methoxy-groups in the 3'-, 4'-, 5-, and 7-positions, under varied conditions of temperature, solvent, and acidity. Finally we have applied the knowledge so gained to the degradation of the tannins from *Calluna vulgaris* and from *Picea pungens* with benzenethiol.

[1] M. J. Betts, B. R. Brown, P. E. Brown, and W. T. Pike, *Chem. Comm.*, 1967, 1110.
[2] M. J. Betts, B. R. Brown, and M. R. Shaw, *J. Chem. Soc.* (*C*), 1969, 1178.
[3] I. C. du Preez, D. Ferreira, and D. J. Roux, *J. Chem. Soc.* (*C*), 1971, 336.
[4] I. C. du Preez, T. G. Fourie, and D. G. Roux, *Chem. Comm.*, 1971, 333.
[5] T. G. Fourie, I. C. du Preez, and D. G. Roux, *Phytochem.*, 1972, **11**, 1763.
[6] F. Delle-Monache, F. Ferrari, and G. M. B. Bettolo, *Gazzetta*, 1971, **101**, 387.
[7] K. D. Sears and R. L. Casebier, *Phytochem.*, 1970, **9**, 1589.
[8] K. D. Sears and R. L. Casebier, *Chem. Comm.*, 1968, 1437.
[9] R. S. Thompson, D. Jaques, E. Haslam, and R. J. N. Tanner, *J.C.S. Perkin I*, 1972, 1387.

Our results for the reactions between benzenethiol and flavan-4-ols and flavan-3,4-diols are collected



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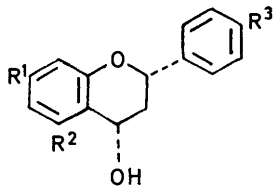

(III) $R^1 = R^2 = R^3 = H$
(IV) $R^1 = OMe$, $R^2 = R^3 = H$
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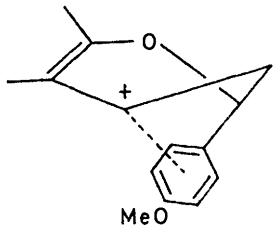

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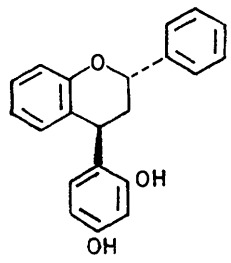

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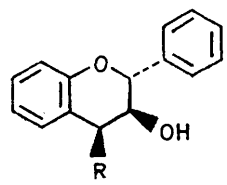
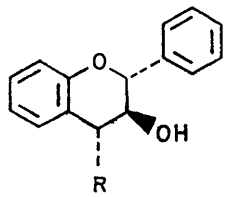


(IX) R = OH
(X) R = SPh
(XI) $R = SO_2Ph$



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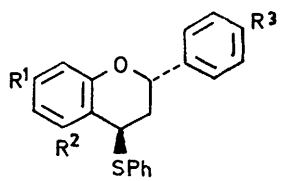
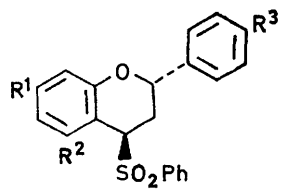
(XIII) R = SPh
(XIV) $R = SO_2Ph$



(XV) $R^1 = R^2 = R^3 = H$
(XVI) $R^1 = OMe$, $R^2 = R^3 = H$
(XVII) $R^1 = R^2 = OMe$, $R^3 = H$
(XVIII) $R^1 = R^2 = H$, $R^3 = OMe$



(XIX) $R^1 = R^2 = R^3 = H$
(XX) $R^1 = OMe$, $R^2 = R^3 = H$
(XXI) $R^1 = R^2 = OMe$, $R^3 = H$
(XXII) $R^1 = R^2 = H$, $R^3 = OMe$

in Table 1. As expected for an S_N1 mechanism,[2] progressive introduction of methoxy-groups into the 7- and 5-positions of flavan-4-ols enables the reaction to be conducted at progressively lower acid concentrations. Thus, 5,7-dimethoxyflavan-4β-ol (V) is smoothly converted into the corresponding thioether (XVII) in the absence of added acid and at a relatively low temperature. As we found for the analogous reaction with mercaptoacetic acid,[2] the stereochemistry of the resulting thioethers (4α, *i.e.* 2,4-*trans*) is the same whatever the stereochemistry of the reacting flavan-4-ols. Introduction of a 4′-methoxy-group (VI) enables milder conditions to be used than those for unsubstituted flavan-4β-ol (III), and this controls the unwanted opening of the heterocyclic ring to which 4′-methoxyflavanoids are prone (*cf.* ref. 2). The easier replacement of a 4-hydroxy-group in the presence of a 4′-methoxy-group can be interpreted in terms of the assistance given by enhanced π-bonding from ring B and the stability of the π-bonded carbonium ion intermediate (VII) will also explain the 4α-stereochemistry of the products resulting from flavan-4-ols since the incoming group must approach *trans* to ring B. Compared with flavan-4-ols, 2,3-*trans*-flavan-3,4-diols require more vigorous conditions for replacement of the 4-hydroxy-group. The mixed 3,4-stereochemistry of the products is probably a result of steric hindrance by the neighbouring 3-hydroxy-group. In contrast to the above flavanoids, 4α-(2,4-dihydroxyphenyl)-flavan (VIII), which has a carbon–carbon rather than a carbon–oxygen link at the 4-position, is unaffected by the most vigorous conditions we have used.

The products of the reaction of either 2,3-*trans*-3,4-*cis*- or 2,3-*trans*-3,4-*trans*-flavan-3,4-diols [(IX) and (XII), respectively] with benzenethiol in aqueous acidic dioxan could not be separated, but were shown to be 2,3-*trans*-3,4-*cis*-4-phenylthioflavan-3-ol (X) and its 2,3-*trans*-3,4-*trans*-isomer (XIII), in the ratio 1 : 1, by independent synthesis of each compound. The 3,4-*trans*-isomer (XIII) resulted as expected from the reaction of 2,3-*trans*-flav-3-ene epoxide [10] with sodium benzenethiolate. The 3,4-*cis*-isomer (X) was obtained by hydrolysis of its crystalline formate, isolated from the reaction of 2,3-*trans*-3,4-*cis*-flavan-3,4-diol (IX) with benzenethiol in hot formic acid (see later).

Table 2 shows that the reaction of benzenesulphinic acid with flavanoids follows the same pattern as observed for benzenethiol. Formic acid was found by Kenyon *et al.*[11] to be a good solvent for reactions of sulphinic acids with benzyloxy-compounds and we have followed their procedure. Benzyl alcohol does not react with benzenesulphinic acid in 100% formic acid but *p*-methoxybenzyl alcohol gives a good yield of the benzyl sulphone, as do flavan-4β-ol (III), 4α-methoxyflavan (II), and 4′-methoxyflavan-4β-ol (VI). Introduction of methoxy-groups at the 7- and at the 5- and 7-positions allows reaction to occur in 8% acetic

[10] B. J. Bolger, K. G. Marathe, E. M. Philbin, T. S. Wheeler, and C. P. Lillya, *Tetrahedron*, 1967, **23**, 341.
[11] M. P. Balfe, J. Kenyon, and E. M. Thain, *J. Chem. Soc.*, 1952, 790.

acid in aqueous ethanol. As with benzenethiol, 2,3-*trans*-3,4-*cis*-flavan-3,4-diol (IX) reacts with benzenesulphinic acid to give products of mixed stereochemistry [(XI) and (XIV)], which are separable by column chromatography.

4α-Phenylsulphonylflavan (XIX) and its 4′-methoxy-derivative (XXII) were also prepared by oxidation of the corresponding thioethers. Both 4-deuterio-4α-phenylthioflavan and the corresponding sulphone were prepared from 4-deuterioflavan-4β-ol, which allowed n.m.r. assignments for the 2- and 4-protons to be confirmed, and the 4-deuterio-sulphone was also obtained by equilibration of 4α-phenylsulphonylflavan (XIX) with sodium deuterioxide in deuterium oxide.

In order to define more clearly the optimum conditions for tannin degradation we have investigated the lability under acidic conditions of the 4-substituent for a number of 4-thio-substituted flavans, as presented in Table 3 (see Experimental section). Two trends are evident: first the sulphones are more stable than the corresponding thioethers, and secondly the effect of a 7-methoxy-substituent is to enhance the lability of the 4-substituent. In addition, the stereochemistry of the products is 4α in all cases, and it is clear that the mechanism is S_N1. Only some of the reactants investigated enter into equilibrium with the corresponding benzylic carbonium ion under the conditions originally used for their preparation (see Tables 1 and 2), and the exceptions to this lend credence to the suggestion that kinetic rather than thermodynamic factors control the stereochemistry of all these S_N1 reactions. Conclusive evidence for this must await corresponding investigations on the as yet unknown 4β-thio-substituted flavans.

The results of the above model investigations suggested that, for the degradation of procyanidin tannins, benzenethiol would be a more convenient nucleophile than mercaptoacetic acid, since the acidity of the reaction medium could more easily be controlled. In particular, a distinction between an ether linkage and a carbon–carbon linkage might be feasible under conditions of low acidity, since 4-aryl substituents are expected to be less acid-labile than 4-aryloxy-substituents. Furthermore, conditions of low acidity should lead to higher yields of the degradation products since continual regeneration of the benzylic carbonium ion intermediate and its subsequent loss from the reaction medium as a result of condensation reactions and/or cyanidin formation could then be controlled.

It has been shown [12] that in the reaction of flavan-4β-ol (III) with mercaptoacetic acid,[2] low yields of the resulting 4α-thio-substituted flavan (XXIII) are attributable both to aerial oxidation of the 4-hydroxy-group giving flavan-4-one (see also refs. 3—5) and to loss of a proton from the benzylic carbonium ion inter-

[12] M. J. Betts, D.Phil. Thesis, Oxford, 1968.

TABLE 1

Reaction of flavanoids with benzenethiol in boiling aqueous dioxan

Compound	Concentration of HCl	Time (h)	Product	Yield (%)
Flavan-4α-ol (I)	1·0N	5	4α-Thioether (XV)	70
Flavan-4β-ol (III)	Zero	5	No reaction	
	0·25N	1	Virtually no reaction	
	1·0N	5	4α-Thioether (XV)	81
4α-Methoxyflavan (II)	1·0N	5	4α-Thioether (XV)	85
7-Methoxyflavan-4β-ol (IV)	Zero	2	No reaction	
	0·25N	1	4α-Thioether (XVI)	77
	1·0N	5	4α-Thioether (XVI)	80
5,7-Dimethoxyflavan-4β-ol (V)	Zero *	4	4α-Thioether (XVII)	88
4′-Methoxyflavan-4β-ol (VI)	0·25N	1	4α-Thioether (XVIII)	68
2,3-*trans*-3,4-*cis*-Flavan-3,4-diol (IX)	1·0N	5	Incomplete reaction	
	2·5N	18	3,4-*cis*- and 3,4-*trans*-4-thioethers (1 : 1)	90
2,3-*trans*-3,4-*trans*-Flavan-3,4-diol (XII)	1·0N	5	Incomplete reaction	
	2·5N	18	3,4-*cis*- and 3,4-*trans*-4-thioethers (1 : 1)	91
4α-(2,4-Dihydroxyphenyl)flavan (VIII)	2·5N	30	No thioether	

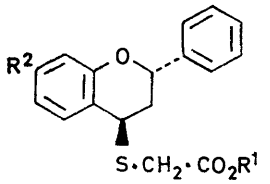
* In boiling aqueous ethanol.

TABLE 2

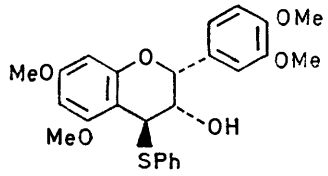
Reaction with benzenesulphinic acid

Compound	Solvent	Temp. (°C)	Time (h)	Product	Yield (%)
Benzyl alcohol	100% HCO_2H	100	15	No sulphone	
p-Methoxybenzyl alcohol	100% HCO_2H	100	3	Sulphone	88
Flavan-4β-ol (III)	8% AcOH in aq. EtOH	Reflux	4	No reaction	
	100% HCO_2H	100	3	4α-Sulphone (XIX)	83
4α-Methoxyflavan (II)	100% HCO_2H	100	3	4α-Sulphone (XIX)	86
7-Methoxyflavan-4β-ol (IV)	8% AcOH in aq. EtOH	Reflux	4	4α-Sulphone (XX)	84
	100% HCO_2H	100	1	4α-Sulphone (XX)	81
5,7-Dimethoxyflavan-4β-ol (V)	8% AcOH in aq. EtOH	Reflux	4	4α-Sulphone (XXI)	78
4′-Methoxyflavan-4β-ol (VI)	8% AcOH in aq. EtOH	Reflux	4	No reaction	
	100% HCO_2H	100	0·75	4α-Sulphone (XXII)	54
2,3-*trans*-3,4-*cis*-Flavan-3,4-diol (IX)	90% aq. HCO_2H	100	3	3,4-*cis*-(XI) and 3,4-*trans*-(XIV) sulphones	30
2,3-*trans*-3,4-*trans*-3′,4′,5,7-Tetramethoxy-flavan-3,4-diol	2% AcOH in aq. EtOH	Reflux	2	No sulphone	

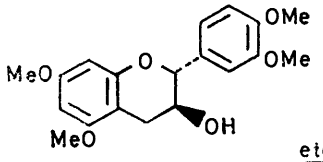
mediate giving flav-3-ene. Our present results have indicated that the importance of both these side-reactions is greatly diminished when benzenethiol is used as the nucleophile, presumably reflecting the facts that benzenethiol is oxidised faster than mercaptoacetic acid [13] and that it is a better nucleophile towards the carbonium ion intermediate under the conditions employed.



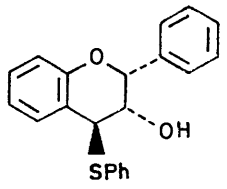
(XXIII) $R^1 = R^2 = H$
(XXIV) $R^1 = Me$, $R^2 = H$
(XXV) $R^1 = H$, $R^2 = OMe$



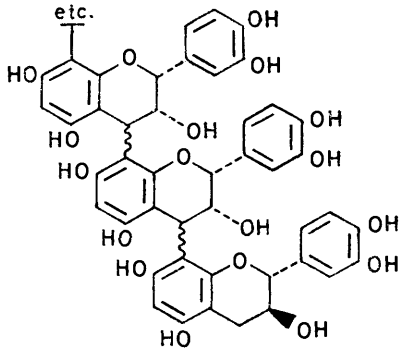
(XXVI)



(XXVII)



(XXIX)



(XXVIII)

Although benzenesulphinic acids had been found to react smoothly with various flavan-4-ols and flavan-3,4-diols, including some naturally occurring flavanoids,[14,15] our attempts to utilise these sulphur nucleophiles for the degradation of procyanidin tannins have not been successful. We conclude that in the presence of flanking hydroxy-substituents at both the 3- and 5-positions, the bulky benzenesulphinate ion is unable to approach the benzylic carbonium ion. This conclusion is supported by our failure to detect a 4-sulphone derivative of 2,3-*trans*-3,4-*trans*-3′,4′,5,7-tetramethoxyflavan-3,4-diol when a small sample of the latter was treated with benzenesulphinate ion in weakly acidic aqueous ethanol. The formation of a flavanoid whose molecular ion corresponded to a 4-ethoxy-derivative indicated that the conditions were sufficient for the generation of the benzylic carbonium ion.

As we expected, degradation of *Calluna vulgaris* tannin with benzenethiol in 3% acetic acid in aqueous alcohol gave, after methylation, (+)-2,3-*cis*-3,4-*trans*-3′,4′,5,7-tetramethoxy-4-phenylthioflavan-3-ol (XXVI), which yielded (−)-tetra-*O*-methylepicatechin on desulphurisation with Raney nickel, a result identical from a structural and stereochemical point of view with that already reported for the action of mercaptoacetic acid on the tanin.[1,2] A reaction in which *Calluna* tannin was boiled with benzenethiol in aqueous ethanol yielded, after methylation, the thioether (XXVI). This result may indicate the presence of some 4-ether linkages in the tannin but the relevant model experiments are not yet available to make this more than an indication.

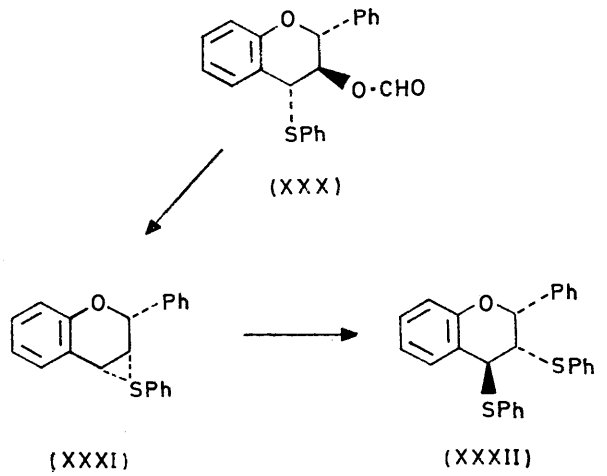
The behaviour of the tannin isolated from *Picea pungens* needles contrasts with that of *Calluna* tannin. The *P. pungens* tannin was obtained as a tannin–salt mixture by our usual method.[16] We did not attempt to remove salt from this mixture since our previous experience had shown that the presence of about 20% of salt did not interfere with the degradation of *Calluna* tannin, and from our knowledge of the limited stability of 4-aryloxyflavans [17] it seemed unwise to prolong

[13] M. S. Kharasch, W. Nudenberg, and G. J. Mantell, *J. Org. Chem.*, 1951, **16**, 524.
[14] J. W. Clark-Lewis and P. I. Mortimer, *J. Chem. Soc.*, 1960, 4106.
[15] J. W. Clark-Lewis, G. F. Katekar, and P. I. Mortimer, *J. Chem. Soc.*, 1961, 499.
[16] B. R. Brown and C. W. Love, *Reports Forest Res.*, 1961, 90.
[17] G. Bateman and B. R. Brown, *Chem. Comm.*, 1971, 409; B. R. Brown and M. R. Shaw, *ibid.*, p. 1571.

the extraction and risk the formation of artefacts (*e.g.* carbon–carbon linked polymers) should 4-ether links be present initially. Degradation of *P. pungens* tannin with benzenethiol in 3% acetic acid in aqueous ethanol gave, after methylation, (+)-2,3-*cis*-3,4-*trans*-3′,4′,5,7-tetramethoxy-4-phenylthioflavan-3-ol (XXVI), identical with that obtained from *Calluna* tannin, accompanied by (−)-tetra-*O*-methylcatechin (XXVII). Small-scale experiments showed that, after prolonged dialysis, which would be expected to remove monomeric catechin, the tannin still yielded tetra-*O*-methylcatechin on degradation and methylation, and extraction of undegraded tannin–salt mixture with acetone yielded no catechin. On the other hand, treatment of the tannin–salt mixture with 17% acetic acid in boiling aqueous ethanol produced a compound with the same R_F value as (±)-catechin. By contrast with *Calluna* tannin, *P. pungens* tannin was degraded to a negligible extent by benzenethiol in the absence of acid. These results indicate that *P. pungens* tannin probably consists of 3,3′,4′,5,7-pentahydroxyflavanoid units connected by carbon–carbon links with (+)-catechin as an end group [*e.g.* (XXVIII) or analogous structures involving linkage to the 6-position].

Our experience is that maximum yields of monomeric flavanoids from the degradation of tannins with benzenethiol are best obtained by choice of the minimum acceptable acidity and time of degradation. Further, the methylation stage is crucial, in that rapid and complete methylation is essential if polymerisation of the monomeric polyphenolic flavanoids to give intractable phlobaphenes is to be effectively controlled. For this reason, degradations are best conducted on a scale convenient for rapid methylation and we have found that extraction of the unmethylated degradation mixture with ether rather than with ethyl acetate leads to the almost complete recovery of monomeric flavanoids, virtually unaccompanied by extraneous polymeric material, and this facilitates subsequent rapid and complete methylation of the monomer. Our most recent degradations (*e.g.* of *Calluna* tannin in the absence of acid) have been carried out in this way.

Arising out of the work, the reaction of benzenethiol in 100% formic acid with 2,3-*trans*-3,4-*cis*-flavan-3,4-diol (IX) proved to be important in that it provided a means of obtaining pure 2,3-*trans*-3,4-*cis*-4-phenylthioflavan-3-ol (X), and interesting in that 2,3-*cis*-3,4-*trans*-3,4-bis(phenylthio)flavan (XXXII) and 2,3-*cis*-3,4-*trans*-4-phenylthioflavan-3-ol (XXIX) were also formed. The flavanoids isolated were 2,3-*trans*-3,4-*cis*-4-phenylthioflavan-3-yl formate (16%), which on hydrolysis gave the required 3-ol (X), compounds (XXXII) (13%) and (XXIX) (7%), and an inseparable mixture (21%) of 2,3-*trans*-3,4-*trans*- (XIII) and 2,3-*trans*-3,4-*cis*-4-phenylthioflavan-3-ol (X). We have shown that the 3-hydroxy-group in 2,3-*trans*-flavan-3-ol, even when formylated, does not react with benzenethiol in formic acid, and we conclude that the 3,4-bis(phenylthio)flavan (XXXII) is probably formed from the 3-formyl derivative (XXX) of the thioether (XIII) by involvement of a 4-phenylthio-group in the replacement of the 3-formyl group to give a 2,3-*cis*-3,4-*cis*-episulphonium intermediate (XXXI) which is opened at C-4 by reaction with benzenethiol as in the Scheme. The formation of 2,3-*cis*-3,4-*trans*-4-phenylthioflavan-3-ol



SCHEME

(XXIX) is less easy to understand but it may occur by opening of the heterocyclic ring and consequent inversion at C-2, a process which could be aided by an axial 4-phenylthio-group as in the phenyl thioether (X).

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. Microanalyses were performed by Dr. F. B. Strauss, Oxford. N.m.r. spectra were recorded with a Perkin-Elmer R14 instrument; coupling constants and τ values are first-order, and (where appropriate) 3-H* and 4-H* refer to quasi-axial protons. I.r. spectra (chloroform) were recorded with a Perkin-Elmer 257 spectrophotometer; u.v. spectra (ethanol) were recorded with a Cary 14 spectrophotometer; and mass spectra were recorded with a Varian CH7 instrument. Silica gel plates (Merck HF_{254}) were used for analytical and preparative t.l.c.; solvent systems were (A) 3 : 1 ether–light petroleum, (B) 1 : 1 benzene–petroleum (b.p. 60—80°), and (C) 5 : 4 : 1 chloroform–ethyl acetate–formic acid. Flavanoid material was detected by spraying with 1% (w/v) isovanillin in concentrated sulphuric acid, followed by heating for a few minutes in a hot cupboard, and phenolic material was also developed by spraying with bis-diazotised *o*-tolidine solution.[18] Light petroleum refers to the fraction of boiling range 40—60°. Organic extracts were washed with brine and dried over magnesium sulphate. T-1 [19] and W-3 [20] Raney nickel were used for desulphurisations.

4-Deuterioflavan-4β-ol.—Flavan-4-one (2·86 g) in methanol at 0° was treated with finely powdered sodium borodeuteride (150 mg) over *ca.* 30 s. The mixture was kept at 0° for 2 h and poured into cold aqueous 2% acetic acid (400 ml). Ethereal extracts (2 × 100 ml) were washed

[18] D. G. Roux and A. E. Maiks, *J. Chromatog.*, 1960, **4**, 65.
[19] X. A. Dominiguez, I. C. Lopez, and R. Franco, *J. Org. Chem.*, 1961, **26**, 1625.
[20] H. Adkins and A. A. Pavlic, *J. Amer. Chem. Soc.*, 1946, **68**, 1471; 1947, **69**, 3039.

with saturated aqueous sodium hydrogen carbonate (2 × 150 ml), dried, and evaporated to yield a white solid which after fractional recrystallisation from methanol gave 4-*deuterioflavan*-4β-*ol* (1·40 g) as needles, m.p. 148—149·5° (Found: C, 79·3; H + D, 6·4. $C_{15}H_{13}DO_2$ requires C, 79·3; H + D, 6·6%): *m/e* (60°) 227 (M^+, 23%) and 104 (100); τ [$(CD_3)_2SO$] 2·35—3·20 (9H, complex, aromatic), 4·47 (1H, s, exchanges with D_2O, OH), 4·72 (1H, q, 2-H), 7·65 (1H, q, 3-H), and 8·03 (1H, incompletely resolved q, 3-H*) ($J_{2.3}$ 2·2, $J_{2.3*}$ 11·6, $J_{3.3*}$ *ca.* 13 Hz) (a 4-H signal at τ *ca.* 4·95 was not detected); $\nu_{max.}$ 3595, 3400br, 1614, 1583, 1485, 1453, 1305, 1119, 1043, 929, and 699 cm^{-1}.

4α-*Methoxyflavan* (II).—Flavan-4β-ol (1·0 g) in methanol (100 ml) and concentrated hydrochloric acid (5 ml) was heated under reflux for 2 h. The mixture was poured into water (300 ml) and extracted with ether (2 × 70 ml). Evaporation left a gum which was eluted from a silica column (170 g) with ether–light petroleum mixtures of increasing polarity. 4α-Methoxyflavan (880 mg) was obtained from fractions of composition 1 : 19 v/v as an oil (Found: C, 80·1; H, 6·8. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%); *m/e* (100°) 240 (M^+, 70%) and 208 (100); τ ($CDCl_3$) 2·45—3·25 (9H, complex, aromatic), 4·74 (1H, q, 2-H), 5·83 (1H, t, 4-H), 6·60 (3H, s, 4-OMe), and 7·45—8·24 (2H, complex, 3-H_2) ($J_{2.3}$ 2·5, $J_{2.3*}$ 11·2, $J_{3.4} = J_{3*.4}$ 3·0 Hz); $\nu_{max.}$ 1610, 1584, 1485, 1462, 1452, 1149, 1117, 1040, 1023, 1007, and 696 $cm.^{-1}$.

4α-*Phenylthioflavan* (XV).—(a) *From flavan*-4α-*ol*. Flavan-4α-ol (250 mg) in dioxan (12·5 ml) and 2N-hydrochloric acid (12·5 ml) was treated with benzenethiol (1 ml) and the two-phase mixture was heated under reflux for 5 h. Ether (75 ml) was added, and the mixture was washed with water (50 ml) and 2N-sodium hydroxide (4 × 50 ml). Removal of ether left a mixture of flavanoid and diphenyl disulphide from which the *thioether* (XV) (245 mg) was isolated, by recrystallisation from methanol, as needles, m.p. 127—128° (Found: C, 79·0; H, 5·7; S, 9·8. $C_{21}H_{18}OS$ requires C, 79·2; H, 5·7; S, 10·0%); *m/e* (175°) 318 (M^+, 7%) and 209 (100); τ ($CDCl_3$) 2·35—3·17 (14H, complex, aromatic), 4·45 (1H, incompletely resolved q, 2-H), 5·41 (1H, t, 4-H), and 7·66—7·82 (2H, complex, 3-H_2) ($J_{2.3}$ 5·9, $J_{2.3*}$ 7·0, $J_{3.4} = J_{3*.4}$ 3·0 Hz); $\nu_{max.}$ 1608, 1581, 1484, 1451, 1243, 1113, 1063, 1033, 1020, 900, and 693 cm^{-1}; $\lambda_{max.}$ 287 (log ε 3·63), 281 (3·73), 258 (3·63), and 202 nm (4·91).

(b) *From flavan*-4β-*ol*. An identical preparation from flavan-4β-ol (2·5 g) gave the thioether (2·86 g), m.p. and mixed m.p. 127—128°, identical with material prepared from flavan-4α-ol.

In another experiment flavan-4β-ol (500 mg), dioxan (25 ml), and 0·5N-hydrochloric acid (25 ml) were heated under reflux with benzenethiol (2 ml) for 1 h. The mixture was worked up as above to give an extract which was shown by t.l.c. to contain flavan-4β-ol with a trace of 4α-phenylthioflavan.

A small-scale experiment in which flavan-4β-ol was heated under reflux for 5 h with dioxan, water, and benzenethiol yielded only starting material and no trace of the thioether (t.l.c.).

(c) *From* 4α-*methoxyflavan*. 4α-Methoxyflavan (960 mg) on treatment with benzenethiol (4 ml), 2N-hydrochloric acid (50 ml), and dioxan (50 ml) for 5 h as above gave the thioether (1·08 g), m.p. and mixed m.p. 127—128°.

4α-p-*Tolylthioflavan*.—Flavan-4β-ol (500 mg) was treated with toluene-*p*-thiol (2·0 g), 2N-hydrochloric acid (25 ml), and dioxan (25 ml) as above for 3 h. Recrystallisation from methanol gave the *thioether* (445 mg) as needles, m.p. 97—98° (Found: C, 79·6; H, 6·2; S, 9·8. $C_{22}H_{20}OS$ requires C, 79·5; H, 6·0; S, 9·6%); *m/e* (60°) 332 (M^+, 3%) and 209 (100); τ ($CDCl_3$) 2·50—3·23 (13H, complex, aromatic), 4·50 (1H, incompletely resolved q, 2-H), 5·55 (1H, t, 4-H), 7·68 (3H, s, ArMe), and 7·73—7·88 (2H, complex, 3-H_2) ($J_{2.3}$ 6·0, $J_{2.3*}$ 7·1, $J_{3.4} = J_{3*.4}$ 3·0 Hz); $\nu_{max.}$ 1607, 1580, 1483, 1451, 1242, 1114, 1064, 1035, 1018, 902, 811, and 698 cm^{-1}.

4-*Deuterio*-4α-*phenylthioflavan*.— 4-Deuterioflavan-4-ol (340 mg) was treated with benzenethiol (2 ml), 2N-hydrochloric acid (25 ml), and dioxan (25 ml) as above for 5 h. Recrystallisation from methanol gave the *thioether* (362 mg) as needles, m.p. 127—128° (Found: C, 79·2; H + D, 5·7; S, 10·3. $C_{21}H_{17}DOS$ requires C, 79·0; H + D, 5·9; S, 10·0%); *m/e* (80°) 319 (M^+, 1%) and 210 (100); τ ($CDCl_3$) 2·40—3·15 (14H, complex, aromatic), 4·45 (1H, q, 2-H), and 7·70—7·82 (2H, complex, 3-H_2) ($J_{2.3}$ 6·0, $J_{2.3*}$ 7·2 Hz) [a signal (*ca.* 0·02H) at τ 5·42, corresponding to a C-4 proton, was observed]; $\nu_{max.}$ 1606, 1579, 1481, 1450, 1239, 1113, 1064, 1039, 1021, 924, and 696 cm^{-1}. The thioether (89%) was recovered unchanged, as judged from its n.m.r. spectrum, after being heated at 70° with aqueous 40% sodium hydroxide in dioxan for 1 h.

7-*Methoxy*-4α-*phenylthioflavan* (XVI).—7-Methoxyflavan-4β-ol (750 mg) was treated with benzenethiol (3 ml), 2N-hydrochloric acid (25 ml), and dioxan (25 ml) as above for 5 h. Recrystallisation from aqueous methanol gave the *thioether* (XVI) (817 mg) as needles, m.p. 75—77° (Found: C, 76·1; H, 5·7; S, 9·5. $C_{22}H_{20}O_2S$ requires, C, 75·9; H, 5·7; S, 9·2%); *m/e* (165°) 348 (M^+, 0·5%) and 239 (100); τ ($CDCl_3$) 2·40—2·75 (11H, complex, aromatic), 3·36—3·52 (2H, complex, 6-H and 8-H), 4·46 (1H, incompletely resolved q, 2-H), 5·43 (1H, t, 4-H), 6·22 (3H, s, 7-OMe), and 7·70—7·86 (2H, complex, 3-H_2) ($J_{2.3}$ 6·0, $J_{2.3*}$ 7·2, $J_{3.4} = J_{3*.4}$ 3·0 Hz) [at 220 MHz (Varian HR-220) $J_{2.3}$ 4·5, $J_{2.3*}$ 8·5, $J_{3.4} = J_{3*.4}$ 3·0 Hz, and the multiplet due to 3-H_2 remained unresolved]; $\nu_{max.}$ 1611, 1577, 1497, 1436, 1259, 1189, 1151, 1122, 1106, 1059, 1018, 948, 879, 830, and 690 cm^{-1}; $\lambda_{max.}$ 247 (log ε 4·08) and 209 nm (4·78).

In another experiment 7-methoxyflavan-4β-ol (500 mg) in dioxan (25 ml) and 0·5N-hydrochloric acid (25 ml) was heated under reflux with benzenethiol (2 ml) for 1 h. The mixture was worked up as above, and recrystallisation from aqueous methanol afforded 7-methoxy-4α-phenylthioflavan (538 mg) as needles, m.p. and mixed m.p. 75—77°.

A small-scale experiment was conducted under the same conditions, except that water was substituted for hydrochloric acid, and heating was continued for 2 h. T.l.c. analysis of the extracts showed that 7-methoxyflavan-4-ol was the major flavanoid present, accompanied by a trace of 7-methoxyflavan-4-one as the only other flavanoid.

5,7-*Dimethoxyflavan*-4β-*ol* (V).—5,7-Dimethoxyflavan-4-one (1·75 g) in redistilled methanol (150 ml) was treated with sodium borohydride (0·6 g) at 0° for 1 h and then added to water. Ethereal extracts were washed with water, dried, and evaporated to give 5,7-*dimethoxyflavan*-4β-*ol* as a chromatographically homogeneous gum (Found: C, 71·3; H, 6·3. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%); *m/e* (40°) 286 (M^+, 30%), 182 (100), 268 (57), 267 (50), and 269 (48); τ (CCl_4) 2·55—2·80 (5H, complex, aromatic), 4·02 (2H, s, 6-H and 8-H), 4·91 (1H, q, 4-H), 5·11 (1H, q,

2-H), 6·20 and 6·31 (each 3H, s, 5-OMe and 7-OMe), 6·63br (1H, exchanges with D_2O, OH), and 7·50—8·10 (2H, complex, 3-H_2) ($J_{2,3}$ 2·0, $J_{2,3^*}$ 11·3, $J_{3,4}$ 7·2, $J_{3^*,4}$ 9·6 Hz); $\nu_{max.}$ 3570, 1620, 1595, 1496, 1468, 1457, 1441, 1197, 1150, 1114, 820, and 700 cm^{-1}.

5,7-*Dimethoxy*-4α-*phenylthioflavan* (XVII).—5,7-Dimethoxyflavan-4β-ol (1·14 g) in 1 : 1 water–ethanol (60 ml) was heated under reflux with benzenethiol (8 ml) for 4 h. The usual procedure led to an oil; t.l.c. [solvent (A)] showed that only one flavanoid (R_F 0·66) was present which was not the starting material (R_F 0·37). Column chromatography (silica; ether–light petroleum) led to the *thioether* (XVII) (1·33 g) as an odourless gum (Found: C, 73·3; H, 6·0; S, 8·7. $C_{23}H_{22}O_3S$ requires C, 73·0; H, 5·8; S, 8·5%); *m/e* (45°) 269 (M^+ — 109, 100%); τ (CCl_4) 2·42—2·85 (10H, complex, aromatic), 3·95—4·15 (2H, complex, 6-H and 8-H), 4·47 (1H, q, 2-H), 5·45 (1H, q, 4-H), 6·17 and 6·29 (each 3H, s, 5-OMe and 7-OMe), and 7·84—8·02 (2H, complex, 3-H_2) ($J_{2,3}$ 3·8, $J_{2,3^*}$ 10·2, $J_{3,4}$ 2·4, $J_{3^*,4}$ 3·8 Hz; $\nu_{max.}$ 1617, 1593, 1493, 1467, 1456, 1440, 1199, 1150, 1113, 820, and 700 cm^{-1}; $\lambda_{max.}$ 290 (log ε 3·78), 284 (3·82), 241 (4·12), and 207 nm (4·86).

4′-*Methoxy*-4α-*phenylthioflavan* (XVIII).—4′-Methoxyflavan-4β-ol (1·0 g) in dioxan (50 ml) and 0·5N-hydrochloric acid (50 ml) was heated under reflux with benzenethiol (4 ml) for 1 h and the mixture was worked up as before. Recrystallisation from methanol gave the *thioether* (XVIII) (905 mg) as plates, m.p. 104—105° (Found: C, 75·6; H, 5·7; S, 9·4. $C_{22}H_{20}O_2S$ requires C, 75·9; H, 5·7; S, 9·2%); *m/e* (145°) 348 (M^+, 2%) and 239 (100); τ ($CDCl_3$) 2·40—3·20 (13H, complex, aromatic), 4·52 (1H, q, 2-H), 5·42 (1H, t, 4-H), 6·19 (3H, s, 4′-OMe), and 7·65—7·95 (2H, complex, 3-H_2) ($J_{2,3}$ 5·0, $J_{2,3^*}$ 8·8, $J_{3,4} = J_{3^*,4}$ 3·0 Hz); $\nu_{max.}$ 1607, 1576, 1509, 1477, 1236, 1169, 1109, 1060, 1029, 900, 823, and 685 cm^{-1}; $\lambda_{max.}$ 288sh (log ε 3·66), 281 (3·77), 273 (3·75), 259sh (3·71), and 225 nm (4·51).

T.l.c. of the mother liquors [solvent (A)] showed that only a trace of 4′-methoxyflavan-4β-ol remained unchanged, and that a phenolic compound had been produced (*o*-tolidine spray reagent; R_F 0·62). Similar experiments involving more strongly acidic conditions or longer periods of heating led to no residual 4′-methoxyflavan-4β-ol but to more of the phenolic compound (as judged by t.l.c.), and the yield of thioether isolated could not be improved by these means.

2,3-trans-3,4-trans-4-*Phenylthioflavan*-3-*ol* (XIII).—2,3-*trans*-Flav-3-ene epoxide (110 mg) and benzenethiol (2·5 ml) in dimethylformamide (25 ml) were subjected to a stream of nitrogen for 15 min at room temperature. Sodium hydroxide (*ca.* 300 mg) was added, and the mixture was heated under nitrogen at 100° for 1 h. Ether (200 ml) was added, and the mixture was washed with water (2 × 150 ml) and 2N-sodium hydroxide (4 × 150 ml). Evaporation of the dried extracts left an oil which was eluted on two 20 cm preparative t.l.c. plates (one elution; ethyl acetate–benzene, 1 : 49). The only flavanoid band was stripped, giving the *thioether* (XIII) (150 mg) as a gum (Found: C, 75·3; H, 5·5; S, 9·3. $C_{21}H_{18}O_2S$ requires C, 75·5; H, 5·4; S, 9·6%); *m/e* (60°) 334 (M^+, 13%) and 225 (100); τ ($CDCl_3$) 2·10—3·20 (14H, complex, aromatic), 5·25 (1H, d, 2-H), 5·63 (1H, d, 4-H), 6·10 (1H, t, 3-H), and 7·51 (1H, s, OH) ($J_{2,3}$ 9·0, $J_{3,4}$ 9·0 Hz); $\nu_{max.}$ 3580, 3660br, 1604, 1579, 1477, 1449, 1435, 1300, 1270, 1112, 909, and 694 cm^{-1}. A portion of the gum (50 mg) was treated with acetic anhydride (1 ml) in pyridine (1 ml) at room temperature for 7 days. The usual procedure gave the 3-O-*acetate* (46 mg), which separated from ether–light petroleum as cubes, m.p. 100—102°. A second recrystallisation led to needles, m.p. 79—80° (Found: C, 73·1; H, 5·6; S, 8·7. $C_{23}H_{20}O_3S$ requires C, 73·4; H, 5·3; S, 8·5%); *m/e* (85°) 376 (M^+, 3%) and 207 (100); τ ($CDCl_3$) 2·18—3·18 (14H, complex, aromatic), 4·47 (1H, t, 3-H), 5·10 (1H, d, 2-H), 5·42 (1H, d, 4-H), and 8·33 (3H, s, Ac) ($J_{2,3}$ 8·9, $J_{3,4}$ 8·6 Hz); $\nu_{max.}$ 1750, 1608, 1582, 1483, 1452, 1371, 1270, 1040, 910, and 694 cm^{-1}.

2,3-trans-3,4-cis-4-*Phenylthioflavan*-3-*ol* (X).—Hydrolysis of 2,3-*trans*-3,4-*cis*-4-phenylthioflavan-3-yl formate (40 mg; see later) in aqueous alcoholic potassium hydroxide at room temperature gave a solid which was recrystallised from aqueous methanol to give the *thioether* (X) (29 mg) as needles, m.p. 106—108° (Found: C, 75·2; H, 5·4; S, 9·5. $C_{21}H_{18}O_2S$ requires C, 75·5; H, 5·4; S, 9·6%); *m/e* (50°) 334 (M^+, 10%) and 225 (100); τ (CDCl) 2·45—3·18 (14H, complex, aromatic), 4·99 (1H, d, 2-H), 5·46 (1H, d, 4-H), 5·70 (1H, complex, collapses to q on addition of D_2O, 3-H), and 7·45 (1H, d, exchanges with D_2O, OH) ($J_{2,3}$ 8·2, $J_{3,4}$ 5·0, $J_{3\,OH}$ 7·5 Hz); $\nu_{max.}$ 3590, 3480, 1611, 1586, 1487, 1458, 1443, 1319, 1118, 1041, 903, and 700 cm^{-1}.

2,3-trans-3,4-cis- (X) *and* 2,3-trans-3,4-trans- (XIII) 4-*Phenylthioflavan*-3-*ols*.—(a) *From* 2,3-trans-3,4-cis-*flavan*-3,4-*diol*. The diol (70 mg) and benzenethiol (1 ml) were heated under reflux in dioxan (10 ml) and 5N-hydrochloric acid (10 ml) for 18 h (2 phases). The mixture was extracted with ether, the extracts being washed with water and 2N-sodium hydroxide. T.l.c. of the extracts showed that no unchanged diol remained, and the yellow oil (174 mg) left after removal of ether was eluted on two 20 cm preparative t.l.c. plates (2 elutions; benzene). The only flavanoid band was stripped, and gave an oil [87 mg; *m/e* 334 (M^+) and 225 (100%)], identified from its n.m.r. spectrum as a 1 : 1 mixture of the 2,3-*trans*-3,4-*trans*- and the 2,3-*trans*-3,4-*cis*-thioether. Neither this mixture nor the mixture obtained by acetylation could be separated.

(b) *From* 2,3-trans-3,4-trans-*flavan*-3,4-*diol*. Treatment of this diol (500 mg) in the same way yielded an oil which was eluted from a silica column (170 g) with benzene–light petroleum (b.p. 60—80°) mixtures of progressively increasing polarity and finally with ethyl acetate–benzene 1 : 49; the latter eluate yielded a gum (625 mg) identified as above as a 1 : 1 mixture of 2,3-*trans*-3,4-*trans*- and 2,3-*trans*-3,4-*cis*-thioethers.

(c) Treatment of either the 3,4-*cis*- or the 3,4-*trans*-diol (100 mg) with benzenethiol (1 ml) in dioxan (12 ml) and 2N-hydrochloric acid (12 ml) under reflux for 5 h gave extracts shown by t.l.c. to contain unchanged diols with a trace of thioethers. From the *cis*-diol unchanged starting material (39 mg), m.p. 160—163°, was isolated.

Reaction of 2,3-trans-3,4-cis-*Flavan*-3,4-*diol* (IX) *with Benzenethiol in Formic Acid*.—The diol (570 mg) was treated with benzenethiol (5 ml) in formic acid (50 ml) at 100° (2 phases) for 3 h. The mixture was shaken with ether and the extracts were washed with water and 2N-sodium hydroxide. Evaporation left a yellow oil which was eluted from a silica column (180 g) with benzene–petroleum (b.p. 60—80°) mixtures of progressively increasing polarity. Diphenyl disulphide (207 mg) and triphenyl trithio-orthoformate (1·89 g) were eluted in early fractions, and subsequent elution with solvent of composition 3 : 2 gave a solid (131 mg) which was recrystallised from methanol to give 2,3-cis-3,4-trans-3,4-*bis*(*phenylthio*)-

flavan (XXXII) as needles, m.p. 125—127° (Found: C, 75·8; H, 5·3; S, 15·0. $C_{27}H_{22}OS_2$ requires C, 76·0; H, 5·2; S, 15·0%); *m/e* (110°) 426 (M^+, 1%) and 207 (100); τ ($CDCl_3$) 2·40—3·28 (19H, complex, aromatic), 3·99 (1H, d, 2-H), 5·40 (1H, d, 4-H), and 6·45 (1H, t, 3-H) ($J_{2,3} = J_{3,4}$ *ca.* 1·7 Hz); $\nu_{max.}$ 1610, 1586, 1487, 1460, 1453, 1440, 1111, 1063, 1027, and 694 cm^{-1}. Continued elution of the column with benzene gave a partially crystalline gum (534 mg) which was eluted on two 100 cm preparative t.l.c. plates [5 elutions; benzene–petroleum (b.p. 60—80°), 1 : 1] to give three bands. Material from band A (352 mg) became partially crystalline and recrystallisation from methanol gave 2,3-trans-3,4-cis-4-*phenylthioflavan*-3-*yl formate* (139 mg) as plates, m.p. 106—108° (Found: C, 72·9; H, 5·3; S, 8·8. $C_{22}H_{18}O_3S$ requires C, 72·9; H, 5·0; S, 8·8%); *m/e* (95°) 362 (M^+, 11%) and 207 (100); τ ($CDCl_3$) 2·45—3·15 (15H, complex, aromatic and HCO), 4·34—4·60 (2H, complex, 2-H and 3-H), and 5·22 (1H, d, 4-H) ($J_{3,4}$ 3·9 Hz); $\nu_{max.}$ 1730, 1611, 1586, 1485, 1457, 1441, 1169, 1005, 902, and 697 cm^{-1}. Evaporation of the mother liquors left a gum (200 mg) from which no crystalline material could be obtained, but which showed *m/e* at 362 (base peak 207) and $\nu_{max.}$ (film) 1720—1750br. The n.m.r. spectrum was not, however, indicative of a pure compound. This gum (194 mg) was treated with aqueous methanolic potassium hydroxide at room temperature for 12 h, and the yellow gum so obtained (128 mg) was eluted on two 20 cm preparative t.l.c. plates [9 elutions; ethyl acetate–benzene–petroleum (b.p. 60—80°), 2 : 49 : 49] giving two bands. The upper band was stripped, giving a gum (65 mg) which was identified from its n.m.r. spectrum as a *ca.* 4 : 1 mixture of 2,3-*trans*-3,4-*trans*- and 2,3-*trans*-3,4-*cis*-4-phenylthioflavan-3-ols. The lower band gave a solid (40 mg) which was recrystallised from methanol to give 2,3-cis-3,4-trans-4-*phenylthioflavan*-3-*ol* as needles, m.p. 159—161° (Found: C, 75·2; H, 5·6. $C_{21}H_{19}O_2S$ requires C, 75·5; H, 5·4%); *m/e* (115°) 334 (M^+, 11%) and 225 (100); τ ($CDCl_3$) 2·42—3·14 (14H, complex, aromatic), 4·41 (1H, incompletely resolved d, 2-H), 5·52 (1H, d, 4-H), 5·93 (1H, dq, collapses to q on addition of D_2O, 3-H), and 8·11 (1H, d, exchanges with D_2O, OH) ($J_{2,3}$ 1·0, $J_{3,4}$ 2·0, $J_{3,OH}$ 6·4 Hz); $\nu_{max.}$ 3580, 1611, 1586, 1489, 1455, 1442, 1114, 1048, 1029, 913, and 700 cm^{-1}. Material from band B (99 mg) was identified from its n.m.r. spectrum as a *ca.* 1 : 1 mixture of 2,3-*trans*-3,4-*trans*- and 2,3-*trans*-3,4-*cis*-4-phenylthioflavan-3-ols.

Material from band C (18 mg) was obtained as a crystalline solid. Recrystallisation from methanol gave 2,3-*cis*-3,4-*trans*-4-phenylthioflavan-3-ol, m.p. and mixed m.p. with authentic material (see above) 159—161°.

Reaction of 2,3-trans-3,4-trans-*Flavan*-3,4-*diol* (XII) *with Formic Acid*.—The diol (200 mg) in formic acid (20 ml) was heated at 100° for 3 h. The mixture was poured into ether (200 ml) and washed with water (2 × 150 ml) and saturated aqueous sodium hydrogen carbonate (2 × 100 ml). Evaporation left a pale yellow gum (230 mg) which was dissolved in methanol (10 ml) and treated with 15% methanolic potassium hydroxide (10 ml). After 24 at room temperature the mixture was poured into ether (200 ml) and washed with water (2 × 150 ml). Evaporation of the dried ethereal phase left a white solid (133 mg) which was chromatographically homogeneous [solvent (A), R_F 0·25, corresponding to that of the starting material]. The n.m.r. spectrum [$(CD_3)_2SO$] of the solid showed it to be a *ca.* 1 : 2 mixture of 2,3-*trans*-3,4-*trans*- and 2,3-*trans*-3,4-*cis*-flavan-3,4-diols. A portion of the solid (80 mg) was kept under deuteriochloroform for 3 h but an n.m.r. spectrum of the resulting saturated solution showed that no 2,3-*cis*-3,4-*trans*-flavan-3,4-diol was present.

2,3-trans-3-*Tosyloxyflavan*.—2,3-*trans*-Flavan-3-ol (410 mg) was treated with toluene-*p*-sulphonyl chloride (630 mg) in dry pyridine (8·0 ml) at room temperature for 2 days. The *product* was isolated by addition of water, extraction with ether, and evaporation, and crystallised from methanol as needles (523 mg), m.p. 153—154° (Found: C, 69·4; H, 5·2; S, 8·2. $C_{22}H_{20}O_4S$ requires C, 69·4; H, 5·2; S, 8·4%).

2,3-cis-3-*Phenylthioflavan*.—A stream of dry nitrogen was passed through a solution of benzenethiol (3 ml) and sodium hydroxide (1 g) in dimethylformamide (30 ml) while it was heated at 130° for 20 min. 2,3-*trans*-3-Tosyloxyflavan (240 mg) was added, and the mixture was heated under reflux (*ca.* 150°) under nitrogen for 2 h. The mixture was worked up in the usual way and the sticky orange solid left after evaporation of the dried extracts was eluted from a silica column (80 g) by benzene–petroleum (b.p. 60—80°) mixtures of progressively increasing polarity. Diphenyl disulphide (374 mg) was obtained from early fractions, and elution with a 4 : 1 mixture gave a solid which was recrystallised from ether–light petroleum to afford 2,3-cis-3-*phenylthioflavan* (75 mg) as long needles, m.p. 138—154°, unchanged by further recrystallisation (Found: C, 79·4; H, 5·7; S, 10·2. $C_{21}H_{18}OS$ requires C, 79·3; H, 5·7; S, 10·1%); *m/e* (55°) 318 (M^+, 14%) and 91 (100); τ ($CDCl_3$) 2·38—3·08 (14H, complex, aromatic), 4·55 (1H, d, 2-H), 6·09 (1H, complex, 3-H), 6·61 (1H, q, 4-H*), and 7·03 (1H, q, 4-H) ($J_{2,3}$ 2·3, $J_{3,4*}$ 5·0, $J_{3,4}$ 4·4, $J_{4,4*}$ 16·6 Hz); $\nu_{max.}$ 1610, 1581, 1485, 1450, 1437, 1108, 1060, and 696 cm^{-1}.

2,3-trans-*Flavan*-3-*yl Formate*.—2,3-*trans*-Flavan-3-ol (104 mg) in formic acid (25 ml) was heated at 100° for 4 h. Ether (150 ml) was added, and the mixture was washed with water (2 × 150 ml) and saturated aqueous sodium hydrogen carbonate (2 × 200 ml). Evaporation of the dried extract left a pink solid (111 mg) which was twice recrystallised from methanol to give the *formate* (56 mg) as needles, m.p. 74—75° (Found: C, 75·8; H, 5·5. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%); *m/e* (30°) 254 (M^+, 27%) and 91 (100); τ ($CDCl_3$) 2·00 (1H, s, HCO), 2·50—3·10 (9H, complex, aromatic), 4·46 (1H, complex, 3-H), 4·75 (1H, d, 2-H), and 7·01 (2H, complex, 4-H_2) ($J_{2,3}$ 6·2, $J_{3,4}$ 5·5, $J_{3,4*}$ 11·0 Hz); $\nu_{max.}$ 1728, 1615, 1589, 1489, 1460, 1452, 1175, 1120, 1013, and 700 cm^{-1}.

Treatment of 2,3-trans-*Flavan*-3-*ol with Formic Acid and Benzenethiol*.—2,3-*trans*-Flavan-3-ol (440 mg) was heated with benzenethiol (5 ml) and formic acid (50 ml) at 100° for 14 h. T.l.c. of the ethereal extract [solvent (B)] showed that 2,3-flavan-3-yl formate (R_F 0·15) was the only flavanoid present, there being no spot at R_F 0·38 corresponding to 2,3-*cis*-3-phenylthioflavan.

Treatment of 4α-(2,4-*Dihydroxyphenyl*)*flavan* (VIII) *with Benzenethiol*.—4α-(2,4-Dihydroxyphenyl)flavan (200 mg) in dioxan (20 ml) and 5N-hydrochloric acid (20 ml) was treated with benzenethiol (4 ml) for 30 h as above. T.l.c. of the extract showed that no 4-phenylthioflavan was present.

p-*Methoxybenzyl Phenyl Sulphone*.—Anisyl alcohol (1·25 g) in formic acid (125 ml) was treated with benzenesulphinic acid (2 g; sodium salt) and the uniphase mixture was heated at 100° for 3 h. Ether (500 ml) was added and the mixture washed with water (2 × 375 ml) and saturated

aqueous sodium hydrogen carbonate (3 × 500 ml). Evaporation left a mixture of the product and *S*-phenyl benzenethiosulphonate. Recrystallisation from methanol gave p-*methoxybenzyl phenyl sulphone* (2·70 g) as plates, m.p. 140—141° (Found: C, 64·4; H, 5·3; S, 12·2. $C_{14}H_{14}O_3S$ requires C, 64·1; H, 5·3; S, 12·2%); *m/e* (145°) 262 (M^+, 3%) and 121 (100); τ ($CDCl_3$) 2·26—3·27 (9H, complex, aromatic), 5·76 (2H, $ArCH_2$), and 6·23 (3H, s, ArOMe); $\nu_{max.}$ 1615, 1590, 1515, 1420, 1411, 1253, 1209, 1157, 1131, and 839 cm^{-1}; $\lambda_{max.}$ 283 (log ε 3·01), 272 (3·30), 265 (3·34), 258 (3·37), and 232 nm (4·24). Redistilled benzyl alcohol (1·9 g) was treated with benzenesulphinic acid (2·5 g) in the same way for 15 h. T.l.c. [solvent (A)] revealed the presence of benzyl formate (R_F 0·69) and the usual decomposition products of benzenesulphinic acid (R_F 0·31 and 0·56). No other compounds were detected.

4α-*Phenylsulphonylflavan* (XIX).—(a) *From flavan-4β-ol.* Flavan-4β-ol (2·0 g) in formic acid (200 ml) was treated with benzenesulphinic acid (10 g) for 3 h and the product worked up as above. Recrystallisation from methanol gave the *sulphone* (XIX) (2·57 g) as needles, m.p. 135—136° (Found: C, 71·8; H, 5·2; S, 9·3. $C_{21}H_{18}O_3S$ requires C, 72·0; H, 5·1; S, 9·1%); *m/e* (150°) 350 (M^+, 2%) and 209 (100); τ ($CDCl_3$) 2·10—3·20 (14H, complex, aromatic), 4·66 (1H, q, 2-H), 5·63 (1H, incompletely resolved q, 4-H), 7·32 (1H, dq, 3-H), and 7·84 (1H, dq, 3-H*) ($J_{2,3}$ 2·6, $J_{2,3*}$ 12·1, $J_{3,4}$ 1·7, $J_{3*,4}$ 6·0, $J_{3,3*}$ 15·5 Hz); τ (benzene) 4·39 (1H, q, 2-H), 5·98 (1H, incompletely resolved q, 4-H), 7·37 (1H, dq, 3-H), and 8·19 (1H, dq, 3-H*) ($J_{2,3}$ 2·7, $J_{2,3*}$ 12·2, $J_{3,4}$ 1·7, $J_{3*,4}$ 6·1 Hz), τ (MeCN) separation of 2-H from 4-H, 85 Hz ($J_{2,3}$ 3·8, $J_{2,3*}$ 11·1, $J_{3,4}$ 2·2, $J_{3*,4}$ 5·3 Hz), τ [$(CD_3)_2SO$; 100 mg in 0·4 ml] 4·56 (1H, incompletely resolved q, 2-H), 5·06 (1H, t, 4-H), and 7·60—7·84 (2H, complex, 3-H_2) ($J_{2,3}$ 6·4, $J_{2,3*}$ 7·0, $J_{3,4} = J_{3*,4}$ 3·3 Hz); $\nu_{max.}$ 1613, 1587, 1490, 1459, 1452, 1322, 1312, 1149, 1140, 1089, 908, 703, and 693 cm^{-1}; $\lambda_{max.}$ 288 (log ε 3·45), 281 (3·47), 273 (3·42), 266 (3·31), 259 (3·18), and 217sh nm (4·76).

Another experiment in which flavan-4β-ol (500 mg), sodium benzenesulphinate (2 g), and glacial acetic acid (4 ml) in 1 : 1 v/v water–ethanol (50 ml) were heated under reflux for 4 h yielded an extract, t.l.c. of which showed that flavan-4-ol was the only flavanoid present.

(b) *From* 4α-*methoxyflavan.* 4α-Methoxyflavan (1·06 g) was treated with benzenesulphinic acid (6·0 g) in formic acid as above for 3 h. Recrystallisation from methanol gave the sulphone (1·32 g) as needles, m.p. and mixed m.p. 135—136°.

(c) *From* 4α-*phenylthioflavan by oxidation.* *p*-Nitroperbenzoic acid (1·0 g) was added in small portions during 5 min to a solution of the thioether (400 mg) in chloroform (15 ml) at room temperature. The mixture was kept for 3 days, diluted with chloroform (40 ml), and washed with saturated aqueous sodium hydrogen carbonate (2 × 100 ml). Evaporation left a yellow solid which was twice recrystallised from methanol to give the sulphone (220 mg) as needles, m.p. and mixed m.p. 134—135°, identical (n.m.r. spectrum) with authentic samples.

4α-p-*Tolylsulphonylflavan.*—Flavan-4β-ol (500 mg) was treated with toluene-*p*-sulphinic acid (3 g) in formic acid as above for 3 h. Recrystallisation from methanol gave the *sulphone* (740 mg) as needles, m.p. 123—125° (Found: C, 72·7; H, 5·6; S, 8·9. $C_{22}H_{20}O_3S$ requires C, 72·5; H, 5·4; S, 8·8%); *m/e* (155°) 364 (M^+, 1·5%) and 209 (100); τ ($CDCl_3$) 2·15—3·20 (13H, complex, aromatic), 4·64 (1H, q, 2-H), 5·62 (1H, incompletely resolved q, 4-H), 7·31 (1H, dq, 3-H), 7·55 (3H, s, ArMe), and 7·83 (1H, dq, 3-H*) ($J_{2,3}$ 2·6, $J_{2,3*}$ 12·2, $J_{3,4}$ 1·5, $J_{3*,4}$ 6·0, $J_{3,3*}$ 15·8 Hz); $\nu_{max.}$ 1603, 1585, 1490, 1457, 1318, 1308, 1146, 1089, 819, and 701 cm^{-1}; $\lambda_{max.}$ 288 (log ε 3·48), 281 (3·51), 275 (3·44), and 224sh nm (4·30).

4-*Deuterio* 4α-*phenylsulphonylflavan.*—(a) *From* 4-*deuterioflavan-4β-ol.* 4-Deuterioflavan-4β-ol (184 mg) was treated with benzenesulphinic acid (1·2 g) in formic acid as above for 3 h. Recrystallisation from methanol gave the *sulphone* (227 mg) as needles, m.p. 135—136° (Found: C, 71·6; H + D, 5·2; S, 9·4. $C_{22}H_{17}DO_3S$ requires C, 71·8; H + D, 5·4; S, 9·1%); *m/e* (65°) 351 (M^+, 0·8%) and 210 (100); τ ($CDCl_3$) 2·10—3·24 (14H, complex, aromatic), 4·66 (1H, q, 2-H), 7·32 (1H, q, 3-H), and 7·83 (1H, q, 3-H*) ($J_{2,3}$ 2·6, $J_{2,3*}$ 12·0, $J_{3,3*}$ 15·0 Hz) [a signal (*ca.* 0·02H) at τ 5·63, corresponding to a C-4 proton, was observed]; $\nu_{max.}$ 1610, 1585, 1489, 1455, 1450, 1316, 1309, 1150, 1047, 899, 700, and 692 cm^{-1}.

(b) *From* 4α-*phenylsulphonylflavan.* The sulphone (88 mg) was dissolved in dry dioxan (5 ml) to which 40% sodium deuterioxide in deuterium oxide (0·5 ml) was added. The mixture was kept at room temperature for 20 h and then evaporated to dryness under reduced pressure at 60—90° (45 min). The solid residue was triturated with dry ether; evaporation of the filtered extract left crystals (79 mg) which had a n.m.r. spectrum identical with that of authentic 4-deuterio-4α-phenylsulphonylflavan. Recrystallisation from methanol gave pure material, m.p. and mixed m.p. 135—136°.

7-*Methoxy*-4α-*phenylsulphonyl* (XX).—7-Methoxyflavan-4β-ol (1·0 g) was treated with benzenesulphinic acid (5·0 g) in formic acid as above except that heating was discontinued after 1 h. Recrystallisation from methanol gave the *sulphone* (1·23 g) as plates, m.p. 142—148°. A second recrystallisation from methanol gave needles, m.p. 146—148° (Found: C, 69·6; H, 5·2; S, 8·3. $C_{22}H_{20}O_4S$ requires C, 69·5; H, 5·3; S, 8·4%); *m/e* (165°) 380 (M^+, 0·2%) and 239 (100); τ ($CDCl_3$) 2·05—3·04 and 3·43—3·57 (13H, complex, aromatic), 4·66 (1H, q, 2-H), 5·67 (1H, incompletely resolved q, 4-H), 6·22 (3H, s, 7-OMe), 7·34 (1H, dq, 3-H), and 7·85 (1H, dq, 3-H*) ($J_{2,3}$ 2·6, $J_{2,3*}$ 12·1, $J_{3,4}$ 1·7, $J_{3*,4}$ 6·1, $J_{3,3*}$ 15·7 Hz); $\nu_{max.}$ 1622, 1583, 1306, 1447, 1317, 1309, 1165, 1145, 1138, 1087, 840, 702, and 692 cm^{-1}, $\lambda_{max.}$ 289 (log ε 3·56), 282 (3·56), 273 (3·52), 265 (3·52), 258 (3·53), and 207 nm (4·87).

Another experiment in which 7-methoxyflavan-4β-ol (500 mg), sodium benzenesulphinate (3·0 g), and glacial acetic acid (4 ml) in 1 : 1 water–ethanol (50 ml) were heated under reflux for 4 h was worked up as above. Recrystallisation from methanol gave 7-methoxyflavan-4α-yl phenyl sulphone (624 mg) as needles, m.p. and mixed m.p. 145—148°.

7-*Methoxy*-4α-p-*tolylsulphonylflavan.*— 7-Methoxyflavan-4β-ol (500 mg) was treated with toluene-*p*-sulphinic acid (3 g) in formic acid as above for 1 h. Recrystallisation from methanol gave the *sulphone* (750 mg) as plates, m.p. 155—157° (slight decomp.) (Found: C, 70·3; H, 5·6; S, 8·3. $C_{23}H_{22}O_4S$ requires C, 70·1; H, 5·6; S, 8·1%); *m/e* (190°) 394 (M^+, 0·1%) and 239 (100); τ ($CDCl_3$) 2·20—3·00 and 3·45—3·58 (12H, complex, aromatic), 4·68 (1H, q, 2-H), 5·71 (H, incompletely resolved q, 4-H), 6·23 (3H, s, 7-OMe), 7·36 (1H, dq, 3-H), 7·57 (3H, s, ArMe), and 7·87 (1H, dq, 3-H*) ($J_{2,3}$ 2·4, $J_{2,3*}$ 12·3, $J_{3,4}$ 1·5, $J_{3*,4}$ 6·1, $J_{3,3*}$ 15·5 Hz); $\nu_{max.}$ 1622, 1505, 1447, 1315, 1305, 1165, 1145, 1137, 1088,

840, 816, and 701 cm^{-1}; $\lambda_{max.}$ 288 (log ε 3·53), 282 (3·5), 275 (3·47), and 226sh nm (4·30).

5,7-*Dimethoxy*-4α-*phenylsulphonylflavan* (XXI).—5,7-Dimethoxyflavan-4β-ol (380 mg), sodium benzenesulphinate (3 g), and glacial acetic acid (4 ml) in 1 : 1 water–ethanol (50 ml) were heated under reflux for 4 h and the product was worked up as above. Recrystallisation from methanol gave the *sulphone* (416 mg) as needles, m.p. 112—114° (Found: C, 67·0; H, 5·6; S, 8·1. $C_{23}H_{22}O_5S$ requires C, 67·3; H, 5·4; S, 7·8%); *m/e* (100°) 269 (M^+ − 141, 100%); τ ($CDCl_3$) 2·10—2·75 (10H, complex, aromatic), 3·80 and 4·18 (each 1H, d, *J* 2·2 Hz, 6-H and 8-H), 4·02 (1H, q, 2-H), 5·30 (1H, q, 4-H), 6·23 (3H, s, 7-OMe), 6·90 (3H, s, 5-OMe), *ca.* 6·95 (1H, dq, partially obscured by signal at 6·90, 3-H), and 7·93 (1H, dq, 3-H*) ($J_{2.3}$ 3·0, $J_{2.3*}$ 12·5, $J_{3.4}$ 1·8, $J_{3*.4}$ 5·5, $J_{3.3*}$ 15·5 Hz); τ (benzene) 5·41 (1H, q, 4-H), 6·68 (3H, s, 7-OMe), 6·93 (1H, dq, 3-H), 7·35 (3H, s, 5-OMe), and 8·21 (1H, dq, 3-H*); $\nu_{max.}$ 1620, 1595, 1497, 1470, 1457, 1450, 1443, 1307, 1297, 1191, 1180, 1152, 1142, 1120, 1084, 911, 820, 701, and 690 cm^{-1}; $\lambda_{max.}$ 273 (log ε 3·42), 266 (3·50), and 213 nm (4·88).

4′-*Methoxy*-4-*phenylsulphonylflavan* (XXII).—(a) *From* 4′-*methoxyflavan*-4β-*ol*. 4′-Methoxyflavan-4β-ol (500 mg) in formic acid was treated with benzenesulphinic acid (3·0 g) as above except that heating was discontinued after 45 min. Recrystallisation from methanol gave the *sulphone* (400 mg) as needles, m.p. 161—163° (Found: C, 69·6; H, 5·2; S, 8·2. $C_{22}H_{20}O_4S$ requires C, 69·5; H, 5·3; S, 8·4%); *m/e* (200°) 380 (M^+, 1·3%) and 239 (100); τ ($CDCl_3$) 2·10—3·15 (13H, complex, aromatic), 4·71 (1H, q, 2-H), 5·62 (1H, incompletely resolved q, 4-H), 6·20 (3H, s, 4′-OMe), 7·35 (1H, dq, 3-H), and 7·83 (1H, dq, 3-H*) ($J_{2.3}$ 2·6, $J_{2.3*}$ 12·1, $J_{3.4}$ 1·9, $J_{3*.4}$ 6·1, $J_{3.3*}$ 15·4 Hz); $\nu_{max.}$ 1616, 1585, 1518, 1488, 1320, 1310, 1146, 910, 833, and 693 cm^{-1}; $\lambda_{max.}$ 288 (log ε 3·47), 281 (3·61), 274 (3·59), 266 (3·47), and 260 nm (3·27).

T.l.c. of the mother liquors [solvent (A)] showed a strong spot, R_F 0·08, which was shown to be phenolic (*o*-tolidine spray reagent and extractable into Claisen's alkali). Another experiment in which 4′-methoxyflavan-4β-ol (500 mg), sodium benzenesulphinate (3·0 g), and glacial acetic acid (4 ml) in 1 : 1 water–ethanol (50 ml) were heated under reflux for 4 h, was worked up as usual. T.l.c. of the extract showed that 4′-methoxyflavan-4-ol was the only flavanoid present, and unchanged starting material was recovered by recrystallisation from methanol as needles (421 mg), m.p. 150—152°.

(b) *From* 4′-*methoxy*-4α-*phenylthioflavan by oxidation*. *p*-Nitroperbenzoic acid (1·0 g) was added in small portions during 5 min to a cooled solution of the thioether (240 mg) in chloroform (15 ml). The mixture was kept at room temperature for 5 days, diluted with chloroform (40 ml), and washed with saturated aqueous sodium hydrogen carbonate (2 × 100 ml). Evaporation of the dried organic phase and three recrystallisations of the residue from methanol gave the sulphone (52 mg) as needles, identical (m.p., mixed m.p., and n.m.r. spectrum) with the sample prepared from 4′-methoxyflavan-4β-ol.

4′-*Methoxy*-4α-p-*tolylsulphonylflavan*.—4′-Methoxyflavan-4β-ol (500 mg) in formic acid was treated with toluene-*p*-sulphonic acid (3·0 g) as above except that heating was discontinued after 15 min. Recrystallisation from methanol gave the *sulphone* (683 mg) as plates, m.p. 148—160° (slight decomp.). Recrystallisation of this material gave either prisms, m.p. 145—147°, or rhombohedra, m.p. 159—161°; the two forms were spectroscopically identical, and mutually interconvertible, in that the separation of either form could be induced by seeding (Found: C, 70·0; H, 5·6; S, 8·3. $C_{23}H_{22}O_4S$ requires C, 70·1; H, 5·6; S, 8·1%); *m/e* (190°) 394 (M^+, 1·7%) and 239 (100); τ ($CDCl_3$) 2·18—3·20 (12H, complex, aromatic), 4·68 (1H, q, 2-H), 5·63 (1H, incompletely resolved q, 4-H), 6·17 (3H, s, 4′-OMe), 7·34 (1H, dq, 3-H), 7·53 (3H, s, ArMe), and 7·82 (1H, dq, 3-H*) ($J_{2.3}$ 2·6, $J_{2.3*}$ 12·3, $J_{3.4}$ 1·5, $J_{3*.4}$ 6·2, $J_{3.3*}$ 15·4 Hz); $\nu_{max.}$ 1618, 1585, 1490, 1318, 1307, 1180, 1145, 1090, 1040, 833, and 819 cm^{-1}; $\lambda_{max.}$ 288 (log ε 3·46), 281 (3·61), 275 (3·59), and 226 nm (4·69). T.l.c. of the mother liquors [solvent (A)] showed the presence of a small amount of a phenolic compound, R_F 0·12, but no unchanged 4′-methoxyflavan-4-ol.

Reaction of 4′-*Methoxyflavan with Benzenesulphinic Acid*.—4′-Methoxyflavan (500 mg) was treated with benzenesulphinic acid (3·0 g) in formic acid for 3 h as above. The ethereal extract so obtained (150 ml) was extracted with 2N-sodium hydroxide (10 × 70 ml), and the alkaline extracts were acidified and re-extracted with ether (2 × 100 ml). Evaporation of this dried extract left a gum. Preparative t.l.c. (one 1 m plate; single elutions with ether-light petroleum, successively 1 : 4, 1 : 1, and 3 : 1 v/v) gave a solid (312 mg) corresponding to the phenolic constituent (*o*-tolidine spray reagent). Recrystallisation from ether–light petroleum gave 3-o-*hydroxyphenyl*-1-p-*methoxyphenylpropyl phenyl sulphone* (264 mg) as minute needles, m.p. 125—126° (Found: C, 69·3; H, 5·8; S, 8·5. $C_{22}H_{22}O_4S$ requires C, 69·1; H, 5·8; S, 8·4%); *m/e* (185°) 382 (M^+, 0·2%) and 106 (100); τ ($CDCl_3$) 2·35—3·30 (13H, complex, aromatic), 4·21br (1H, ArOH), 5·92 (1H, q, 1-H), 6·21 (3H, s, ArOMe), and 7·10—7·75 (4H, complex, 2-H_2 and 3-H_2) ($J_{1.2}$ 3·5, $J_{1.2*}$ 11·6 Hz); $\nu_{max.}$ 3330br, 1612, 1514, 1254, 1086, 1036, and 841 cm^{-1}.

Treatment of 3-o-*Hydroxyphenyl*-1-*phenylpropan*-1-*ol with Acids and with Acids and Sulphur Nucleophiles*.—(a) *With acetic acid*. The alcohol (500 mg) in glacial acetic acid (10 ml) was heated at 100° for 2 h. Ether (200 ml) was added, and the mixture was washed with saturated aqueous sodium hydrogen carbonate. T.l.c. of the ethereal phase showed that only starting material was present, and unchanged alcohol (430 mg) was recovered, m.p. and mixed m.p. 94—96°.

(b) *With formic acid*. The alcohol (150 mg) in formic acid (18 ml) was heated at 100° for 1 h. The mixture was worked up as described above, and the oily residue (130 mg) left after evaporation of ether was eluted on two 20 cm preparative t.l.c. plates (one elution; ether–light petroleum, 1 : 9). The upper band gave flavan (110 mg) as a solid which separated from aqueous ethanol as needles, m.p. 42—43°, identical (n.m.r. spectrum) with an authentic sample. The lower band was stripped to give an oil which was identified (n.m.r. and i.r. spectra) as 3-*o*-hydroxyphenyl-1-phenylpropene (14 mg); *m/e* (25°) 210 (M^+, 100%) and 104 (56).

(c) *With benzenesulphinic acid in formic acid*. The alcohol (500 mg) was treated with benzenesulphinic acid (3 g) in formic acid (50 ml) at 100° for 3 h. The oil left after evaporation of ether was eluted from a silica column (150 g) with ether–light petroleum mixtures of progressively increasing polarity. The fraction of composition 1 : 9 gave flavan as an oil which slowly solidified (419 mg), m.p. and mixed m.p. 42—43° (from aqueous ethanol).

(d) *With benzenethiol in aqueous acidic dioxan*. The

alcohol (200 mg) was boiled with benzenethiol (1 ml) in dioxan (12·5 ml) and 2N-hydrochloric acid (12·5 ml). The pale orange oil (227 mg) left after evaporation of ether was eluted on two 20 cm preparative t.l.c. plates (2 elutions; ether–light petroleum, 1 : 6) and the major band was stripped. Recrystallisation from aqueous ethanol gave flavan (139 mg) as needles, m.p. and mixed m.p. 42—43°. Four minor bands, which developed very slowly with isovanillin spray reagent, were removed but in no case did the material recovered (3—4 mg in each case) show a peak at *m/e* 320 in the mass spectrum, as required by 1-phenyl-3-*o*-hydroxyphenylpropyl phenyl sulphide.

2,3-trans-4-*Phenylsulphonylflavan*-3-*ols*.— 2,3-*trans*-3,4-*cis*-Flavan-3,4-diol (1·5 g) was treated with benzenesulphinic acid (7 g) and aqueous 90% formic acid at 100° for 3 h. T.l.c. of the ethereal extract [solvent (A)] showed that three flavanoid compounds were present (isovanillin spray), in roughly equal quantities, R_F 0·47, 0·32, and 0·20 (the last corresponded to unchanged flavan-3,4-diol). The colourless gum left after evaporation of solvent from the dried extract was eluted from a silica column (180 g) with ether–light petroleum mixtures of progressively increasing polarity. Fractions of composition 2 : 3 gave a colourless solid which was recrystallised from methanol to give 2,3-trans-3,4-trans-4-*phenylsulphonylflavan*-3-*ol* (XIV) (618 mg) as prisms, m.p. 152—154° (Found: C, 68·7; H, 4·9; S, 8·9. $C_{21}H_{18}O_4S$ requires C, 68·8; H, 4·9; S, 8·7%); *m/e* (85°) 366 (M^+, 2%), 107 (100), and 225 (78); τ ($CDCl_3$) 2·08—3·24 (14H, complex, aromatic), 5·31 (1H, d, 4-H), 5·51 (1H, d, 2-H), 5·70 (1H, complex, collapses to q on addition of D_2O, 3-H), and 6·68 (1H, d, exchanges with D_2O, OH) [$J_{2,3}$ 9·8, $J_{3,4}$ 6·3, $J_{3,OH}$ 2·9 Hz, at 220 MHz (Varian HR-220), $J_{2,3}$ 10·0, $J_{3,4}$ 6·8 Hz]; $\nu_{max.}$ 3550, 3400br, 1612, 1588, 1490, 1459, 1450, 1306, 1242, 1135, 1088, 1040, 1030, 911, 701, and 691 cm^{-1}; $\lambda_{max.}$ 285 (log ε 3·17), 274 (3·28), 267 (3·19), and 260 nm (3·04).

Further elution of the column with solvent of composition 4 : 1 led to a solid which was recrystallised from methanol to give 2,3-trans-3,4-cis-4-*phenylsulphonylflavan*-3-*ol* (XI) (676 mg) as needles, m.p. 188—192°, unchanged by further recrystallisation [Found: C, 68·6; H, 5·0; S, 8·4 (after being dried under vacuum for 20 days at room temperature). $C_{21}H_{18}O_4S$ requires C, 68·8; H, 4·9; S, 8·7%]; *m/e* (100°) 366 (M^+, 5%), 107 (100), and 225 (80); τ ($CDCl_3$) 2·12—3·22 (14H, complex, aromatic), 4·48 (1H, d, 2-H), 5·37 (1H, d, 4-H), 5·67 (1H, complex, collapses to q on addition of D_2O, 3-H), and 6·17 (1H, d, exchanges with D_2O, OH) ($J_{2,3}$ 10·0, $J_{3,4}$ 4·9, $J_{3,OH}$ 7·7 Hz); $\nu_{max.}$ 3560, 3475, 1609, 1586, 1489, 1458, 1451, 1310, 1139, 1085, 1040, 1018, 897, 700, and 690 cm^{-1}; $\lambda_{max.}$ 289 (log ε 3·51), 283 (3·53), 275 (3·46), 267 (3·33), and 219sh nm (4·40).

2,3-trans-3,4-trans-4-*Deuterioflavan*-3,4-*diol*.— 2,3-*trans*-3-Hydroxyflavan-4-one (1·89 g) in methanol (200 ml) was treated with sodium borodeuteride (226 mg) in small portions during 3 h at 0°. The mixture was poured into aqueous 0·5% acetic acid (700 ml) and extracted with ether (2 × 200 ml). Removal of ether left a white solid which was twice recrystallised from methanol to give the *diol* (1·07 g) as needles, m.p. 143—144° [Found: C, 73·9; H + D, 5·9 (after powdered material had been dried under vacuum at 74° for 4 h). $C_{15}H_{13}DO_3$ requires C, 74·1; H + D, 6·2%]; *m/e* (95°) 243 (M^+, 13%) and 120 (100); τ [$(CD)_2SO$; 46 mg in 0·4 ml] 2·38—3·24 (9H, complex, aromatic), 4·37 (1H, s, exchanges with D_2O, 4-OH), 4·75 (1H, d, exchanges with D_2O, 3-OH), 5·13 (1H, d, 2-H), and 6·25 (1H, complex, collapses to broadened doublet on addition of D_2O, 3-H) ($J_{2,3}$ 10·0, $J_{3,OH}$ 5·9 Hz) [a signal (0·02H) at τ 5·31, corresponding to a C-4 proton, was observed]; $\nu_{max.}$ 3590, 3390br, 1615, 1588, 1487, 1458, 1140, 1027, 873, and 701 cm^{-1}.

2,3-trans-4-*Deuterio*-4-*phenylsulphonylflavan*-3-*ols*.— 2,3-*trans*-3,4-*trans*-4-Deuterioflavan-3,4-diol (407 mg) was treated with benzenesulphinic acid (3 g) and formic acid (50 ml) at 100° for 6 h. T.l.c. of the ethereal extract indicated that no unchanged flavan-3,4-diol remained. The oil left after evaporation was eluted from a silica column (150 g) with ether–light petroleum mixtures of progressively increasing polarity. Fractions of composition 1 : 9 gave a gum (51 mg) which was eluted on one 20 cm preparative t.l.c. plate (2 elutions; ether–light petroleum, 1 : 3). The major band was stripped to give an oil (34 mg) which could not be caused to crystallise, but which was probably 4-deuterio-2,3-*trans*-flavan-3,4-diyl diformate, of uncertain 3,4-stereochemistry; *m/e* (55°) 299 (M^+, 15%) and 208 (100); τ ($CDCl_3$) 1·92 (1H, s, HCO), 2·33 (1H, s, HCO), 2·50—3·20 (9H, complex, aromatic), 4·48 (1H, d, 2-H), and 4·77 (1H, d, 3-H) ($J_{2,3}$ 9·8 Hz); $\nu_{max.}$ 1725—1740br cm^{-1}. Elution of the column with a 2 : 3 mixture gave a solid (134 mg) which was recrystallised from methanol to give 2,3-trans-3,4-trans-4-*deuterio*-4-*phenylsulphonylflavan*-3-*ol* as prisms, m.p. 152—154° (Found: C, 68·8; H + D, 5·0. $C_{21}H_{17}DO_4S$ requires C, 68·6; H + D, 5·2%); *m/e* (120°) 367 (M^+, 3%), 226 (100), and 107 (96); τ ($CDCl_3$) 2·08—3·26 (14H, complex, aromatic), 5·50 (1H, d, 2-H), 5·72 (1H, q, collapses to d on addition of D_2O, 3-H), and 6·70 (1H, d, exchanges with D_2O, OH) ($J_{2,3}$ 10·0, $J_{3,OH}$ 2·8 Hz) [a doublet (*ca.* 0·02H) at τ 5·32, corresponding to a C-4 proton, was observed]; $\nu_{max.}$ 3550, 3370br, 1612, 1589, 1490, 1459, 1450, 1305, 1240, 1150, 1085, 1040, 1030, 700, and 690 cm^{-1}.

Further elution of the column with solvent of composition 4 : 1 led to a solid (178 mg) which was recrystallised from methanol and then from ethanol–light petroleum to give 2,3-trans-3,4-cis-4-*deuterio*-4-*phenylsulphonylflavan*-3-*ol*, m.p. 189—192° [Found: C, 68·3; H + D, 5·2 (after being kept in a desiccator for several months). $C_{21}H_{17}DO_4S$ requires C, 68·6; H + D, 5·2%]; *m/e* (100°) 367 (M^+, 3%), 226 (100), and 107 (100); τ ($CDCl_3$) 2·13—3·20 (14H, complex, aromatic), 4·47 (1H, d, 2-H), 5·66 (1H, q, collapses to d on addition of D_2O, 3-H), and 6·19 (1H, d, exchanges with D_2O, OH) ($J_{2,3}$ 10·0, $J_{3,OH}$ 7·8 Hz) [a doublet (*ca.* 0·05H) at τ 5·37, corresponding to a C-4 proton, was observed]; $\nu_{max.}$ 3575, 3490, 1610, 1586, 1488, 1456, 1450, 1309, 1141, 1085, 897, 699, and 689 cm^{-1}.

4-*Deuterioflavan*.—4-Deuterio-4-phenylthioflavan (300 mg) in ethanol (80 ml) and ether (25 ml) was stirred with W-3 Raney nickel (*ca.* 4 g) at room temperature for 4 days. Evaporation of the filtrate left a gum (192 mg) which was eluted on two 20 cm preparative t.l.c. plates [3 elutions; benzene–petroleum (b.p. 60—80°), 2 : 3] to give two bands. The upper band was stripped to give a gum which was crystallised from aqueous ethanol giving 4-*deuterioflavan* (99 mg) as needles, m.p. 42—45° (Found: C, 85·3; H + D, 6·9. $C_{15}H_{13}SO$ requires C, 85·3; H + D, 7·1%); *m/e* (40°) 211 (M^+, 100%) and 104 (75); τ (CCl_4) 2·60—3·35 (9H, complex, aromatic), 5·04 (1H, q, 2-H) 7·00—7·30 (1H, complex, 4-H), and 7·85—8·15 (2H, complex, 3-H_2) ($J_{2,3}$ 3·7, $J_{2,3*}$ 8·7 Hz); $\nu_{max.}$ 1610, 1582, 1298, 1274, 1112, 1060, 1023, and 698 cm^{-1}.

4′-*Methoxyflavan*.—(a) *From* 4′-*methoxy*-4α-*phenylthio*-

flavan. The thioether (500 mg) in ether (50 ml) and methanol (50 ml) was stirred with W-3 Raney nickel (*ca.* 5 g) at room temperature for 6 days. Evaporation of the filtrate left a solid which was recrystallised from methanol to give 4'-methoxyflavan (290 mg) as needles, m.p. and mixed m.p. 82°, identical (n.m.r. spectrum) with an authentic sample.

(b) *From 4'-methoxy-4α-phenylsulphonylflavan*. The sulphone (260 mg) in ethanol (100 ml) was treated with W-3 Raney nickel (*ca.* 6 g) and the mixture was stirred at 60—70° for 6 h and subsequently kept at room temperature for 3 days. Evaporation of the filtrate left a solid which was recrystallised from methanol to give 4'-methoxyflavan (108 mg) as needles, m.p. and mixed m.p. with authentic material, 82°.

2,3-trans-*Flavan*-3-*ol*.—A 1 : 1 mixture (estimated from its n.m.r. spectrum; see above) of 2,3-*trans*-3,4-*trans*- and 2,3-*trans*-3,4-*cis*-4-phenylthioflavan-3-ols (71 mg) in methanol (8 ml) was stirred with T-1 Raney nickel (*ca.* 0·5 g) at room temperature for 1 h. Evaporation of the filtrate left a solid which was recrystallised from aqueous methanol to give 2,3-*trans*-flavan-3-ol (38 mg) as needles, m.p. and mixed m.p. 109—110°, identical (n.m.r. spectrum) with an authentic sample.

2,3-cis-*Flavan*-3-ol.— 2,3-*cis*-3,4-*trans*-4-Phenylthioflavan-3-ol (29 mg) in methanol (8 ml) was stirred with T-1 Raney nickel (*ca.* 0·3 g) at room temperature for 1 h. Evaporation of the filtrate left a chromatographically homogeneous [solvent (A); R_F 0·43] gum (17 mg) identified as 2,3-*cis*-flavan-3-ol; *m/e* (25°) 226 (M^+, 26%), 107 (100), 91 (76), and 120 (28); τ ($CDCl_3$) 2·40—3·18 (9H, complex, aromatic), 4·92 (1H, s, $W_{\frac{1}{2}}$ 3·0 Hz, 2-H), 5·70 (1H, complex, collapses to t on addition of D_2O, 3-H), 6·72 (1H, q, 4-H*), 7·06 (1H, q, 4-H), and 8·25 (1H, d, exchanges with D_2O, OH) ($J_{3,4}$ 2·4, $J_{3,4*}$ 4·0, $J_{4,4*}$ 16·5, $J_{3,OH}$ 7·0 Hz); $\nu_{max.}$ 3585, 3380br, 1613, 1584, 1486, 1452, 1110, 1073, 1055, 1000, 875, and 699 cm^{-1}. Bolger *et al.*[10] report a liquid. Acetylation of the gum was carried out as reported[10] to yield 2,3-*cis*-3-acetoxyflavan which separated from ether-light petroleum as plates, m.p. 108—110°; *m/e* (40°) 268 (M^+, 14%), 208 (100), and 107 (65); τ ($CDCl_3$) 2·43—3·18 (9H, complex, aromatic), 4·54 (1H, complex, 3-H), 4·83 (1H, s, $W_{\frac{1}{2}}$ 3·0 Hz, 2-H), 6·65 (1H, q, 4*-H), 7·03 (1H, q, 4-H), and 8·13 (3H, s, Ac) ($J_{3,4}$ 2·6, $J_{3,4*}$ 4·0, $J_{4,4*}$ 17·0 Hz); $\nu_{max.}$ 1737, 1612, 1586, 1489, 1455, 1375, 1112, 1044, 951, and 700 cm^{-1} (lit.,[10] m.p. 110°).

Degradation of Calluna vulgaris *Tannin with Benzenethiol under Acidic Conditions*.—The tannin salt mixture[16] (40·0 g) (Found: C, 29·6; H, 3·0; N, 0·05; Cl^-, 23·7%) in 1 : 1 v/v water–ethanol (700 ml) and glacial acetic acid (20 ml) was heated under reflux with benzenethiol (40 ml) under a stream of nitrogen for 4 h (2 phases). The mixture was washed with light petroleum (3 × 1000 ml) and then diluted with water (500 ml) and extracted with ether (200 ml). A quantity of tarry phlobaphene separated; this was precipitated from its solution in acetone with ether and allowed to dry in the air, giving a chocolate brown amorphous solid (Found: C, 48·8; H, 4·7; S, 2·1%) which was shown by t.l.c. [solvent (C)] to contain no mobile material.

The ethereal phase was washed with dilute aqueous sodium hydrogen carbonate and brine. An equal volume of redistilled methanol was added, and the volume was reduced to one fourth under reduced pressure at room temperature. Diazomethane (*ca.* 8 g) in ether (300 ml) was added in two portions to the stirred solution at 0°, leaving a pale yellow solution (no precipitation). After being kept at 0° for 12 h and then subjected to a stream of nitrogen at room temperature for 6 h, the mixture was treated with glacial acetic acid (10 ml) and partitioned between ethyl acetate (800 ml) and water (2000 ml). The organic phase was washed with saturated aqueous sodium hydrogen carbonate (200 ml); evaporation of the dried extract left a yellow gum (1·25 g) which became partially solid after some time at room temperature. This material was eluted from a silica column (500 g) with acetone–light petroleum mixtures of progressively increasing polarity; fractions of composition 2 : 3 v/v gave a solid (383 mg). Recrystallisation from ethyl acetate–ether gave (+)-2,3-cis-3,4-trans-3',4',5,7-*tetramethoxy*-4-*phenylthioflavan*-3-*ol* (XXVI) (288 mg) as plates, m.p. 208—210° (Found: C, 66·0; H, 5·9; S, 7·1. $C_{25}H_{26}O_6S$ requires

TABLE 3

Replacement reactions

Reactions of 4-thio-substituted flavans with sulphur nucleophiles in presence of acid

All reactions conducted at 100°

Compound	Solvent	Reagent	Time (h)	Product	Yield (%)
4α-Phenylthioflavan (XV)	Dioxan-2N-HCl (1 : 1 v/v)	MAA *	5	Unchanged	87
Methyl (flavan-4α-ylthio)-acetate (XXIV)		PhSH	5	Unchanged	66
4α-Phenylsulphonylflavan (XIX)		PhSH	5	Unchanged	75
		PhSH	5	Unchanged	(T.l.c.)
4α-Phenylthioflavan (XV)	HCO_2H	MAA *	15	(Flavan-4α-ylthio)acetic acid (XXII)	59 §†
		$PhSO_2H$	3	4α-Phenylsulphonylflavan (XIX)	93
Methyl (flavan-4α-ylthio)-acetate (XXIV)		$PhSO_2H$	3		85
7-Methoxy-4α-phenylthioflavan (XVI)	Dioxan-2N-HCl (1 : 1 v/v)	MAA *	4	(7-Methoxyflavan-4α-ylthio)-acetic acid (XXV)	42 §†
		PhSH	1·5	Unchanged	83
7-Methoxy-4α-phenylsulphonylflavan (XX)	HCO_2H	PhSH	1	7-Methoxy-4α-phenylthioflavan (XVI)	(T.l.c.) §
		MAA *	0·75	(7-Methoxyflavan-4α-ylthio)-acetic acid (XXV)	12 §†

* MAA = mercaptoacetic acid. † Variable recorded yields reflect the difficulty of isolating the pure acids by recrystallisation. § All starting material had reacted.

C, 66·0; H, 5·7; S, 7·1%); $[\alpha]_{589}^{20}$ +8·6°, $[\alpha]_{578}^{20}$ +8·4°, $[\alpha]_{546}^{20}$ +10·6°, $[\alpha]_{436}^{20}$ +22·9°, $[\alpha]_{365}^{20}$ +40·7° (*c* 1 in $CHCl_3$); *m/e* (410°) 454 (M^+, 0·2%), 345 (100), 327 (40), and 436 (4); τ ($CDCl_3$) 2·35—2·80 (5H, complex, PhS), 2·85—3·20 (3H, complex, ring B aromatic), 3·80 and 3·87 (each 1H, *J* 2·2 Hz, ring A aromatic), 4·39 (1H, $W_{\frac{1}{2}}$ 2·4 Hz, 2-H), 5·44 (1H, 4-H), 5·97br (1H, resolves to broad d on addition of D_2O, 3-H), 6·13 (9H, 3 × $ArOCH_3$), 6·23 (3H, $ArOCH_3$), and 8·16 (1H, exchanges with D_2O, OH) ($J_{3,4}$ 2·6, $J_{3,OH}$ 6·0 Hz); $\nu_{max.}$ 3570, 1615, 1590, 1513, 1464, 1267, 1147, 1114, 1026, 821, and 694 cm^{-1}; $\lambda_{max.}$ 275 (log ε 3·91) and 206 nm (4·94).

The aqueous phase was acidified with 2N-hydrochloric acid (700 ml) and extracted with ethyl acetate (3 × 1000 ml). The combined extracts were washed with brine (3 × 400 ml), leaving a deep red-brown solution which was dried. Evaporation left a red-brown glass (13·0 g) which was taken up in methanol (200 ml) and treated at 0° with successive batches of diazomethane (*ca.* 4 g) in ether (*ca.* 140 ml). After two such additions, an extensive precipitate separated; removal of ether under reduced pressure caused only a fraction to redissolve. The remainder (4·8 g) was collected and separately treated at 0° with ethereal diazomethane (*ca.* 4 g) in chloroform–methanol, which again caused extensive precipitation. The precipitate was washed with methanol and ether, and allowed to dry in the air. The pale brown amorphous powder (Found: C, 61·3; H, 5·4; S, 1·2%) was freely soluble in chloroform, but t.l.c. (chloroform) showed that a uniform streak constituted the only mobile material present, and the n.m.r. spectrum showed only broad bands with no clearly defined peaks. Methylation of the supernatant fraction (*i.e.* from which the precipitate first separated) was continued; the addition of chloroform (150 ml) prevented significant precipitation, and after the addition of two further batches of ethereal diazomethane (each *ca.* 4 g) a pale yellow solution containing an excess of diazomethane was obtained. This was kept at 0° for 6 h and then left open to the air overnight at room temperature. A little glacial acetic acid was added to remove traces of diazomethane, and evaporation left a pale orange gum which was dissolved in ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate. Evaporation of the dried organic phase left a reddish glass (4·7 g) which was eluted from a silica column with acetone–light petroleum mixtures of progressively increasing polarity. Fractions of composition 2 : 3 v/v led to a solid which was recrystallised from chloroform–ether to give 2,3-*cis*-3,4-*trans*-3′,4′,5,7-tetramethoxy-4-phenylthioflavan-3-ol (139 mg) as plates, m.p. and mixed m.p. 208—210°. The n.m.r. spectra of the two samples were identical. Other flavanoids were also present in minute amounts in the mother liquors, but insufficiency of material prevented the isolation of any component in pure form. Later fractions from the column gave amorphous material (*ca.* 1 g) which on t.l.c. (acetone–light petroleum, 2 : 3 v/v) showed only a streak to R_F 0·3. Remethylation of this material did not alter its chromatographic properties, and it was not further investigated.

Degradation of Calluna vulgaris *Tannin with Benzenethiol in the Absence of Acid.*—The tannin–salt mixture (500 mg) in 1 : 1 v/v water–ethanol (20 ml) and benzenethiol (8 ml) was heated under reflux for 40 h (2 phases). The mixture was washed with light petroleum (4 × 500 ml) and partitioned between ether (200 ml) and water (100 ml). Relatively little phlobaphene separated, and it did so as a solid rather than as a tar. The aqueous phase was extracted with more ether (2 × 150 ml) and the combined extracts were dried. The resulting solution was diluted with methanol (30 ml) and reduced in volume (to 100 ml) before being treated at 0° with diazomethane (*ca.* 1·4 g) in ether (*ca.* 50 ml). The resulting pale yellow solution was kept at 0° for 8 h and then left open to the air at room temperature for 12 h. Evaporation left a yellow gum (148 mg) which was eluted on two 20 cm preparative t.l.c. plates (2 elutions; ethyl acetate–benzene 1 : 9 v/v). The major band, at R_F (total) 0·37, was stripped, giving a solid which was recrystallised from ethyl acetate–ether to give (+)-2,3-*cis*-3,4-*trans*-3′,4′,5,7-tetramethoxy-4-phenylthioflavan-3-ol as plates (32 mg), m.p. and mixed m.p. 208—210°; identical n.m.r. spectrum; $[\alpha]_{589}^{20}$ +8·4° (*c* 0·5 in $CHCl_3$).

Desulphurisation of (+)-2,3-cis-3,4-trans-3′,4′,5,7-*Tetramethoxy-4-phenylthioflavan-3-ol.*—The thioether (111 mg) in ethyl acetate (40 ml) was stirred with T-1 Raney nickel (*ca.* 5 g) for 100 min at room temperature. Evaporation of the filtrate left a solid which was recrystallised from methanol–ether and gave (−)-tetra-*O*-methylepicatechin (84·6 mg) as needles, m.p. and mixed m.p. 142—143° (Found: C, 65·9; H, 6·4. Calc. for $C_{19}H_{22}O_6$: C, 65·9; H, 6·4%); $[\alpha]_{589}^{20}$ −43·1° (*c* 1 in $CHCl_3$); *m/e* (85°) 346 (M^+, 83%) and 167 (100); identical (n.m.r., i.r., and u.v. spectra) with authentic material which had $[\alpha]_{589}^{20}$ −42·1° (*c* 1 in $CHCl_3$).

Action of Acid on Calluna vulgaris *Tannin in the Absence of Sulphur Nucleophiles.*—The tannin–salt mixture (500 was heated under reflux in 1 : 1 v/v water–ethanol (20 ml) and glacial acetic acid (4 ml) for 2 h. Water (150 ml) was added and the mixture was extracted with ethyl acetate (200 ml). Evaporation of the dried extract left a brown gum which on t.l.c. [solvent (C)] migrated only as a weak background streak, there being no defined spots.

Isolation of Tannin–Salt Mixture from Picea pungens *Needles.*—The needles (*ca.* 5 kg) were steeped in the minimum volume of 1 : 1 v/v water–acetone which completely covered them, and the mixture was kept in the dark at room temperature for 30 days. The liquid was drawn off (leaf press) and periodically shaken with solid sodium chloride until no more dissolved, resulting in a separation into two liquid phases. The upper phase (1 vol) was filtered and diluted with ethanol (2 vol); addition of ether (12 vol) led to the separation of tannin–salt mixture (45 g) as a buff precipitate which was collected by centrifugation, washed well with ether, and allowed to dry in the air (Found: C, 45·8; H, 4·3; N, 0·6; Cl^-, 9·0%). Two-dimensional chromatography of the tannin–salt mixture on Whatman no. 1 papers and elution with aqueous 2% acetic acid followed by butan-2-ol–acetic acid–water (14 : 1 : 5 v/v; uniphase) showed the presence of polyphenolic material (aqueous ferric chloride–potassium ferricyanide dip [21]) which was also identified as flavanoid (vanillin–ethanolic hydrochloric acid spray [22]), appearing as a streak mobile only in 2% acetic acid. Cyanidin chloride, identified by comparison with authentic material (paper chromatography), was the only anthocyanidin generated when the

[21] G. M. Barton, R. S. Evans, and J. A. F. Gardener, *Nature*, 1952, **170**, 249.

[22] D. E. Hathway and J. W. T. Seakins, *J. Chem. Soc.*, 1957, 1562.

tannin–salt mixture was boiled with ethanolic hydrochloric acid.

Degradation of Picea pungens *Tannin with Benzenethiol under Acidic Conditions.*—(i) The tannin–salt mixture (38·3 g) in 1 : 1 v/v water–ethanol (700 ml) and glacial acetic acid (20 ml) was heated under reflux with benzenethiol (40 ml) for 4 h (2 phases). The mixture was shaken together with ether (200 ml) and water (700 ml). The black tar suspended between the two phases was discarded with the ethereal phase, and the aqueous phase was acidified with 2N-hydrochloric acid (700 ml), and extracted with ethyl acetate (3 × 750 ml). The combined extracts were washed with brine (3 × 500 ml) and dried. Evaporation at room temperature left a dark brown gum (9·2 g) which was dissolved in methanol (200 ml) giving a deep red solution. Batches of diazomethane (*ca.* 4 g) in ether (*ca.* 140 ml) were added to the stirred solution at 0°; after three such additions an extensive light brown precipitate separated, which only partially redissolved on addition of methanol (200 ml). After the addition of a fourth batch of diazomethane the solution, which was pale yellow, was kept at 0° for 12 h. The mixture was kept open to the air at room temperature for 12 h, and a stream of nitrogen was passed through it for 2 h. Evaporation at room temperature caused the precipitate to redissolve, leaving a reddish brown gum (8·5 g). This was dissolved in chloroform (100 ml); addition of methanol (100 ml) and ether (200 ml) caused a precipitate to separate, which was collected by centrifugation, washed with methanol and ether, and dried in air, giving a buff amorphous powder (2·5 g), whose n.m.r. spectrum showed only bands, with no sharp peaks (Found: C, 62·2; H, 5·2; S, 1·2%). T.l.c. (acetone–light petroleum, 7 : 13 v/v; and neat chloroform) showed that no discrete spots were present, though a portion of the material was to some extent mobile in both solvents. T.l.c. of the supernatant liquid (acetone–light petroleum, 7 : 13 v/v) showed, in addition to immobile material, the presence of discrete flavanoid spots at R_F 0·33 and 0·25, the latter having the same R_F as authentic (±)-tetra-*O*-methylcatechin. The gum (*ca.* 6 g) left after evaporation of solvent was injected on to a silica column (550 g) and eluted with acetone–light petroleum mixtures of progressively increasing polarity. Fractions of composition 2 : 3 v/v gave crystalline flavanoid material (220 mg) which was seen from t.l.c. (acetone–light petroleum, 7 : 13 v/v) to be a mixture of the two compounds of R_F 0·33 and 0·25. The material was eluted on one 100 cm preparative t.l.c. plate (3 elutions; ethyl acetate–benzene, 1 : 11 v/v).

Two major bands were seen, the upper of which gave (+)-2,3-*cis*-3,4-*trans*-3′,4′,5,7-tetramethoxy-4-phenylthioflavan-3-ol (XXVI) (102 mg), which separated from chloroform–ether as plates, m.p. and mixed m.p. with material isolated from *Calluna vulgaris* tannin, 208—210° (Found: C, 65·7; H, 5·8. Calc. for $C_{25}H_{26}O_6S$: C, 66·0; H, 5·7%); $[\alpha]_{589}^{20}$ +8·0° (*c* 0·5 in $CHCl_3$); identical (n.m.r. spectrum) with material isolated from *Calluna vulgaris* tannin.

[23] A. J. Birch, J. W. Clark-Lewis, and A. V. Robertson, *J. Chem. Soc.*, 1957, 3586.

Desulphurisation of this material (30 mg) as before and recrystallisation from ethyl acetate–ether–light petroleum gave (−)-tetra-*O*-methylepicatechin (22 mg) as needles, m.p. and mixed m.p. with material similarly obtained from *Calluna vulgaris* tannin, 142—143° (Found: C, 66·2; H, 6·5. Calc. for $C_{19}H_{22}O_6$: C, 65·9; H, 6·4%); $[\alpha]_{589}^{20}$ −40·7° (*c* 0·75 in $CHCl_3$); identical (n.m.r., i.r., u.v., and mass spectra) with an authentic sample.

The lower band gave (−)-tetra-*O*-methylcatechin [(2*R*, 3*S*)-configuration as in (+)-catechin], which separated from ethyl acetate–light petroleum as prisms (65 mg), m.p. 143—144° (Found: C, 65·9; H, 6·5. Calc. for $C_{19}H_{22}O_6$: C, 65·9; H, 6·4%); $[\alpha]_{589}^{20}$ −8·9° (*c* 0·3 in $CHCl_3$); *m/e* (100°) 346 (M^+, 30%), 167 (100), and 180 (29); $\nu_{max.}$ 3585, 3400br, 1620, 1597, 1514, 1500, 1467, 1264, 1148, 1119, 862, and 819 cm^{-1}; identical (n.m.r. spectrum) with authentic (±)-tetra-*O*-methylcatechin {lit.,[23] m.p. 143—144°; lit.,[24] $[\alpha]_{589}^{18}$ −9·8° (*c* 1·6 in $CHCl_3$)}.

(ii) The tannin–salt mixture (500 mg) was dialysed as a partially soluble suspension in water (10 ml) against running tap-water for 10 days, and then against distilled water for 15 h. The suspension was diluted with ethanol (10 ml) and the resulting solution was heated under reflux with glacial acetic acid (4 ml) and benzenethiol (2 ml) for 2 h. The mixture was worked up as described in (i); t.l.c. of the ethyl acetate extract [solvent (C)] showed the presence of spots at R_F 0·62 and 0·44 which developed a strong red colour with 1% isovanillin in concentrated sulphuric acid. (±)-Catechin had R_F 0·44 on the same plate and a portion of the solution before treatment with benzenethiol and acetic acid gave no mobile spots. A saturated solution prepared by keeping a sample of tannin–salt mixture under acetone for 2 h similarly showed no mobile spots.

Action of Benzenethiol on Picea pungens *Tannin in the Absence of Acid.*—The tannin–salt mixture (500 mg) was heated under reflux in 1 : 1 v/v water–ethanol (20 ml) with benzenethiol (4 ml) for 2 h (2 phases). The mixture was washed with light petroleum (3 × 500 ml) and partitioned between ethyl acetate (200 ml) and water (100 ml). Evaporation of the dried organic phase left a reddish gum which was found from t.l.c. [solvent (C)] to contain almost no mobile material, very weak spots at relative R_F values 1·00, 0·69 (corresponding to catechin), and 0·56 being only just discernible.

Degradation of Picea pungens *Tannin with Acid in the Absence of Sulphur Nucleophiles.*—The tannin–salt mixture (500 mg) was heated under reflux in 1 : 1 v/v water–ethanol (20 ml) with glacial acetic acid (4 ml) for 2 h. Water (150 ml) was added and the mixture was extracted with ethyl acetate (200 ml). Evaporation of the dried extract left a brown gum which on t.l.c. [solvent (C)] gave a single mobile flavanoid spot having the same R_F as authentic (±)-catechin (R_F 0·42), against a weak background streak.

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[24] J. W. Clark-Lewis and W. Korytnyk, *Chem. and Ind.*, 1957, 1418.