732. *New Methods for Assignment of Relative Configuration to* 2,3-trans-*Flavan*-3,4-*diols.*

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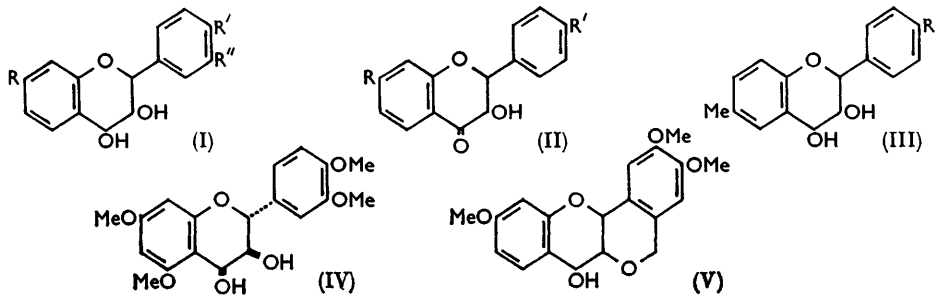
Film chromatography on silica and reaction with 2,2-dimethoxypropane are shown to be diagnostic for assignment of relative stereochemistry to five pairs of 2,3-*trans*-flavan-3,4-diols of known stereochemistry. The assignments made in the literature to two other pairs of 2,3-*trans*-flavan-3,4-diols, the 7-methoxy- and the 4′,7-dimethoxy-diols, are shown to require revision. The tetra-*O*-methyl-leucocyanidin previously obtained from (+)-tetra-*O*-methylcatechin is shown to be a 3,4-*cis*-diol. Relative stereochemistry is assigned to the 2,3-*trans*-2′-hydroxymethyl-4′,5′,7-trimethoxyflavan-3,4-diols and provisionally to 2,3-*trans*-4′,5′,7-trimethoxyflavan-3,4-*trans*-diol-2′-carboxylic acid.

The first attempts [1,2] to assign relative configuration to 2,3-*trans*-flavan-3,4-diols (I and III) were based upon known principles of conformational analysis taken from other fields

[1] Bognár and Rákosi, *Chem. and Ind.*, 1956, 188.
[2] Joshi and Kulkarni, *J. Indian Chem. Soc.*, 1957, **54**, 753.

(*e.g.*, steroids) and upon the ease with which the isomers formed cyclic carbonates, isopropylidene derivatives, and borate complexes. Many of these assignments have subsequently been shown to be erroneous,[3,4] since both flavan-3,4-*cis*- and 3,4-*trans*-diols give the isopropylidene derivative of the *cis*-isomer by reaction with acetone under



conventional conditions,[3,5] and the *cis*- and *trans*-isomers form distinct cyclic carbonates.[3,4] Current methods of determining relative configurations in this field are largely physical: proton magnetic resonance,[3,4,6-8] infrared studies of hydroxyl stretching frequencies,[9] and comparative rates of reaction with lead tetra-acetate[3] or periodic acid.[10] In addition, methods of preparation can yield information.[3,10,11] We now report two simple methods which can be applied for the assignment of relative configurations to flavan-3,4-diols.

The 2,3-*trans*-3-hydroxyflavan-4-ones (II), from which 2,3-*trans*-flavan-3,4-diols (I) are obtained, are often difficult to prepare by oxidative ring closure of 2'-hydroxychalcones with alkaline hydrogen peroxide.[12] This difficulty usually arises from the insolubility of the potassium or sodium salts of 2'-hydroxychalcones in the reaction medium. Substitution of Triton B (benzyltrimethylammonium hydroxide) for sodium or potassium hydroxide sometimes yields soluble salts and this enables 3-hydroxy-7-methoxy- and 3-hydroxy-4',7-dimethoxyflavan-4-ones (II; R = OMe, R' = H or OMe) to be prepared satisfactorily.

The reaction of seven pairs of (±)-2,3-*trans*-flavan-3,4-diols (I and III) with 2,2-dimethoxypropane[11,13] at 18° in presence of catalytic amounts of toluene-*p*-sulphonic acid has been found to give high yields of the isopropylidene derivative from the *cis*-isomer and none, or trace quantities, from the *trans*-isomer. The *trans*-diols that lack 7-methoxy-groups (I; R = H) were recovered unchanged, while *trans*-diols with 7-methoxy-groups (I; R = OMe) were converted into oils, which were shown by film chromatography to contain traces of unchanged diol and of the isopropylidene derivative, but which consisted largely of two compounds of intermediate R_F values, probably open-chain acetals.

The same pairs of diols were examined by film chromatography and it has been found generally that the R_F values of *cis*-diols are greater than those of *trans*-diols (see Table 1). The effect may occur because *trans*-diols form stronger hydrogen bonds to the stationary phase than do *cis*-diols, which have been shown spectrographically[9] to contain stronger intramolecular hydrogen bonds.

[3] Bokadia, Brown, Kolker, Love, Newbould, Somerfield, and Wood, *J.*, 1961, 4663.
[4] Corey, Philbin, and Wheeler, *Tetrahedron Letters*, 1961, **13**, 429.
[5] S. I. Fujise, Hishida, Onuma, Adachi, Y. Fujise, and Munekata, *Bull. Chem. Soc. Japan*, 1962, **35**, 1245.
[6] Clark-Lewis and Jackman, *Proc. Chem. Soc.*, 1961, 165.
[7] Clark-Lewis, Jackman, and Williams, *J.*, 1962, 3858.
[8] S.I. Fujise, Y. Fujise, and Hishida, *J. Chem. Soc. Japan*, 1963, **84**, 78.
[9] Philbin, Wheeler, Brutcher, and Bauer, *J. Org. Chem.*, 1962, **27**, 4114.
[10] Drewes and Roux, *Chem. and Ind.*, 1963, 532.
[11] Brown and MacBride, *Chem. and Ind.*, 1963, 1037.
[12] Reichel and Steudel, *Annalen*, 1942, **553**, 83.
[13] Cf. Angyal and Hoskinson, *J.*, 1962, 2985.

The relative configurations of the isomeric pairs of 2,3-*trans*-flavan-3,4-diol (I; R = R′ = R″ = H), 6-methylflavan-3,4-diol (III; R = H), 4′-methoxyflavan-3,4-diol (I; R = R″ = H, R′ = OMe) and 4′-methoxy-6-methylflavan-3,4-diol (III; R = OMe) are well established [3] as are those of 3′,4′,7-trimethoxyflavan-3,4-diol (I; R = R′ = R″ = OMe).[8,10,11,14] The assignments made recently [15] to the 7-methoxyflavan-3,4-diols (I; R = OMe, R′ = R″ = H) and earlier [16] to the 4′,7-dimethoxyflavan-3,4-diols (I; R = R′ = OMe, R″ = H) should be reversed, as the following evidence shows.

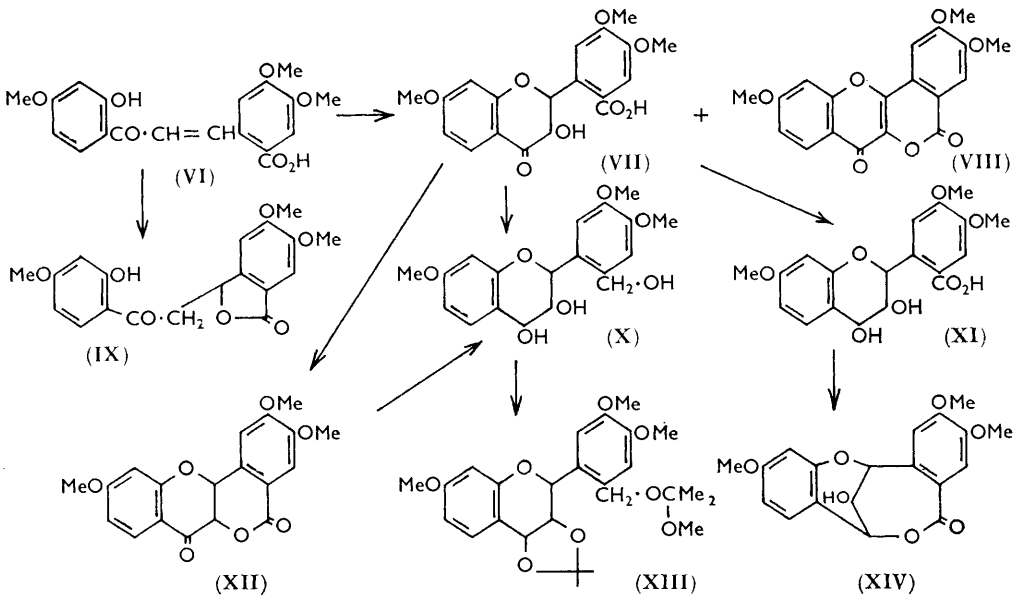
A specimen of (±)-2,3-*trans*-7-methoxyflavan-3,4-*cis*-diol, m. p. 137—139°, was obtained, together with its 3,4-*trans*-isomer, m. p. 122—122·5°, by reduction of (±)-2,3-*trans*-3-hydroxy-7-methoxyflavan-4-one with lithium aluminium hydride (cf. ref. 15). Separation was effected by fractional crystallisation. The infrared spectrum of a dilute solution of the *cis*-diol in carbon tetrachloride showed a doublet at $\nu_{max.}$ *ca.* 3615 and 3582 cm.$^{-1}$, indicating an intramolecular hydrogen bond and a *cis*-configuration.[9] It also gave an isopropylidene derivative with 2,2-dimethoxypropane. The *trans*-diol showed a singlet, $\nu_{max.}$ *ca.* 3610 cm.$^{-1}$ and yielded only a trace (film chromatography) of the isopropylidene derivative with 2,2-dimethoxypropane. Reduction of the 3-hydroxyflavanone with lithium aluminium hydride in presence of aluminium chloride gave an oil, probably (film chromatography) impure 7-methoxyflavan-3-ol produced by hydrogenolysis of the keto group.[17]

The compound (±)-2,3-*trans*-4′,7-dimethoxyflavan-3,4-*cis*-diol, m. p. 146—148° (from ethanol) and 166·5—166° (from chloroform–ether), was obtained as the major product of reduction of (±)-2,3-*trans*-4′,7-dimethoxy-3-hydroxyflavan-4-one with a mixture of lithium aluminium hydride and aluminium chloride. Its infrared spectrum in carbon tetrachloride showed hydroxyl stretching frequencies at *ca.* 3606 and 3582 cm.$^{-1}$, indicating an intramolecular hydrogen bond and a *cis*-configuration,[9] which was expected from its method of preparation.[3] In addition, this diol gave an isopropylidene derivative with 2,2-dimethoxypropane. On the other hand, (±)-2,3-*trans*-4′,7-dimethoxyflavan-3,4-*trans*-diol, m. p. 116—118°, obtained by reduction of the 3-hydroxyflavanone with lithium aluminium hydride, showed a singlet, $\nu_{max.}$ *ca.* 3610 cm.$^{-1}$ in its infrared spectrum and yielded none of the isopropylidene derivative with 2,2-dimethoxypropane. Further, the proton magnetic resonance of its diacetate indicated the presence of equatorial acetoxy groups.[3] A second product from this reaction, recrystallised (ethanol) to constant m. p. 136—139°, was shown by film chromatography to be a mixture of *ca.* 50% of the 3,4-*cis*-diol with *ca.* 50% of the 3,4-*trans*-diol (cf. ref. 16).

The tetra-*O*-methyl-leucocyanidin, produced by the action of lead tetraacetate on (+)-tetra-*O*-methylcatechin followed by hydrolysis,[18] has been shown, on the basis of the following evidence, to be a 3,4-*cis*-diol. Its infrared spectrum in carbon tetrachloride showed two hydroxyl stretching frequencies (3618 and 3556 cm.$^{-1}$), and with 2,2-dimethoxypropane it yielded an isopropylidene derivative, also obtained on reaction with acetone in presence of copper sulphate. The proton magnetic resonance spectrum of the diacetate of the diol in chloroform indicates the presence of 3-equatorial and 4-quasi-axial acetoxy groups.[3] Reduction of (+)-tetra-*O*-methyldihydroquercetin ($[\alpha]_D$ −14°) of unknown optical purity [19] with a mixture of lithium aluminium hydride and aluminium chloride and repeated recrystallisation of the product has yielded the same diol. On the basis of this evidence and its production from (+)-tetra-*O*-methylcatechin and from (+)-tetra-*O*-methyldihydroquercetin, the absolute configuration of this diol is as shown in formula (IV). Thus reaction of lead tetra-acetate with a flavan [18] yields, after hydrolysis, a 4-quasi-axial

[14] Clark-Lewis and Katekar, *J.*, 1962, 4502.
[15] S. I. Fujise, Munekata, Ishikawa, Kobayashi, Sokai, Ueno, Yuki, and Hishida, *J. Chem. Soc. Japan*, 1963, **84**, 81.
[16] Phatak and Kulkarni, *Current Sci.*, 1959, **28**, 328.
[17] Bokadia, Brown, Cobern, Roberts, and Somerfield, *J.*, 1962, 1658.
[18] Bokadia, Brown, and Cummings, *J.*, 1960, 3308.
[19] Clark-Lewis and Korytnyk, *J.*, 1958, 2367.

hydroxyl group, contrary to the suggestion of Bognár *et al.*,[20] later, by implication, amended.[21] This is in agreement with the finding [18] that flavan-4α-ols, now known from proton magnetic resonance spectra to contain 4-quasi-axial hydroxyl groups,[22] result from this reaction.



Synthesis of compounds related to peltogynol trimethyl ether (V) [23] has led to the preparation and stereochemical determination of 2,3-*trans*-2′-hydroxymethyl-4′,5′,7-trimethoxyflavan-3,4-diols (X) and provisionally to 2,3-*trans*-4′,5′,7-trimethoxyflavan-3,4-*trans*-diol-2′-carboxylic acid (XI). Condensation of peonol with *m*-opianic acid gave 2′-hydroxy-4,4′,5-trimthoxychalcone-2-carboxylic acid (VI) [24] which is readily converted into an isomer, formulated from its spectral properties as the lactone (IX). Oxidative ring closure of the dipotassium salt of the chalcone (VI) with alkaline hydrogen peroxide under carefully controlled conditions gave 2,3,10-trimethoxy-[2]-benzopyran[4,3-*b*]-[1]-benzopyran-5,7-dione (VIII) (5%) and the 3-hydroxyflavanone-2′- carboxylic acid (VII) (24%). Lactonisation of (VII) did not occur readily; variable yields up to 60% of compound (XII) were obtained by the use of toluene-*p*-sulphonic acid in boiling chloroform and better yields with di-isopropylcarbodi-imide in chloroform at room temperature. Reduction of the 3-hydroxyflavanone-2′-carboxylic acid (VII) with lithium aluminium hydride in tetrahydrofuran gave a mixture of the 4-epimers of 2,3-*trans*-2′-hydroxymethyl-4′,5′,7-trimethoxyflavan-3,4-diol (X) which was easily separated by fractional crystallisation into an isomer of m. p. 199—201° (20%) and another of m. p. 106—109° (40%). Similar reduction of compound (XII) yielded the diol of m. p. 106—109° as the major product (79%). The higher-melting isomer has been assigned the 3,4-*cis*-configuration since it is the minor product of these reductions and it reacted with 2,2-dimethoxypropane to give a crystalline compound whose elemental analysis and infra-red spectrum support its formation as the isopropylidene derivative (XIII). These

[20] Bognár, Rákosi, Fletcher, Kehoe, Philbin, and Wheeler, *Tetrahedron*, 1962, **18**, 135.
[21] Bognár, Rákosi, Fletcher, Philbin, and Wheeler, *Tetrahedron*, 1963, **19**, 391.
[22] Lillya, Kehoe, Philbin, Vickars, and Wheeler, *Chem. and Ind.*, 1963, 84; Brown and Munro, unpublished work.
[23] Chan, Forsyth, and Hassall, *J.*, 1958, 3174.
[24] During the course of the work it became known to us that Professor C. H. Hassall and his co-workers had already prepared this chalcone: Bryant, Ph.D. Thesis, Swansea, 1960.

assignments are confirmed by the relative R_F values (*cis*-diol 0·49, *trans*-diol 0·46) of the isomers on a silica film.

Provisionally, 2,3-*trans*-4′,5′,7-Trimethoxyflavan-3,4-*trans*-diol-2′-carboxylic acid (XI), obtained by hydrogenation of 2,3-*trans*-3-hydroxy-4′,5′,7-trimethoxyflavanone-2′-carboxylic acid (VII), is assigned this stereochemistry from its method of preparation. Lactonisation of this carboxylic acid (XI) occurred on treatment with di-isopropylcarbodiimide in chloroform. The product (XIV) is thought to have a seven-membered lactone ring because it is unaffected by manganese dioxide, behaviour expected of a flavan-3-ol with a seven-membered lactone ring (XIV) but not of the alternative flavan-4-ol with a six-membered lactone ring.[23,25]

Experimental

Infrared spectra were measured with a Perkin-Elmer 237 spectrometer or a Unicam S.P. 100 spectrometer.

Melting points were measured on a Kofler hot-stage apparatus.

Alumina refers to Spence grade H chromatographic alumina deactivated with 10% w/w of 10% v/v acetic acid.

Chloroform refers to reagent grade, stabilised with *ca.* 1% w/w of ethanol.

Film Chromatography (Table 1) was carried out on unbaked glass plates coated with Kieselgel H silica, eluted with chloroform containing 5% v/v of ethanol, and developed with iodine vapour. Spots resulting from diols or their derivatives were usually brown, rarely grey. Treatment of the plates with hydrogen chloride followed by brief heating at 100° gave yellow, orange, or red spots from 7-methoxydiols; other diols remained colourless.

Table 1.

Film chromatography of flavan-3,4-diols.

Flavan-3,4-diols	R_F Value		Ratio
	cis	*trans*	R_F(*cis*) : R_F(*trans*)
Unsubstituted (I, R = R′ = R″ = H)	0·33	0·30	1·10
6-Methyl (III, R = H)	0·46	0·40	1·15
4′-Methoxy (I; R = R″ = H, R′ = OMe)	0·37	0·31	1·19
4′-Methoxy-6-methyl (III; R = OMe)	0·40	0·34	1·18
7-Methoxy (I; R = OMe, R′ = R″ = H)	0·37	0·32	1·16
4′,7-Dimethoxy (I; R = R′ = OMe, R″ = H)	0·38	0·33	1·15
3′,4′,7-Trimethoxy (I; R = R′ = R″ = OMe)	0·37	0·34	1·09

Isopropylidene Derivatives (Table 2).—The crystalline diols (30—100 mg.) were treated with 2,2-dimethoxypropane (2·0 ml./100 mg. of diol) and toluene-*p*-sulphonic acid (4—6 mg./100 mg. of diol) and kept at 18° with occasional swirling. The *trans*-diol dissolved in the reagent before addition of toluene-*p*-sulphonic acid except for diol (III; R = OMe) (*trans*-diol largely undissolved throughout) and diol (I; R = R′ = R″ = OMe) (*trans*-diol dissolved slowly after acidification), while the *cis*-diols all dissolved slowly after acidification. When the *cis*-diol had dissolved completly, the mixtures were allowed to stand for a further 30 min. [except in experiment (b)], diluted with chloroform, and washed with 5% potassium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated *in vacuo*. The residues were examined by film chromatography [experiments (f), (g), and (h)] and recrystallised, where possible, from methanol [experiments (a)—(g)] or ethanol [experiments (h)]. Known products (recovered diols and isopropylidene derivatives) were identified by m. p. and mixed m. p. The yields are quoted after one recrystallisation, but some products required a second recrystallisation to give a sharp m. p.

3-*Hydroxy*-7-*methoxyflavan*-4-*one* (II; R′ = H, R = OMe).—2′-Hydroxy-4′-methoxychalcone (10·0 g.), 40% aqueous benzyltrimethylammonium hydroxide (Triton B) (35·0 g.), and 67% aqueous ethanol (300 ml.) were treated at 10° with 6% aqueous hydrogen peroxide (80 ml.). The addition took 20 min. and stirring was continued at 10—12° for a further 3 hr.

[25] Madharan, Nair, and Venkatamaran, *Tetrahedron Letters*, 1963, **5**, 317.

Aqueous sodium bisulphite (4%, 60 ml.) was added slowly at 10—12° and then 2N-hydrochloric acid (50 ml.). The precipitate was washed with 50% aqueous ethanol (3 × 15 ml.) and recrystallised from ethanol (60 ml.) to give crude 3-hydroxy-7-methoxyflavan-4-one (4·4 g.). Further recrystallisation from methanol yielded the pure compound (2·9 g.), m. p. 149—151° (lit.,[26] 146—147°). The ethanolic mother-liquor from the first recrystallisation afforded 7-methoxyflavan-4-one (0·7 g.), m. p. and mixed m. p. 88—90°.

TABLE 2.

Reaction of flavan-3,4-diols with 2,2-dimethoxypropane.

Flavan-3,4-diol	Config. at C_3, C_4	Reactn. time (hr.)	Products	R_F †	Yield (%)	M. p.	Lit. m. p.
(*a*) Unsubstituted*	*cis*	3	Isopropylidene	—	85	112—114°	113—114°
(I, R = R′ = R″ = H)	*trans*	3	(*trans*-diol)	—	81	146—147 *	146—146·5
(*b*) ,, ,,	*cis*	30	Isopropylidene	—	76	112—114	113—114
	trans	30	(*trans*-diol)	—	57	146—147 *	146—146·5
(*c*) 6-Methyl	*cis*	1	Isopropylidene	—	57	89—91	91·5—92·5
(III, R = H)	*trans*	1	(*trans*-diol)	—	61	117—119 *	118—119
(*d*) 4′-Methoxy	*cis*	2	Isopropylidene	—	80	112—113·5	110—110·5
(I; R = R″ = H, R′ = OMe)	*trans*	2	(*trans*-diol)	—	66	175—177	177—177·5
(*e*) 4′-Methoxy-6-methyl	*cis*	6·5	Isopropylidene	—	79	126—127	129—130
(III; R = OMe)	*trans*	6·5	(*trans*-diol)	—	90	171—173	172—173
(*f*) 7-Methoxy	*cis*	0·75	Isopropylidene	0·71	38	107·5—109 *§	113—114
(III; R = OMe,	*trans*	0·75	Isopropylidene	0·71	(trace)	—	—
R′ = R″ = H)			(*trans*-diol)	0·71	(trace)	—	—
			Other products	0·65		—	—
				0·51		—	—
(*g*) 4′,7-Dimethoxy	*cis*	1	Isopropylidene	0·65	73	117—118·5 *‖	—
(III; R = R′ = OMe, R″ = H)	*trans*	1	(*trans*-diol)	0·06	(trace)	—	—
			Other products	0·43	—	—	—
				0·79	—	—	—
(*h*) 3′,4′,7-Trimethoxy	*cis*	1	Isopropylidene	0·77 ‡	71	134—136	134—136
(I; R = R′ = R″ = OMe)	*trans*	1	Isopropylidene	0·77 ‡	(trace)	—	—
			(*trans*-diol)	0·33 ‡	(trace)	—	—
			Other products	0·58 ‡	—	—	—
				0·66 ‡	—	—	—

* Twice recrystallised. † R_F values are for reagent chloroform, except those marked ‡ which are for chloroform containing 4% v/v of ethanol. Plates were fumed with hydrogen chloride and then heated to 100° to make the spots visible. § Found: C, 73·25; H, 6·45. Calc. for $C_{19}H_{20}O_4$: C, 73·1; H, 6·45%. ‖ Found: C, 70·45; H, 6·55. $C_{20}H_{22}O_5$ requires C, 70·15; H, 6·5%.

From a similar experiment in which the starting material was 2′-hydroxy-4,4′-dimethoxychalcone (10·0 g.), 3-hydroxy-4′,7-dimethoxyflavan-4-one (II; R = R′ = OMe) (2·5 g.), m. p. 130—131·5° (lit.,[26] 130°) and 3-hydroxy-4′,7-dimethoxyflavonol (1·65 g.), m. p. 195—197° (lit.,[27] 196—197°) were obtained.

2,3-trans-7-*Methoxyflavan*-3,4-cis- *and* trans-*diols* (I; R = OMe, R′ = R″ = H) (cf. ref. 15).—3-Hydroxy-7-methoxyflavanone (II; R′ = H, R = OMe) (750 mg.) in ether (100 ml.) was stirred with lithium aluminium hydride (300 mg.) for 30 min. at 18°. Decomposition with methyl formate and aqueous potassium sodium tartrate (200 g., 50% w/w), separation, and further extraction with chloroform gave, after evaporation, a mixture of the two diols (755 mg.). Fractional crystallisation from 70% aqueous methanol and of the more soluble fractions from carbon tetrachloride and then from 50% aqueous methanol gave the pure diols: (i) the cis-*diol* (360 mg.) as silky needles, m. p. 137—139° (Found: C, 70·5; H, 6·0. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%), $\nu_{max.}$ (in CCl_4, *ca.* 2 mg./ml.) 3615 and 3582 cm.$^{-1}$ (*cis*-diol); $\nu_{max.}$ (in $CHCl_3$): 3570, 3370 (OH), 1626, 1592 (aromatic), 1268 (C–O), and 1161 cm.$^{-1}$; (ii) the trans-*diol* (130 mg.) as short needles, m. p. 122—122·5° (Found: C, 70·85; H, 5·75%), $\nu_{max.}$ (in CCl_4 *ca.* 2 mg./ml.) 3610 cm.$^{-1}$ (*trans*-diol), $\nu_{max.}$ (in $CHCl_3$): 3570, 3360 (OH), 1627, 1590 (aromatic), 1304, 1284, 1260 (C–O), and 1161 cm.$^{-1}$.

[26] Oyamada, *J. Chem. Soc. Japan*, 1943, **64**, 471.
[27] Juppen and von Kostanecki, *Ber.*, 1904, **37**, 4161.

Treatment of the *cis*-diol (100 mg.) with acetic anhydride (1·0 ml.) and pyridine (0·8 ml.) at 75—80° for 15 hr. and isolation in ether gave the *diacetate* (32 mg.) as plates (from benzene–light petroleum) m. p. 99—102° (Found: C, 67·75; H, 5·65. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·65%). Both diols gave an intense lemon-yellow colour on being warmed with ethanolic hydrochloric acid.

Reduction of 3-*Hydroxy*-7-*methoxyflavanone with a Mixture of Lithium Aluminium Hydride and Aluminium Chloride.*—The flavanone (II; R′ = H, R = OMe) (660 mg.) in ether (70 ml.) was added during 10 min. to lithium aluminium hydride (400 mg.) and aluminium chloride (2·70 g.) in ether (100 ml.) at 0° and stirred for a further 40 min. Working up as before gave a gum (710 mg.) which could not be purified effectively by chromatography on alumina. It consisted predominantly of one compound, R_F 0·70 on a silica film, $\nu_{max.}$ (liquid film) 3570s (OH), 1620 and 1590 cm.$^{-1}$ (aromatic). It gave no colour with hot ethanolic hydrochloric acid.

2,3-trans-4′,7-*Dimethoxyflavan*-3,4-trans-*diol* (I; R = R′ = OMe, R″ = H) (cf. ref. 16).—3-Hydroxy-4′,7-dimethoxyflavanone (II; R = R′ = OMe) (484 mg.) in tetrahydrofuran (30 ml.) was stirred with lithium aluminium hydride (300 mg.) at 18° for 20 min. Working up as before gave a brown glass (535 mg.). Crystallisation from 80% aqueous methanol (9·0 ml.) and four recrystallisations from ethanol yielded crystals (65 mg.) m. p. 135—139° (Found: C, 67·1; H, 6·1. $C_{17}H_{18}O_5$ requires C, 67·55; H, 6·0%). Film chromatography showed that this material consisted of *ca.* equal amounts of two compounds, R_F 0·38 and 0·33, corresponding with markers of the *cis*- and *trans*-diols, respectively.

Dilution of the initial mother-liquor with water (8·0 ml.) and recrystallisation of the precipitate (195 mg.) from ethanol and then from methanol gave the trans-*diol* as flat needles, m. p. 116—118° (with softening at *ca.* 55°) (Found: C, 67·65; H, 6·1%), $\nu_{max.}$ (in CCl_4 *ca.* 2 mg./ml.) 3610 cm.$^{-1}$ (*trans*-diol), $\nu_{max.}$ (in $CHCl_3$): 3570 (OH), 1623, 1593 (aromatic) and 1162 cm.$^{-1}$.

The *trans*-diol (173 mg.) was acetylated under the conditions given above; the product, isolated by pouring the reaction mixture into ice, was twice recrystallised from ethanol to give the *diacetate* (147 mg.) as needles, m. p. 106—108°. Subsequent recrystallisation gave prisimatic crystals m. p. and mixed m. p. with the acicular form, 138—139·5° (Found: C, 65·7; H, 5·75. $C_{21}H_{22}O_7$ requires C, 65·3; H, 5·75%). The proton magnetic resonance spectrum of the diacetate in chloroform showed peaks with τ values of 8·08 and 8·22 (equatorial OAc groups).[3]

2,3-trans-4′,7-*Dimethoxyflavan*-3,4-cis-*diol* (I; R = R′ = OMe, R″ = H) (cf. ref. 16).—3-Hydroxy-4′,7-dimethoxyflavanone (II; R = R′ = OMe) (500 mg.) in tetrahydrofuran (15 ml.) was added to lithium aluminium hydride (150 mg.) and aluminium chloride (1·05 g.) in tetrahydrofuran (20 ml.) at 0° and stirred for 30 min. Isolation as before, and two recrystallisations of the product from methanol gave the cis-*diol* (135 mg.) as small needles, m. p. 146—148°. A subsequent recrystallisation from chloroform-ether gave a different crystal form, m. p. 165·5—166° (Found: C, 67·55; H, 6·05%), $\nu_{max.}$ (in CCl_4, *ca.* 2 mg./ml.) 3606 and 3582 cm.$^{-1}$ (*cis*-diol), $\nu_{max.}$ (in $CHCl_3$) 3600, 3570 (OH); 1624, 1593 (aromatic), 1252 (C–O), and 1163 cm.$^{-1}$. The mother-liquors afforded a further crop of the *cis*-diol (187 mg.), and a crystalline mixture of diols (62 mg.) m. p. and mixed m. p. 134—138°.

The *cis*-diol (91 mg.) was treated with benzoyl chloride (0·3 ml.) and pyridine (2·0 ml.) at 75—80° for 15 hr. The product was isolated in chloroform, filtered through alumina, and recrystallised twice from ethanol to give the *dibenzoate* (111 mg.) as rhombic plates, m. p. 161—163° (Found: 72·7; H, 5·15. $C_{31}H_{25}O_7$ requires C, 72·9; H, 5·15%).

2,3-trans-3′,4′,7-*Trimethoxyflavan*-3,4-cis- *and* trans-*Diols* (I; R = R′ = R″ = OMe) (cf. refs. 5, 8, 10, 11, 14, 28).—(*a*) 3-Hydroxy-3′,4′,7-trimethoxyflavanone (600 mg.) was reduced with lithium aluminium hydride (400 mg.). The product, isolated as above, was fractionally crystallised from ethanol to give (i) the *cis*-diol (120 mg.) as small needles, m. p. 180—181° (Found: C, 65·15; H, 6·0. Calc. for $C_{18}H_{20}O_6$: C, 65·05; H, 6·05%), $\nu_{max.}$ (in CCl_4 very dilute) 3590, and 3568 cm.$^{-1}$ (*cis*-diol), $\nu_{max.}$ (in $CHCl_3$) 3490 (OH), 1618, 1584 (aromatic), and 1154 cm.$^{-1}$; (ii) the *trans*-diol (209 mg.) as small needles, m. p. 155—156·5° (Found: C, 64·85; H, 5·95%), $\nu_{max.}$ (in CCl_4, very dilute) 3596 cm.$^{-1}$ (*trans*-diol), $\nu_{max.}$ (in $CHCl_3$) 3500, 3350 (OH), 1618, 1585 (aromatic), and 1154 cm.$^{-1}$.

(*b*) 3-Hydroxy-3′,4′,7-trimethoxyflavanone (600 mg.) was reduced with a mixture of lithium aluminium hydride (300 mg.) and aluminium chloride (2·00 g.) at 0° for 30 min. Isolation of

[28] Chandorkar and Kulkarni, *Current Sci.*, 1957, **26**, 354.

the product as above and recrystallisation from ethanol gave the *cis*-diol (323 mg.), m. p. and mixed m. p. 180—181°. Evaporation of the mother-liquor and recrystallisation of the oily residue from carbon tetrachloride and twice from ethanol gave a crude sample of the *trans*-diol (74 mg.), m. p. and mixed m. p. 151—156°.

The diacetate of the *trans*-diol separated from methanol as needles, m. p. 118·5—121° (Found: C, 63·15; H, 5·85. Calc. for $C_{22}H_{24}O_8$: C, 63·4; H, 5·8%).

The dibenzoate of the *cis*-diol separated from methanol as rectangular prisms, m. p. 149·5—151° (Found: C, 70·75; H, 5·25. Calc. for $C_{30}H_{28}O_6$: C, 71·1; H, 5·2%).

The isopropylidene derivative was obtained from either diol by reaction with acetone in the presence of anhydrous copper sulphate and separated from methanol as needles, m. p. 136—138° (Found: C, 67·35; H, 6·45. Calc. for $C_{21}H_{24}O_6$: C, 67·7; H, 6·5%). The *cis*-diol gave the derivative in 68% yield, and the *trans*-diol in 40% yield.

For hydrolysis the isopropylidene derivative (3·0 mg.) was boiled with ethanol (10 ml.) and sulphuric acid (3·0 ml., 2N) for 4 hr. under nitrogen. Neutralisation with excess of magnesium oxide, filtration, and evaporation of the solvent left a gum (2·0 mg.). Film chromatography in ethanol–chloroform (4% v/v) showed 5 compounds, R_F 0·34 (*trans*-diol), 0·37 (*cis*-diol), 0·56, 0·68, and 0·77 (isopropylidene derivative) [cf. Table 2, experiment (h)]. The diols were present in approximately equal amounts. All the spots gave a pink coloration when the plate was fumed with hydrochloric acid and heated.

Hydrogenation of 3-*Hydroxy*-3′,4′,7-*trimethoxyflavanone*.—(*a*) The flavanone (335 mg.) in ethanol (50 ml.) was hydrogenated at 18°/760 mm. over Adams catalyst (140 mg.). Hydrogen uptake (77·0 ml., 1·4 mol., with allowance for hydrogenation of the catalyst) was stopped after 1·5 hr. Isolation of the product in the usual way and recrystallisation from benzene and then from ethanol gave 2,3-*trans*-3′,4′,7-trimethoxyflavan-3,4-diol (165 mg., 50%) m. p. and mixed m. p. 154—156°. Film chromatography of the crude product showed the presence of both the *cis* and *trans*-diols, R_F 0·37 and 0·34.

(*b*) The 3-hydroxyflavanone (600 mg.) in acetic acid (30 ml.) was hydrogenated at 18°/760 mm. over Adams catalyst (367 mg.). Hydrogen uptake (267 ml., 3·5 mol., with allowance for hydrogenation of the catalyst) was stopped after 2·5 hr. Isolation of the product in the usual way and successive recrystallisations from carbon tetrachloride, carbon tetrachloride–chloroform, and ethanol gave the *trans*-diol (105 mg., 18%) m. p. and mixed m. p. 155—156·5°. Examination of the crude product by film chromatography showed the presence of both the *cis* and the *trans*-diols, as above.

(*c*) Under the conditions of (*b*), but when only 1·0 mol. of hydrogen was absorbed, the unchanged 3-hydroxyflavanone (60%) was recovered.

(+)-2,3-trans-3′,4′,5,7-*Tetramethoxyflavan*-3,4-cis-*diol*[(+)-*Tetra*-O-*methyl-leucocyanidin*](IV) (By M. M. Bokadia).—A solution of (+)-dihydroquercetin tetramethyl ether (300 mg.; m. p. 168—170°; $[\alpha]_D$ −14°, *c* 1·93 in $CHCl_3$ [19]) in tetrahydrofuran (20 ml.) was added slowly to a stirred mixture of aluminium chloride (400 mg.), lithium aluminium hydride (50 mg.), and tetrahydrofuran (25 ml.). After the mixture had been stirred at room temperature for 3 hr., it was treated with solid carbon dioxide and water and a colourless solid was isolated in the usual way. Three recrystallisations from methanol gave needles (150 mg.), m. p. 187—190°, $[\alpha]_D$ +22·5° (*c* 1·9 in $CHCl_3$). Further crystallisations from glycol monomethyl ether gave the 3,4-*cis*-diol, m. p. and mixed m. p.[18] 189—190°, $[\alpha]_D$ +32° (*c* 2·2 in $CHCl_3$), $\nu_{max.}$ (in CCl_4, *ca.* 0·3 mg./ml.) 3618 and 3556 $cm.^{-1}$ (*cis*-diol).

The mother-liquors yielded crystalline solids of m. p. 160—173°.

Treatment of the 3,4-*cis*-diol with acetic anhydride and pyridine gave the *diacetate* which separated from ethyl acetate–light petroleum as needles, m. p. 121—123° (Found: C, 62·0; H, 5·5. $C_{23}H_{26}O_9$ requires C, 61·9; H, 5·9%). The proton magnetic resonance spectrum of the diacetate in chloroform showed peaks with τ values of 7·91 (quaxi-*ax* OAc) and 8·18 (eq OAc).[3]

The *isopropylidene derivative* was prepared in two ways: (*a*) (By J. Newbould). The diol (60 mg.) was shaken with anhydrous copper sulphate (120 mg.) in dry acetone (18 ml.) for 8 days. Filtration and removal of solvent gave the *derivative* (55 mg.) which separated from methanol–acetone (1 : 1 v/v) as needles, m. p. 131—132° resolidifying to plates, m. p. 148—149°, $[\alpha]_D$ +7° (*c* 1·5 in $CHCl_3$) (Found: C, 65·4; H, 6·5. $C_{22}H_{26}O_7$ requires C, 65·6; H, 6·5%).

(*b*) Treatment of the diol (20 mg.) with 2,2-dimethoxypropane and toluene-*p*-sulphonic acid as described above gave the derivative (12 mg.), m. p. and mixed m. p. 130—131°, identical in its infrared spectrum (in Nujol) with material from (*a*).

2'-Hydroxy-4,4',5-trimethoxychalcone-2-carboxylic Acid (VI).—Aquous potassium hydroxide (50%, 40 g.) was added at 45° to *m*-opianic acid (10·0 g.) and peonol (9·2 g.) in ethanol (75 ml.). After 13 hr. at this temperature, the orange needles of the dipotassium salt of the chalcone (20·5 g.) were separated and washed with ethanol. Acidification of the dipotassium salt (1·0 g.) in water (6·0 ml.) with 2N-hydrochloric acid (3·0 ml.) and recrystallisation of the resulting dried precipitate from chloroform which contained a few drops of ethyl acetate gave yellow rhombic plates of the *chalcone-2-carboxylic acid* (0·69 g.), m. p., after re-formation of colourless needles at *ca.* 150°, 231—233° (decomp.). For analysis the chalcone was recrystallised from dichloromethane (Found: C, 63·2; H, 5·25. $C_{19}H_{18}O_7$ requires C, 63·65; H, 5·05%), $\lambda_{max.}$ (in EtOH) 257 and 364 mμ (log ε 4·21 and 4·39).

The chalcone (0·5 g.) was boiled with acetonitrile (8·0 ml.) for 3 min. In the cold an *isomer* (IX) separated as colourless needles, m. p. 231—233° (decomp.) (Found: C, 63·4; H, 5·0; *M* (Rast) 304. $C_{19}H_{18}O_7$ requires *M* 358), $\lambda_{max.}$ (in EtOH) 280 mμ, $\lambda_{infl.}$ 305 mμ; $\nu_{max.}$ (in $CHCl_3$) 1727 (lactone C=O) and 1629 cm.$^{-1}$ (*o*-hydroxyphenyl ketone C=O).

2,3-trans-3-*Hydroxy-4',5',7-trimethoxyflavan-4-one-2'-carboxylic Acid* (VII).—The dipotassium salt of the above chalcone (VI) (19·5 g.) and 4% aqueous potassium hydroxide (60 ml.) in water (760 ml.) was treated at 14° with 6% aqueous hydrogen peroxide (240 ml.) during 30 min. After being stirred at this temperature for a further 3·5 hr., the mixture was treated at 7° with 6% aqueous sodium bisulphite (100 ml.) followed by 2N-hydrochloric acid (140 ml.). The washed and dried precipitate (14·3 g.) was extracted with warm (*ca.* 50°) chloroform (50 ml.). The residue (9·05 g.) was washed with chloroform (2 × 15 ml.) and extracted with boiling 80% aqueous ethanol (200 ml.). The residue separated from nitromethane to yield 2,3,10-*trimethoxy*-[2]-*benzopyran*[4,3-b]-[1]-*benzopyran-5,7-dione* (VIII) (0·80 g.) as colourless needles, m. p. (with change of form at *ca.* 200°) 329—332° (decomp.) (Found: C, 64·35; H, 3·95. $C_{19}H_{14}O_7$ requires C, 64·4; H, 4·0%), $\lambda_{max.}$ (in EtOH) 233, 250, 253 (infl.), 323, 340, and 357 mμ; $\nu_{max.}$ (in Nujol) 1737 (lactone C=O) and 1657 cm.$^{-1}$ (chromone C=O).

The 3-*hydroxyflavanone-2'-carboxylic acid* (4·0 g.) separated from the aqueous ethanol extract and was recrystallised from aqueous ethanol and then from ethanol to give colourless needles, which decomposed *ca.* 200° without melting (Found: C, 61·1; H, 4·85. $C_{19}H_{18}O_8$ requires C, 60·95; H, 4·85%), $\lambda_{max.}$ (in EtOH) 232, 270, and *ca.* 305 (infl.) mμ; $\nu_{max.}$ (in Nujol) 3420 (OH), *ca.* 2600 (carboxyl), and 1680 cm.$^{-1}$ (flavanone and carboxyl C=O unresolved). The compound gave an orange colour with magnesium and aqueous ethanolic hydrochloric acid.

trans-B/c-6a,12a-*Dihydro-2,3,10-trimethoxy*-[2]-*benzopyran*[4,3-b]-[1]-*benzopyran-5,7-dione* (XII).—(*a*) The above 3-hydroxyflavanone-2'-carboxylic acid (VIII) (190 mg.) in chloroform (80 ml.) was slowly (4 hr.) evaporated to half its bulk with toluene-*p*-sulphonic acid (22 mg.). More chloroform (25 ml.) was removed *in vacuo*. The *lactone* (XII) (111 mg.) which separated was recrystallised from nitromethane to give hexagonal plates, m. p. 226—232° (decomp.) (Found: C, 63·7; H, 4·55. $C_{19}H_{16}O_7$ requires C, 64·05; H, 4·55%), $\lambda_{max.}$ (in EtOH) 232, 270; and *ca.* 305 (infl.) mμ; $\nu_{max.}$ (in Nujol) 1730 (lactone C=O) and 1703 cm.$^{-1}$ (flavanone C=O).

(*b*) The 3-Hydroxyflavanone-2'-carboxylic acid (VII) (780 mg.) and *NN*-di-isopropylcarbodi-imide (308 mg.) in dioxan (30 ml.) were kept at 18° for 22 hr. The precipitated lactone (510 mg.) was washed with ethanol and with acetone. Its infrared spectrum was identical with that of the product from (*a*) above. The lactone was not recrystallised since the finely divided form resulting from this preparative method is most suitable for further reactions.

2,3-trans-2'-*Hydroxymethyl-4',5',7-trimethoxyflavan-3,4-diols* (X).—(*a*) The 3-hydroxyflavanone-2'-carboxylic acid (VII) (1·85 g.) was stirred with lithium aluminium hydride (0·60 g.) in tetrahydrofuran (100 ml.) at 18° for 1·5 hr., then under reflux for 30 min. Decomposition with methyl formate and aqueous potassium sodium tartrate, extraction with chloroform, and removal of solvents gave a product which was dissolved in boiling chloroform (60 ml.) and filtered through Celite to remove a gummy impurity. Needles (243 mg.) separated from the filtrate in the cold and more (140 mg.) were obtained when it was evaporated to 15 ml. Recrystallisation from ethanol gave 2,3-trans-2'-*hydroxymethyl-4',5',7-trimethoxyflavan-3,4-cis-diol*, m. p. 199—201° (Found: C, 62·85; H, 6·4. $C_{19}H_{22}O_7$ requires C, 62·95; H, 6·15%), $\nu_{max.}$ (in $CHCl_3$) 3335 (OH), 1625, 1592 cm.$^{-1}$ (aromatic).

Evaporation of the chloroform mother-liquor and three recrystallisations of the residue from benzene gave 2,3-trans-2'-*hydroxymethyl-4',5',7-trimethoxyflavan-3,4-trans-diol* (732 mg.) as square plates, m. p. 106—109° (Found: C, 63·1; H, 6·15%), $\nu_{max.}$ (in Nujol) 3455 and 3455 and 3330 cm.$^{-1}$ (OH).

Both 3,4-diols gave a cherry-red colour and a green fluorescence when warmed with ethanolic hydrochloric acid.

On film chromatography on silica with chloroform–ethanol (9 : 1 v/v), the diols showed the following characteristics: 3,4-*cis*-diol, R_F 0·49, grey spot with iodine; 3,4-*trans*-diol, R_F 0·46, brown spot with iodine.

The 3,4-*cis*-diol (75 mg.) was treated with 2,2-dimethoxypropane as described above and gave an *isopropylidene derivative* (XI) (14 mg.) as plates (from methanol), m. p. 106—111° (Found: C, 66·3; H, 7·4. $C_{26}H_{34}O_8$ requires C, 65·8; H, 7·2%), $\nu_{max.}$ (in $CHCl_3$) 1380 (infl.), 1375, and 1365 cm.$^{-1}$ (infl.) (CMe_2).

The 3,4-*cis*-diol (80 mg.) was boiled under reflux with ethanol (10 ml.) and concentrated hydrochloric acid (2·0 ml.) in a stream of oxygen, in the dark, for 15 hr. After 20 hr. at −5°, the black crystals (with a green glance) of the *flavylium salt* (15 mg.) were dried over phosphorus pentoxide *in vacuo* at 50° for 20 hr. and then had m. p. *ca.* 145° (decomp.) (Found: C, 61·5; H, 4·95. $C_{19}H_{17}ClO_5 \cdot 0{\cdot}5H_2O$ requires C, 61·7; H, 4·9%), $\lambda_{max.}$ (in EtOH) 235 (infl.) 286, 310 (infl.), and 523 mμ (log ε 4·26, 4·00, 3·82, and 3·95); $\nu_{max.}$ (in Nujol) 3593w and 3180w cm.$^{-1}$ (OH).

(*b*) The above lactone (XII) (200 mg.) was stirred with lithium aluminium hydride (160 mg.) in tetrahydrofuran (35 ml.) for 4·5 hr. at 18°. The mixture was treated as described in (*a*) above except that the chloroform extract (10 ml.) of the product was kept at 18° for two days when the 3,4-*trans*-diol (158 mg.) separated. Recrystallised from benzene, it had m. p. and mixed m. p. 106—109° and its infrared spectrum was identical with that of the 3,4-*trans*-diol from (*a*). Examination of the contents of the mother-liquors by chromatography on thin films showed the presence of some 3,4-*cis*-diol.

2,3-trans-4′,5′,7-*Trimethoxyflavan*-3,4-trans-*diol*-2′-*carboxylic Acid* (XI).—The 3-hydroxyflavanone-2′-carboxylic acid (VII) (685 mg.) in dioxan (38 ml.) was hydrogenated at 20·5°/764 mm. over Adams catalyst (228 mg.). After 100 min. (hydrogen-uptake, after allowance for catalyst, 48·5 ml., *i.e.*, 1·1 mol.) the product (740 mg.) was isolated by filtration from the catalyst and evaporation. Two recrystallisations from 50% aqueous ethanol gave the 3,4-trans-*diol*-2′-*carboxylic acid* (380 mg.) as needles, m. p. 167—171° (decomp.) (Found: C, 60·25; H, 5·5. $C_{19}H_{20}O_8$ requires C, 60·6; H, 5·35%), $\nu_{max.}$ (in Nujol) 3460 and 3160 (OH), 1685 cm.$^{-1}$ (C=O). The diol gave an orange colour with warm aqueous ethanolic hydrochloric acid.

14-*Hydroxy*-3,8,9-*trimethoxy*-13H-6,13-*methanodibenzo*[b,g]-[1,5]-*dioxonin*-11(6H)-*one* (XIV).—The above 2′-carboxy-3,4-*trans*-diol (340 mg.) and di-isopropylcarbodi-imide (148 mg.) in dioxan (15 ml.) were kept at 18° for 17 hr. The crystalline precipitate of di-isopropylurea (99 mg.) was removed and the solution evaporated. The residue in chloroform (10 ml.) was washed with 2N-hydrochloric acid (25 ml.) and with water (25 ml.), dried, and evaporated. Two recrystallisations of the resulting solid from nitromethane gave the *lactone* (XIV) (130 mg.) as pale yellow plates, m. p., with decomposition from *ca.* 220°, *ca.* 257° (Found: C, 63·9; H, 4·85. $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·05%), $\nu_{max.}$ (in Nujol) 3555, 3505 (OH), and 1722 cm.$^{-1}$ (lactone C=O).

The lactone was recovered after treatment with manganese dioxide in chloroform for 16 hr. at 18°.

We are grateful to the D.S.I.R. for a maintenance grant (to J. A. H. MacB.) and to Mr. J. R. Bull for recording the infrared spectrum of tetramethyl-leucocyanidin.

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[*Received, December 4th*, 1963.]