714. *Polymerisation of Flavans. Part IV.* The Condensation of Flavan-4-ols with Phenols.*

By B. R. Brown, W. Cummings, and J. Newbould.

Flavan-4-ols and flavan-3,4-diols condense with phenols as expected, to yield 4-arylflavans. The 3-hydroxyl group of the diols does not participate in further condensations to form ethers. 4′-Methoxyflavan-4β-ol condenses with two molecules of a phenol. The structures of some of the condensation products have been proved by synthesis.

During the past decade it has been realised that flavan-3,4-diols (leucoanthocyanidins) play an important rôle in the structure of some vegetable tannins.[1] Hence it was relevant

---

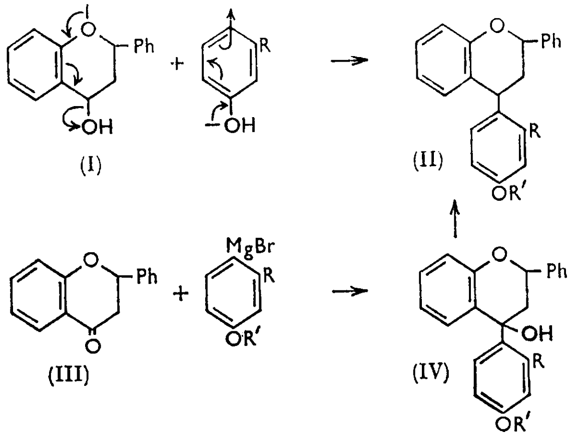
* Part III, *J.*, 1960, 3308.

[1] See, *e.g.*, Bate-Smith and Swain, *Chem. and Ind.*, 1953, 377; King and Bottomley, *J.*, 1954, 1399; Roux, *Nature*, 1958, **181**, 1454.

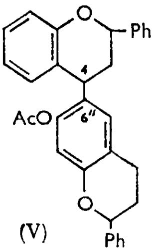
to investigate the acid-catalysed condensation of flavan-4-ols and flavan-3,4-diols with phenols, as has previously been done with 4′-substituted flavans.[2,3]

Since flavan-4-ols (I) are *ortho*-substituted benzyl alcohols, they were expected to condense with phenols to yield 4-arylflavans (II).

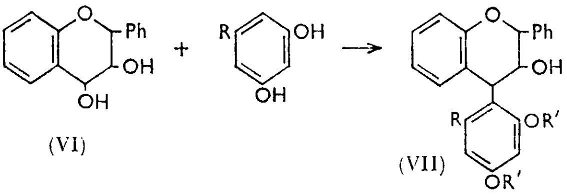
Flavan-4β-ol (I) condensed with phenol in ethanolic hydrogen chloride to yield, after methylation, 4-*p*-methoxyphenylflavan (II; R = H, R′ = Me) whose structure has been proved by synthesis from flavan-4-one (III) and *p*-bromoanisole. An isomeric compound, which was obtained in small amount from the condensation, is thought, from its analysis and its infrared spectrum, to be 4-*o*-methoxyphenylflavan. However, the 4-*o*-methoxyphenylflavan synthesised from flavanone and *o*-bromoanisole was not identical with this compound. 4-*o*-Methoxyphenylflavan can exist in two racemic forms and it may be that, when an *ortho*-substituent is present, synthesis and condensation lead to different racemates. Flavan-4β-ol (I) condensed with resorcinol to yield 4-(2,4-dihydroxyphenyl)-flavan (II; R = OH, R′ = H) which has been characterised as its diacetate and as its dimethoxy-derivative. A biflavanyl, characterised as its acetate (V), resulted from the condensation of flavan-4β-ol with 7-hydroxyflavan. Condensation at the 6-position of 7-hydroxyflavan is expected on the basis of earlier work.[3]



Since the naturally occurring leucoanthocyanidins contain a flavan-3,4-diol structure (VI), we studied their acid-catalysed condensation with phenols. Sterically it appeared possible for the 3-hydroxyl group, provided it were *cis* to the entering 4-aryl group, to undergo a secondary condensation with an *o*-hydroxyl group to yield an ether, as in the acid-catalysed condensation of catechin with phloroglucinol.[4] However, there was no



(V)



---

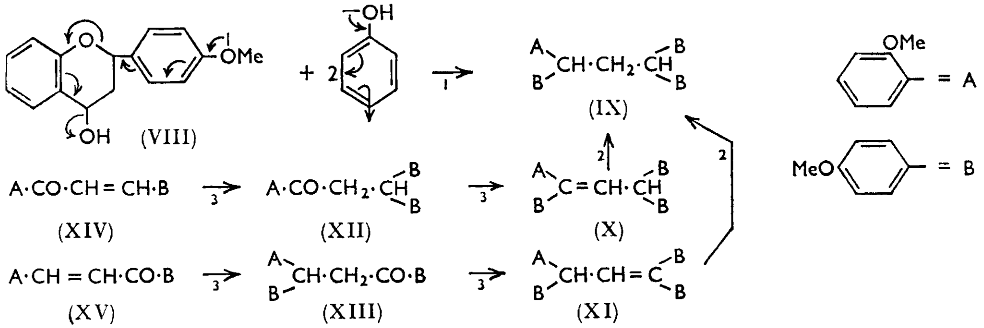
[2] Freudenberg and Weinges, *Annalen*, 1954, **590**, 140; Freudenberg and Alonso de Lama, *ibid.*, 1958, **612**, 78.

[3] Brown, Cummings, and Somerfield, *J.*, 1957, 3757; Brown and Cummings, *J.*, 1958, 4302.

[4] Mayer and Merger, *Chem. and Ind.*, 1959, 485.

secondary ether formation when flavan-3,4-diol (VI) condensed with resorcinol or phloroglucinol: after methylation with dimethyl sulphate and potassium carbonate, the products (VII; R = H or OMe, R′ = Me) still contained a 3-hydroxyl group which could be acetylated.

A 4′-methoxyflavan-4-ol (VIII) combines the functions of an activated benzyl ether with those of a benzyl alcohol and hence should condense with two molecules of a phenol. 4′-Methoxyflavan-4β-ol (VIII) condensed with two molecules of phenol in ethanolic hydrogen chloride to yield, after methylation, a tetra-arylpropane (IX) whose structure has been proved by two independent syntheses from 2′,4-dimethoxychalcone (XIV) and



Reagents: 1, HCl–EtOH, then Me_2SO_4; 2, H_2–Ni; 3, Grignard reagent from *p*-bromoanisole.

from 2,4′-dimethoxychalcone (XV), as shown in the annexed scheme. In a similar way, 4′-methoxyflavan-4β-ol with an excess of 7-acetoxyflavan yielded, after methylation, a product which is thought to contain three flavan units.

EXPERIMENTAL

Light petroleum refers to the fraction of b. p. 40—60°. Alumina was Spence's grade H or O, deactivated, when stated, with acetic acid.

4-o-*Methoxyphenylflavan-4-ol*.—A solution of flavanone (1·20 g.) in ether (20 ml.) was added to *o*-methoxyphenylmagnesium bromide [from magnesium (0·26 g.) and *o*-bromoanisole (2·00 g.) in ether (20 ml.)], and the mixture was boiled for 3 hr. After decomposition with an excess of very dilute aqueous acetic acid, the product, which was insoluble in ether, was extracted into chloroform. Removal of the solvent gave colourless crystals which recrystallised from ether–chloroform (2 : 1 v/v) (60 ml.) to yield 4-o-*methoxyphenylflavan-4-ol* (1·45 g.) as needles, m. p. 207—209° (Found: C, 79·3; H, 6·0. $C_{22}H_{20}O_3$ requires C, 79·4; H, 6·0%), $\nu_{max.}$ (in Nujol) 3480 cm.$^{-1}$ (OH).

4-o-*Methoxyphenylflavan*.—4-*o*-Methoxyphenylflavan-4-ol (0·45 g.) in "AnalaR" acetic acid (25 ml.) was boiled with toluene-*p*-sulphonic acid (10 mg.) for 4 hr. The resulting solution was hydrogenated over Adams catalyst (uptake 34·8 ml. at 20°/750 mm., theor.; 4 hr.). After removal of the catalyst and the solvent, the product was chromatographed (30 g. of grade H alumina). Elution with light petroleum–benzene (1 : 1) (350 ml.) gave an oil which, after several crystallisations from ethanol, yielded 4-o-*methoxyphenylflavan* (0·13 g.) as needles, m. p. 108—109° (Found: C, 83·1, 83·2; H, 6·2, 6·4. $C_{22}H_{20}O_2$ requires C, 83·5; H, 6·3%), $\nu_{max.}$ (in Nujol) 700, 758, and 778 cm.$^{-1}$ (aromatic).

4-p-*Methoxyphenylflavan* (II; R = H, R′ = Me).—(*a*) (i) 4-*p*-Methoxyphenylflavan-4-ol (IV; R = H, R′ = Me). *p*-Bromoanisole (1·50 g.), ether (20 ml.), and magnesium (0·24 g.) were heated until the magnesium had dissolved (2 hr.). Flavanone (1·13 g.) in ether (20 ml.) was added with stirring at 0° and the mixture was boiled for 30 min. The Grignard complex was decomposed at 0° with 10% aqueous acetic acid (20 ml.), and the product (1·66 g.), isolated with ether, was chromatographed (30 g. of 10% deactivated grade H alumina). Elution with light petroleum (100 ml.) gave a mixture (150 mg.) of anisole and unchanged *p*-bromoanisole.

Elution with benzene (200 ml.) gave 4-p-*methoxyphenylflavan*-4-*ol* (1·10 g.), needles, m. p. 116—117° (from ethanol) (Found: C, 79·15; H, 6·0. $C_{22}H_{20}O_3$ requires C, 79·4; H, 6·0%), $\nu_{max.}$ (in Nujol) 3470 cm.$^{-1}$ (OH).

(ii) A solution of 4-*p*-methoxyphenylflavan-4-ol (1·00 g.) in "AnalaR" acetic acid (30 ml.) was boiled with toluene-*p*-sulphonic acid (10 mg.) for 2 hr. The resulting deep yellow solution was hydrogenated over Adams catalyst (uptake 60 ml. at 20°/762 mm.; theor., 79 ml.). Removal of the catalyst and solvent gave a yellow oil which was chromatographed (60 g. of 10% deactivated grade H alumina). Elution with light petroleum–benzene (1 : 1) (350 ml.) gave 4-p-*methoxyphenylflavan* (0·48 g.), colourless needles (from ethanol), m. p. 134—135° (Found: C, 83·2; H, 6·0. $C_{22}H_{20}O_2$ requires C, 83·5; H, 6·3%), $\nu_{max.}$ (in Nujol) 701, 757, and 834 cm.$^{-1}$ (aromatic).

(*b*) Dry hydrogen chloride was passed for 15 min. through a solution of flavan-4β-ol (0·81 g.) and phenol (1·25 g.) in ethanol (25 ml.) at 0°. After 20 days at room temperature, the mixture was poured into water (700 ml.), and the precipitated solid (1·09 g.) was collected, washed with water, and methylated with dimethyl sulphate and aqueous sodium hydroxide. The product, isolated in ether, was chromatographed [40 g. of grade O alumina with light petroleum–benzene (1 : 1) as eluant] to yield, from the first fraction (120 ml.), a solid (0·20 g.) which separated from ethanol or light petroleum (b. p. 88—90°) as prisms, m. p. 195—197° (Found: C, 83·6; H, 6·45. $C_{22}H_{20}O_2$ requires C, 83·5; H, 6·3%), $\nu_{max.}$ (in Nujol) 700, 753, and 784 cm.$^{-1}$ (aromatic).

The second fraction (720 ml., followed by 480 ml. of chloroform) gave an oil (0·86 g.) which separated from ethanol as needles, m. p. 134—136°. This compound was identical with 4-*p*-methoxyphenylflavan (mixed m. p. and infrared comparison) prepared as in (*a*).

4-(2,4-*Dihydroxyphenyl)flavan* (II; R = OH, R′ = H).—Flavan-4β-ol (0·80 g.) and resorcinol (1·33 g.) in ethanol (25 ml.) were treated with hydrogen chloride in the usual way. After 12 days, addition of excess of water gave a solid (A) (1·22 g.). This solid (0·40 g.) was boiled with acetic anhydride (15 ml.) and sodium acetate (1·00 g.) for 2 hr., then poured into water (80 ml.), and the resulting solid chromatographed (20 g. of 10% deactivated grade O alumina). Elution with light petroleum–benzene (1 : 1) (120 ml.) yielded 4-(2,4-*diacetoxyphenyl)flavan* which separated from ethanol as needles (0·25 g.), m. p. 171—172° (Found: C, 74·4; H, 5·65; Ac, 22·0. $C_{25}H_{22}O_5$ requires C, 74·65; H, 5·45; 2Ac, 21·4%).

This acetate (34 mg.) was heated on a water bath for 2 min. with potassium hydroxide (200 mg.) in ethanol (10 ml.). The resulting red solution was diluted with water (20 ml.) and, on cooling, yielded plates. Two recrystallisations from aqueous ethanol gave 4-(2,4-*dihydroxyphenyl)flavan hydrate*, m. p. 95—98° (Found: C, 73·45; H, 6·25. $C_{21}H_{18}O_3,1·5H_2O$ requires C, 73·05; H, 6·1%).

The solid (A) (0·82 g.) was methylated with dimethyl sulphate and aqueous potassium hydroxide. Chromatography of the product on alumina (grade O) with light petroleum–benzene (1 : 1) as eluant gave 4-(2,4-*dimethoxyphenyl)flavan* (0·33 g.) which separated from ethanol or light petroleum (b. p. 88—90°) as prisms, m. p. 159—160° (Found: C, 80·05; H, 6·55. $C_{23}H_{22}O_5$ requires C, 79·75; H, 6·35%), $\lambda_{max.}$ (in EtOH) 224·5, 277, and 283·5 mμ (log ε 4·34, 3·72, and 3·71).

7″-*Acetoxy*-4,6″-*biflavanyl* (V).—Flavan-4β-ol (0·50 g.) and 7-hydroxyflavan (0·50 g.) in ethanol (25 ml.) were treated with hydrogen chloride in the usual way. After 11 days, water (500 ml.) was added and the product was boiled with acetic anhydride (32 ml.) and fused sodium acetate (2·0 g.). The resulting crude acetoxy-compound was purified by chromatography (45 g. of 10% deactivated grade O alumina). Elution with light petroleum–benzene (1 : 1) (120 ml.) yielded the *biflavanyl* (0·62 g.) which separated from ethanol as prisms, m. p. 128—130° [Found: C, 80·9; H, 5·65; Ac, 8·9%; *M* (Rast), 463. $C_{32}H_{28}O_4$ requires C, 80·6; H, 5·9; 1Ac, 9·05%; *M*, 476), $\lambda_{max.}$ (in EtOH) 276·5 and 283·5 mμ (log ε 3·70 and 3·72).

4-(2,4-*Dimethoxyphenyl)flavan*-3-*ol* (VII; R = H, R′ = Me).—A solution of flavan-3,4-diol [5] (1·90 g.) and resorcinol (1·90 g.) in ethanol (50 ml.) was saturated with hydrogen chloride at room temperature. After 7 days, water (250 ml.) was added and the product was extracted into ether. The extract was washed free from resorcinol with water and then shaken with 2N-sodium hydroxide (5 × 5 ml.). The alkaline extract was acidified and the condensation product (isolated in ether) was methylated with dimethyl sulphate and anhydrous potassium carbonate in refluxing acetone. The methylated product (0·80 g.) was purified by chromatography (160 g. of 10% deactivated grade O alumina). Elution with light petroleum containing

[5] Bognár and Rákosi, *Acta Chim. Acad. Sci. Hung.*, 1958, **14**, 369.

benzene (increasing from 5% to 50%) gave a solid (0·40 g.). Sublimation at 150°/0·01 mm. gave 4-(2,4-*dimethoxyphenyl)flavan*-3-*ol* as a colourless amorphous solid, m. p. 61—62·5° (Found: C, 76·4; H, 6·2. $C_{23}H_{22}O_4$ requires C, 76·1; H, 6·1%), $\nu_{max.}$ (in Nujol) 3450 cm.$^{-1}$ (OH). Treatment with pyridine and acetic anhydride, followed by chromatography (5% deactivated grade O alumina with light petroleum as eluant) gave 3-*acetoxy*-4-(2,4-*dimethoxyphenyl)flavan* which separated from acetone as plates, m. p. 70—71° (Found: C, 73·85; H, 6·2; Ac, 10·1. $C_{25}H_{24}O_5$ requires C, 74·2; H, 6·0; 1Ac, 10·65%), $\nu_{max.}$ (in Nujol) 1730 cm.$^{-1}$ (aliphatic ester).

4-(2,4,6-*Trimethoxyphenyl)flavan*-3-*ol* (VII; R = OMe, R′ = Me).—A solution of flavan-3,4-diol (1·00 g.) and phloroglucinol (1·00 g.) in ethanol (25 ml.) was treated at 30° with hydrogen chloride until a 10% increase in weight had occurred. After 21 days at room temperature, the product was isolated and methylated in the usual way to give an oil which was chromatographed (150 g. of 10% deactivated grade H alumina). Elution with light petroleum–benzene (1 : 1) (250 ml.) and benzene (350 ml.) gave an oil which separated from ether to yield 4-(2,4,6-*trimethoxyphenyl)flavan*-3-*ol* (0·44 g.) as needles, m. p. 164—165° (Found: C, 73·5; H, 6·5. $C_{24}H_{24}O_5$ requires C, 73·5; H, 6·1%). Its *acetate* separated from ether as prisms, m. p. 168—169° (Found: C, 71·9; H, 6·1; Ac, 9·6. $C_{26}H_{26}O_6$ requires C, 71·9; H, 6·0; 1Ac, 9·9%).

1-o-*Methoxyphenyl*-1,3,3-*tri*-p-*methoxyphenylpropane* (IX).—(*a*) (i) 2′-Hydroxy-4-methoxychalcone [6] (6·00 g.) with boiling acetone (200 ml.), dimethyl sulphate (12·0 ml.), and anhydrous potassium carbonate (10·5 g.) yielded the 2′,4-*dimethoxychalcone* (XIV) (4·90 g.), light yellow needles (from ethanol), m. p. 68—69° (Found: C, 76·1; H, 6·15; OMe, 22·8. $C_{17}H_{16}O_3$ requires C, 76·1; H, 5·95; 2OMe, 23·1%).

50% w/w Aqueous sodium hydroxide (6·50 g.) was added to a warm solution of *o*-methoxyacetophenone (3·10 g.) and *p*-anisaldehyde (3·70 ml.) in ethanol (35 ml.). After 4 hr., an excess of water was added and the product was isolated with ether and crystallised from ethanol to give 2′,4-dimethoxychalcone (5·50 g.) as needles, m. p. 68—69°, unchanged on admixture with the product obtained as described above.

A solution of 2′,4-dimethoxychalcone (0·43 g.) and 2,4-dinitrophenylhydrazine (0·30 g.) in ethanol (35 ml.) was treated with concentrated hydrochloric acid at the b. p. The red needles (0·60 g.) which separated in the cold were recrystallised from ethanol–chloroform (1 : 2) to give the 2,4-*dinitrophenylhydrazone*, m. p. 224—225° (Found: C, 61·6; H, 4·6; N, 12·9. $C_{23}H_{20}O_6N_4$ requires C, 61·6; H, 4·45; N, 12·5%), $\lambda_{max.}$ (in $CHCl_3$) 425 mμ (log ε 4·59).

(ii) 2′,4-Dimethoxychalcone (1·92 g.) in ether (100 ml.) was added at −10° to the Grignard reagent prepared from *p*-bromoanisole (10·0 g.), ether (90 ml.), and magnesium (1·3 g.) at such a rate that no permanent precipitate was formed. After 4 hr. at room temperature, the Grignard complex was decomposed with dilute acetic acid, and the product was isolated by using ether. Chromatography on alumina (200 g. of 5% deactivated grade H) and elution with benzene (600 ml.) gave a solid (1·60 g.) which separated from ethyl acetate–hexane to yield colourless needles of 2,2-*di*-p-*methoxyphenylethyl* o-*methoxyphenyl ketone* (XII), m. p. 108—108·5° (Found: C, 76·5, 76·4; H, 6·15, 6·6. $C_{24}H_{24}O_4$ requires C, 76·55; H, 6·4%), $\nu_{max.}$ (in Nujol) 1670 cm.$^{-1}$.

(iii) The ketone (XII) (7·00 g.) in tetrahydrofuran (90 ml.) was treated at 0° with the Grignard reagent prepared from *p*-bromoanisole (20 g.), tetrahydrofuran (150 ml.), and magnesium (4·3 g.). After 12 hr. at room temperature, the solution was boiled under reflux for 1 hr. and cooled to 0°. The Grignard complex was decomposed with dilute acetic acid, and the product isolated, by using ether, as an oil (8·2 g.) which was chromatographed on alumina (500 g. of 5% deactivated grade H). Elution with light petroleum–benzene (1 : 4 v/v) (2 l.) gave 1-o-*methoxyphenyl*-1,3,3-*tri*-p-*methoxyphenylprop*-1-*ene* (X), m. p. 45—47°, which was sublimed before analysis (Found: C, 79·9; H, 6·6. $C_{31}H_{30}O_4$ requires C, 79·65; H, 6·4%), $\lambda_{max.}$ (in EtOH) 270 mμ (log ε 4·28).

(iv) The propene (X) (0·80 g.) in ethanol (100 ml.) was hydrogenated at 60°/25 atm. for 4 hr. over Raney nickel (1·0 g.). Removal of solvent and catalyst gave an oil which was chromatographed on alumina (100 g. of 5% deactivated grade H). Elution with benzene (200 ml.) gave a solid (0·69 g.) which, after several recrystallisations from ethanol–benzene and from light petroleum–benzene, yielded 1-o-*methoxyphenyl*-1,3,3-*tri*-p-*methoxyphenylpropane* (IX), m. p. 108—110° (Found: C, 79·7; H, 6·6. $C_{31}H_{32}O_4$ requires C, 79·5; H, 6·8%), $\lambda_{max.}$ (in EtOH) 228·5 and 277 mμ (log ε 4·54 and 3·85), $\nu_{max.}$ (in Nujol) 725, 760, and 840 cm.$^{-1}$ (aromatic).

---

[6] Karrer, Yen, and Reichstein, *Helv. Chim. Acta*, 1930, **13**, 1308.

(*b*) (i) The same conditions and quantities were used as in the preparation of 2,2-di-*p*-methoxyphenylethyl *o*-methoxyphenyl ketone, but from 2,4′-dimethoxychalcone. Chromatography as before and elution with benzene (400 ml.) gave a light yellow solid which from ethanol yielded colourless needles (2·33 g.) of p-*methoxyphenyl* 2-o-*methoxyphenyl*-2-p-*methoxyphenylethyl ketone* (XIII), m. p. 67—68° (Found: C, 76·3, 76·7; H, 6·8, 6·45. $C_{24}H_{24}O_4$ requires C, 76·55; H, 6·4%), $\nu_{max.}$ (in Nujol) 1660 cm.$^{-1}$.

(ii) The ketone (XIII) (1·00 g.) was added at 0° to the Grignard reagent prepared from *p*-bromoanisole (5·0 g.), tetrahydrofuran (30 ml.), and magnesium (1·07 g.). After 1 hr. at room temperature, the solution was boiled under reflux for 1 hr. and cooled to 0°. The Grignard complex was decomposed with dilute acetic acid, and the product was isolated in ether. Removal of the ether and anisole (formed from excess of the Grignard reagent) under reduced pressure gave an oil (1·20 g.) which was chromatographed on alumina (50 g. of grade H). Elution with light petroleum–benzene (1 : 8) (100 ml.) gave 3-o-*methoxyphenyl*-1,1,3-*tri*-p-*methoxyphenylprop*-1-*ene* (XI), m. p. 47—48°, which was sublimed before analysis (Found: C, 79·25; H, 6·4. $C_{31}H_{30}O_4$ requires C, 79·65; H, 6·4%), $\lambda_{max.}$ (in EtOH) 268 mμ (log ε 4·29).

(iii) The above propene (XI) (0·60 g.) in ethanol (100 ml.) was hydrogenated at 60°/40 atm. for 4 hr. over Raney nickel (1·00 g.). Removal of the solvent and catalyst gave a solid which was chromatographed on alumina (50 g. of grade H). Elution with benzene (150 ml.) gave a solid (0·43 g.). Several crystallisations from benzene–ethanol (1 : 3) gave 1-*o*-methoxyphenyl-1,3,3-tri-*p*-methoxyphenylpropane (IX), m. p. and mixed m. p. 107—110° (Found: C, 79·9; H, 6·6%). The infrared and ultraviolet spectra were identical with those of the other synthetic specimen.

(*c*) A solution of 4′-methoxyflavan-4β-ol [7] (1·00 g.) and phenol (2·00 g.) in ethanol (25 ml.) was treated at 0° with hydrogen chloride until a 10% increase in weight had occurred. After 14 days at room temperature, the solution was worked up and methylated in the usual way. The product (1·80 g.) was chromatographed on 10% deactivated grade O alumina. Elution with light petroleum–benzene (3 : 1) gave an oil (0·15 g.) which was not investigated further. Elution with light petroleum–benzene (1 : 9) yielded a solid (1·40 g.). Several recrystallisations from ethanol gave the propane, m. p. and mixed m. p. 107—108° (Found: C, 79·8; H, 6·5%). The infrared and ultraviolet spectra were identical with those of the other specimens.

Condensation of 4′-*Methoxyflavan*-4β-*ol with* 7-*Acetoxyflavan.*—7-Acetoxyflavan (5·00 g.) and 4′-methoxyflavan-4β-ol (1·50 g.) in ethanol (30 ml.) were treated at 0° with hydrogen chloride (5% increase in weight). After 17 days at room temperature, water (250 ml.) was added and a salmon-pink solid separated. Methylation with dimethyl sulphate and potassium carbonate in acetone gave a solid (2·25 g.) which was chromatographed on 10% deactivated grade O alumina (150 g.). Elution with light petroleum–benzene (1 : 1) (800 ml.) gave a solid (1·60 g.), m. p. 140—142°. Crystallisation from a variety of solvents did not change the m. p. The *compound* separated from methanol as an amorphous white powder, m. p. 141·5—142·5° [Found: C, 78·6; H, 6·4; *M* (Rast), 802. $C_{49}H_{48}O_6,CH_3{\cdot}OH$ requires C, 78·5; H, 6·6%; *M*, 764], $\nu_{max.}$ (in $CHCl_3$) 3550w (OH).

We thank the D.S.I.R. for a maintenance grant (to W. C.).

Dyson Perrins Laboratory,
The University, Oxford.

[*Received, April* 4*th,* 1961.]

---

[7] Bokadia, Brown, and Cummings, *J.*, 1960, 3308.