872. *Polymerisation of Flavans. Part II.* The Condensation of 4′-Methoxyflavan with Phenols.*

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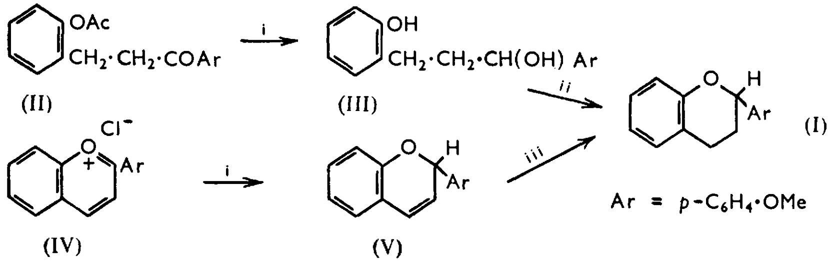
4′-Methoxyflavan condenses with phenol or resorcinol in the presence of hydrogen chloride in ethanol, and it has been proved that the heterocyclic ring of the flavan opens in this process. Condensation of 4′-methoxyflavan with 7-hydroxyflavan yields a compound containing two flavan units whose structure is based upon the known *para*-orientation of these reactions.

In Part I * an approach was made towards elucidation of the polymerisation of flavans under the influence of acids. As a result it is known that *p*-hydroxybenzyl alcohols and related compounds condense with phenols preferentially at a position *para* to a hydroxyl group. Also it has been shown [1, 2] that benzyl ethers rearrange in the presence of hydrogen chloride to yield diphenylpropanes. Thus the mechanism first advanced by Freudenberg and Maitland [3] for the acid polymerisation of flavans is seen to be plausible, and Freudenberg and de Lama [1] isolated, after reaction of catechin with hydrogen chloride in dioxan, a compound (as its polyacetate) which they claim to be a catechin dimer. By using simpler flavans than catechin it has been our aim to discover whether they condense with phenols in presence of acid, and to synthesise a compound of known structure containing two flavan units.



Reagents: i, $LiAlH_4$; ii, HCl–MeOH; iii, H_2–Raney Ni.

The new compound 4′-methoxyflavan (I) was chosen as the simplest flavan whose heterocyclic ring could be expected to open under the influence of acids. It was prepared by two routes. Reduction of β-*o*-acetoxyphenyl-*p*-methoxypropiophenone (II) with lithium aluminium hydride and ring closure [4] of the resulting alcohol (III) gave the flavan (I) in 61% yield (from salicylaldehyde and *p*-methoxyacetophenone). By reduction of the flavylium chloride (IV) with lithium aluminium hydride and hydrogenation of the flaven (V), an overall yield of 54% (from salicylaldehyde and *p*-methoxybenzaldehyde) has been obtained. In agreement with Elstow and Platt [5] we found this method of flavan synthesis to be superior to the direct hydrogenation of a flavylium chloride,[6] though the hydrogenation of flavylium perchlorates is more satisfactory.[1, 7] It is of interest that the flaven (V) has the same melting point (123°) as the compound obtained by Kulkarni and Shah [8] from the hydrogenolysis of 4′-methoxyflavone with lithium aluminium hydride. Although the products of reduction of flavylium salts by lithium aluminium hydride have

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* Part I, *J.*, 1957, 3757.

[1] Freudenberg and de Lama, *Annalen*, 1958, **612**, 78.

[2] von Braun and Reich, *ibid.*, 1925, **445**, 225.

[3] Freudenberg and Maitland, *ibid.*, 1934, **510**, 193.

[4] Harries and Busse, *Ber.*, 1896, **29**, 380.

[5] Elstow and Platt, *Chem. and Ind.*, 1950, 824.

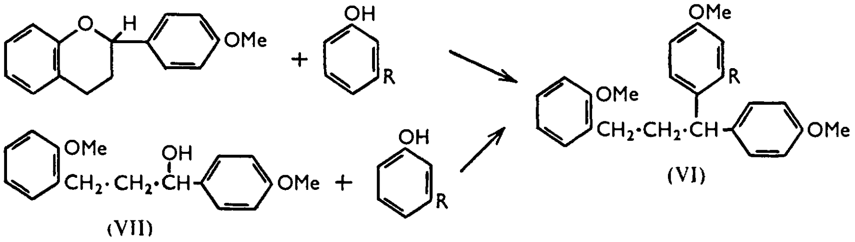
[6] Freudenberg, Stocker, and Porter, *Chem. Ber.*, 1957, **90**, 957.

[7] Brown and Somerfield, unpublished work.

[8] Kulkarni and Shah, *Current Sci.*, 1953, **22**, 339.

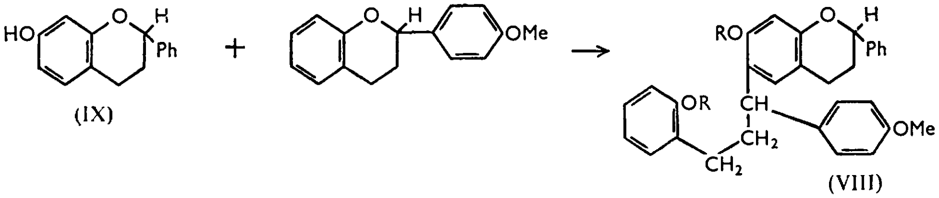
not been rigorously proved to be Δ^3-flavens, this would seem to be the most likely structure.[9,10] Thus Kulkarni and Shah's product may be a Δ^3-flaven, for the migration of double bonds during reduction of αβ-unsaturated ketones with lithium aluminium hydride and aluminium chloride is known to occur in certain circumstances.[11]

Under the influence of hydrogen chloride in ethanol the heterocyclic ring of 4'-methoxyflavan opens and reaction occurs with phenol or resorcinol. After methylation the triarylpropanes (VI; R = H and OMe) were obtained. The alcohol (VII) condenses with phenol to yield, after methylation, a propane (VI; R = H) identical with that resulting from 4'-methoxyflavan and phenol, proving that the oxygen ring of the flavan opens in the reaction. By analogy with previous proved examples[12] it is inferred that the condensation has occurred at a position *para* to a phenolic hydroxyl group.



Reagents: HCl–EtOH, then methyln.

Reaction of 4'-methoxyflavan with a hydroxyflavan whose heterocyclic ring is incapable of fission under the conditions used should yield a compound (VIII), analogous to the catechin dimer of Freudenberg and de Lama,[1] containing two flavan units. To this end 7-hydroxyflavan (IX) has been used and acetylation of the product has yielded a diacetate (VIII; R = Ac). The methoxyl analysis of this compound agrees with that expected for a structure containing two flavan units, and its other structural features follow from the previous condensations.



Under the same conditions 4'-methoxyflavan and flavan itself do not react, presumably because flavan is not sufficiently reactive towards electrophilic reagents of the kind produced by acid fission of the flavan ring.[13]

EXPERIMENTAL

The alumina used was Spence Grade 0; acetic acid was used for deactivation. Light petroleum refers to the fraction of b. p. 30—40° unless otherwise stated.

2 : *4'-Dimethoxychalcone*.—(*a*) A mixture of *o*-methoxybenzaldehyde (5·0 g.), *p*-methoxyacetophenone (5·5 g.), ethanol (30 ml.), and 10% aqueous sodium hydroxide (6·0 ml.) was kept at room temperature for 1 hr., then diluted with water, and the resulting solid crystallised from ether–light petroleum. The *chalcone* (8·5 g.) separated as pale yellow needles, m. p. 44—45° (Found: C, 76·2; H, 6·1. $C_{17}H_{16}O_3$ requires C, 76·1; H, 5·95%).

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[9] Karrer and Seyhan, *Helv. Chim. Acta*, 1950, **33**, 2209.
[10] Freudenberg and Weinges, *Annalen*, 1954, **590**, 140.
[11] Brown *et al.*, unpublished work.
[12] Brown, Cummings, and Somerfield, *J.*, 1957, 3757.
[13] Cf. ref. 10.

(*b*) 2-Hydroxy-4′-methoxychalcone [14] (2·2 g.) was treated with dimethyl sulphate (1·5 ml.) and 10% aqueous sodium hydroxide (4·0 ml.). The chalcone was isolated by means of ether and purified on alumina. Elution with benzene and crystallisation from ether–light petroleum gave pale yellow needles (1·8 g.), m. p. and mixed m. p. 44—45°.

The *dinitrophenylhydrazone* separated from chloroform as orange needles, m. p. 244° (decomp.) (Found: C, 61·75; H, 4·6; N, 12·3. $C_{23}H_{20}O_6N_4$ requires C, 61·6; H, 4·45; N, 12·5%), $\lambda_{max.}$ 4075 Å (log ε 4·56) in chloroform.

p-*Methoxy*-β-o-*methoxyphenylpropiophenone*.—2 : 4′-Dimethoxychalcone (4·15 g.) was hydrogenated in methanol at 20°/764 mm. on Adams catalyst (0·225 g.). The chalcone took up 380 ml. of hydrogen (theor. 370 ml.). Isolation in the usual way gave a colourless oil (3·95 g.) which yielded a *dinitrophenylhydrazone* as brick-red prisms, m. p. 205°, from chloroform–acetone (Found: C, 61·25; H, 4·8; N, 12·35. $C_{23}H_{22}O_6N_4$ requires C, 61·35; H, 4·9; N, 12·45%), $\lambda_{max.}$ 3940 Å (log ε 4·45) in chloroform.

3-o-*Methoxyphenyl*-1-p-*methoxyphenylpropan*-1-*ol* (VII).—The above compound (2·8 g.) was reduced in the usual way with lithium aluminium hydride in ether. The resulting colourless oil (2·8 g.) (whose infrared spectrum in Nujol contained a hydroxyl band at 3400 cm.$^{-1}$) yielded a 3 : 5-*dinitrobenzoate* which separated from acetone–methanol as pale yellow prisms, m. p. 141° (Found: C, 61·5; H, 4·45; N, 6·15. $C_{24}H_{22}O_8N_2$ requires C, 61·8; H, 4·7; N, 6·0%).

4′-*Methoxy*-Δ^3-*flaven* (V).—Dry powdered 4′-methoxyflavylium chloride [15] (hydrated salt, dried *in vacuo* over P_2O_5 for 4 days) (1·5 g.) was added to a slurry of lithium aluminium hydride (1·0 g.) in ether (50 ml.), and the mixture was boiled for 20 min. The complex was decomposed with wet ether, the alumina was washed with ether, and the combined ether extracts were dried and evaporated. Recrystallisation of the residual solid (1·0 g.) from ethanol gave 4′-*methoxy*-Δ^3-*flaven* as needles, m. p. 123° (Found: C, 81·05; H, 5·95. $C_{16}H_{14}O_2$ requires C, 80·7; H, 5·9%).

3-o-*Hydroxyphenyl*-1-p-*methoxyphenylpropan*-1-*ol* (III).—β-*o*-Acetoxyphenyl-*p*-methoxypropiophenone [16] (5·65 g.) was added to a slurry of lithium aluminium hydride (4·4 g.) in ether (250 ml.), and the mixture was boiled for 3 hr. Decomposition in the usual way and evaporation of the ether gave the *alcohol* as a solid (4·74 g.) which separated from aqueous methanol as needles, m. p. 118—119° (Found: C, 74·0; H, 7·15. $C_{16}H_{18}O_3$ requires C, 74·4; H, 6·95%).

4′-*Methoxyflavan* (I).—(*a*) 4′-Methoxyflaven (4·0 g.) in methanol (400 ml.) in presence of Raney nickel (12 g.) took up hydrogen (405 ml.) at 19°/750 mm. (theor. 407 ml.). Filtration and concentration to 20 ml. gave 4′-*methoxyflavan* (3·3 g.) which separated from methanol as plates, m. p. 83—84° (Found: C, 79·8; H, 6·65. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·65%).

(*b*) 3-*o*-Hydroxyphenyl-1-*p*-methoxyphenylpropan-1-ol (2·5 g.) in methanol (50 ml.) and concentrated hydrochloric acid (1·6 ml.) was boiled for 5 min. Addition of water gave 4′-methoxyflavan (2·2 g.) which separated from aqueous methanol as plates, m. p. 83—84°, unchanged on admixture with a specimen from (*a*) above. The ultraviolet spectrum of the flavan in ethanol had max. at 2265 (log ε 4·37), 2750 (log ε 3·60), and 2830 Å (log ε 3·55), and the infrared spectra of the two specimens were identical.

3-o-*Methoxyphenyl*-1 : 1-*di*-p-*methoxyphenylpropane* (VI; R = H).—(*a*) Dry hydrogen chloride was passed for 15 min. into a solution of 4′-methoxyflavan (0·50 g.) and phenol (0·60 g.) in ethanol (20 ml.). After 5 days at room temperature the mixture was poured into water (150 ml.), and the resulting oil isolated in ether. Methylation with dimethyl sulphate and alkali in the usual way yielded an oil which was passed in 2 : 3 v/v benzene–light petroleum (b. p. 40—60°) through alumina. After distillation at 160°/0·05 mm. the *propane* (0·30 g.) separated from light petroleum (b. p. 60—80°) as needles, m. p. 70—71° (Found: C, 79·3; H, 7·4. $C_{24}H_{26}O_3$ requires C, 79·55; H, 7·2%).

(*b*) 3-*o*-Methoxyphenyl-1-*p*-methoxyphenylpropan-1-ol (0·35 g.) was condensed with pheno and worked up as described in (*a*). The colourless oil (0·30 g.) from the column distilled at 170°/0·25 mm. to give a solid which separated from light petroleum as needles, m. p. and mixed m. p. 71—72°. The infrared spectra of the two specimens in Nujol were identical.

1-(2 : 4-*Dimethoxyphenyl*)-3-o-*methoxyphenyl*-1-p-*methoxyphenylpropane* (VI; R = OMe).—With resorcinol 4′-methoxyflavan (1·0 g.) gave the *propane* (1·1 g. after chromatography), b. p. 175°/0·05 mm. (Found: C, 76·15; H, 7·25. $C_{25}H_{28}O_4$ requires C, 76·5; H, 7·15%).

[14] Zwyaer and Kostanecki, *Ber.*, 1908, **41**, 1337.

[15] Kondo and Nakagawa, *J. Pharm. Soc. Japan*, 1930, **50**, 928.

[16] Harford and Hill, *J.*, 1937, 41.

7-Acetoxy-6-[1-(3-o-acetoxyphenyl-1-p-methoxyphenyl)propyl]flavan (VIII; R = Ac).—Dry hydrogen chloride was passed for 20 min. into a mixture of 4′-methoxyflavan (1·06 g.), 7-hydroxyflavan [17] (1·0 g.), and ethanol (75 ml.). The pale yellow solution was kept at room temperature for 8 days, then poured into water, and the product isolated by using ether. The resulting colourless oil was heated with acetic anhydride (30 ml.) and fused sodium acetate (1·0 g.) for 30 min. and poured into excess of water to yield a solid which was twice put through columns of 10% deactivated alumina and eluted with benzene, the initial eluates in 50% benzene–light petroleum being discarded. The solid *product* (1·35 g.) separated from ether–light petroleum as needles, m. p. 65—66° (Found: C, 76·0; H, 6·3; Ac, 14·65; OMe, 5·3, 5·5. $C_{35}H_{34}O_6$ requires C, 76·35; H, 6·2; 2Ac, 15·65; 1OMe, 5·65%), $\lambda_{max.}$ 2785 (log ε 3·68) and 2845 Å (log ε 3·67) in ethanol.

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[17] Robertson, Venkateswarlu, and Whalley, *J.*, 1954, 3137.