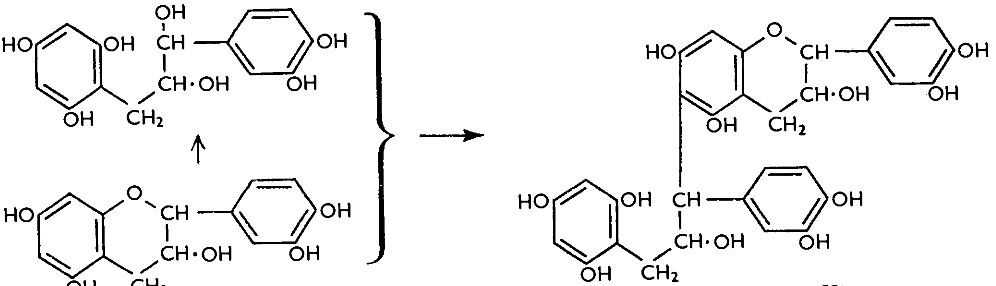
740. *Polymerisation of Flavans. Part I. The Condensation of Methoxybenzyl Alcohols with Phenols.*

By B. R. Brown, W. Cummings, and G. A. Somerfield.

4-Methoxybenzyl alcohol, *p*-methoxydiphenylmethanol, and 1-*p*-methoxyphenyl-3-phenylpropan-1-ol condense with ethyl acetoacetate, phenol, or resorcinol, and α-*p*-hydroxy- and α-*p*-methoxy-phenylphenethyl alcohol condense with resorcinol in presence of hydrogen chloride in ethanol. Condensation occurs *para* to a phenolic hydroxyl group and yields are in the range 20—70%. The bearing of the condensation on the polymerisation of catechin-like compounds to give tannins is discussed.

Commercial tannin extracts are complex mixtures of polyphenols, some of which may be polymerised flavans,[1] and some flavans polymerise readily in the presence of mineral acids to give products which have tanning properties.[2] A molecule as complex as catechin (I) may polymerise (*a*) by autoxidation and coupling,[3] (*b*) by the formation of ethers,[4] or (*c*) by a condensation involving the elimination of water,[5] (I) ⟶ (II). The latter mechanism was first postulated by Freudenberg and Maitland [5] over twenty years ago, but has never been tested on simpler compounds, though Freudenberg and Weinges [6] have made a survey of a series of flavans under conditions where all the above polymerisation mechanisms could have operated. To investigate this condensation we have used simple compounds related to the flavans; and, so that mechanism (*c*) would operate to the exclusion of (*a*) and (*b*), methoxy-compounds have been studied. This has the further advantage that experimental difficulties arising from the manipulation of polyphenols



(I) (II)

---

[1] White, Kirby, and Knowles, *J. Soc. Leather Trades' Chemists*, 1952, **36**, 148.

[2] *E.g.*, Etti, *Annalen*, 1877, **186**, 327.

[3] Hathway and Seakins, *Nature*, 1955, **176**, 218.

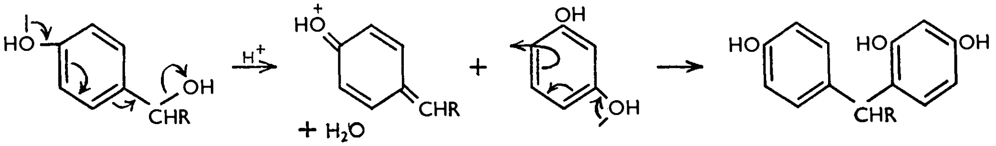
[4] Cf. Roux, *J. Soc. Leather Trades' Chemists*, 1950, **34**, 122.

[5] Freudenberg and Maitland, *Annalen*, 1934, **510**, 193.

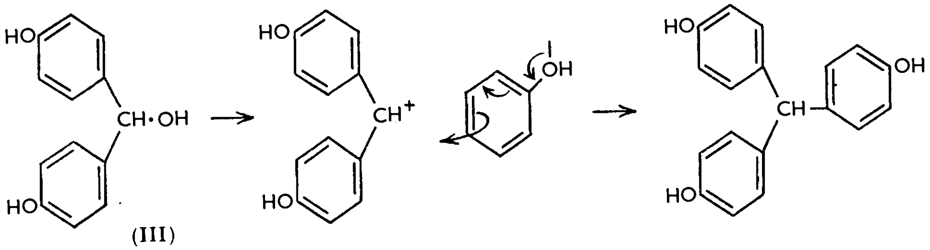
[6] Freudenberg and Weinges, *ibid.*, 1954, **590**, 140.

have been avoided, and this has been helped by the methylation of the condensation products. It has thus been possible to use chromatography on alumina for purification.

The activating influence of a *p*-hydroxyl group appears to be responsible for the attack of a benzyl alcohol on a nucleophilic centre in the presence of acid. Though this type of reaction has not been studied in the exact context presented here, there are sufficient analogies to indicate that such a reaction between simple hydroxy- or methoxy-benzyl alcohols and phenols would be possible. Thus Driver and Sousa [7] investigated the condensation of aromatic aldehydes with phenols and postulated a dihydroxy-intermediate (III) reacting as a carbonium ion. This type of reactivity has been studied in detail by Kenyon *et al.*[8] who have also shown that the simpler molecule *p*-methoxydiphenylmethanol is capable of such alkyl-oxygen fission, and that 2 : 4 : 6-trimethoxydiphenylmethanol condenses with phloroglucinol trimethyl ether in the presence of sulphuric acid. Fosse[9] and Baillon[10] have shown that *p*-methoxydiphenylmethanol readily condenses with malonic acid.



Our aim has been to establish that methoxybenzyl alcohols are capable of reacting as carbonium ions (*e.g.*, with ethyl acetoacetate), and that they are capable of condensing with phenols. A series of benzyl alcohols has been investigated, culminating with alcohols containing the skeleton C_6–C_3–C_6 which is found in the catechin-like molecules that are known to polymerise under acid conditions. It is hoped that the results will be of use in the investigation of the vegetable tannins themselves, and that the method will prove useful for the synthesis of tannin-like molecules by a controlled stepwise procedure.



(III)

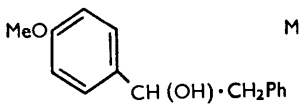
The condensations have all been carried out in ethanolic hydrogen chloride at room temperature, and the yields for alcohols of the series C_6–C, C_6–C–C_6, and C_6–C_3–C_6 are between 20 and 70%. The alcohols of the C_6–C_2–C_6 series presented a difficulty in the ease with which they yielded stilbenes by dehydration in presence of acids. Thus α-*p*-methoxyphenylphenethyl alcohol (IV) yielded only the stilbene with ethanolic hydrogen chloride and ethyl acetoacetate or phenol. However, with the more reactive resorcinol a condensation product has been isolated. α-*p*-Hydroxyphenylphenethyl alcohol, the only phenolic alcohol studied, yields with resorcinol a condensation product **which** has been isolated as its tribenzoate.

The orientation of the condensation with phenol and resorcinol has been proved in several examples. 4-Methoxybenzyl alcohol and *p*-methoxydiphenylmethanol react at

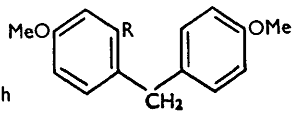
---

[7] Driver and Sousa, *J.*, 1954, 985.
[8] Kenyon *et al.*, *J.*, 1942, 605; 1951, 386; 1952, 790, 4964.
[9] Fosse, *Ann. Chim.* (*France*), 1920, **13**, 106.
[10] Baillon, *ibid.*, 1921, **15**, 63.

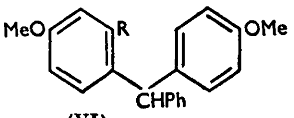
the *para*-position of phenol to yield after methylation the products (V; R = H) and (VI; R = H) whose identities have been established by comparison with specimens synthesised by known methods. Condensation of the same two alcohols with resorcinol occurs in the 4-position to yield after methylation the ethers (V; R = OMe) and (VI; R = OMe). 2 : 4 : 4′-Trimethoxydiphenylmethane (V; R = OMe) was identified by comparison with a specimen synthesised by the hydrogenolysis of 2 : 4 : 4′-trimethoxybenzophenone with aluminium chloride and lithium aluminium hydride,[11] and 2 : 4 : 4′-trimethoxytriphenylmethane (VI; R = OMe) was obtained from the same ketone by a Grignard synthesis followed by reduction of the alcohol. Thus in these examples the condensation has taken place preferentially in the *para*-position to a hydroxyl group, and this orientation has been assumed in the other products.



(IV)



(V)



(VI)

EXPERIMENTAL

The light petroleum was of b. p. 40—60° unless otherwise stated.

4-*Methoxyphenethyl Methyl Ketone*.—Dry hydrogen chloride was passed through a solution of 4-methoxybenzyl alcohol (1·0 g.) in ethyl acetoacetate (10 ml.) for 15 min., during which the temperature rose to 50—60°. After 30 min. at room temperature, the mixture was heated at 90° for 10 min., and added to a solution of potassium hydroxide (10 g.) in ethanol (80 ml.). This mixture was boiled under reflux for 1½ hr., then poured into water (400 ml), and the ketone extracted in ether. Evaporation yielded the crude ketone (0·45 g.) as a pale brown oil. The semicarbazone separated from methanol as colourless needles, m. p. 168—169°. Strauss and Grindel[12] record m. p. 169—170°. The 2 : 4-*dinitrophenylhydrazone* separated from ethanol as orange needles, m. p. 141—142° (Found, in material dried at 80°/10 mm. for 4 hr.: C, 57·2; H, 4·8; N, 15·3. $C_{17}H_{18}O_5N_4$ requires C, 57·0; H, 5·0; N, 15·6%).

4 : 4′-*Dimethoxydiphenylmethane*.—Dry hydrogen chloride was passed for 10 min. into a solution of 4-methoxybenzyl alcohol (1·0 g.) and phenol (1·0 g.) in ethanol (10 ml.). After 7 days at room temperature the mixture was poured into excess of water, the orange oil extracted with ether, and the ethereal solution washed with water to remove phenol. Evaporation yielded a red oil which was dissolved in 10% aqueous sodium hydroxide (40 ml.) and treated gradually with an excess (5·0 ml.) of methyl sulphate. The methylation was completed at 100° (30 min.) and the product extracted from the cold mixture with ether. The oil obtained on evaporation was dissolved in benzene (3·0 ml.) and put on a column of alumina. Elution with light petroleum (350 ml.) and evaporation yielded colourless plates (0·47 g.), m. p. and mixed m. p. 51—52°.

2 : 4 : 4′-*Trimethoxydiphenylmethane*.—An experiment identical with that recorded above, but with resorcinol (1·0 g.) in place of phenol, yielded a pale yellow oil (0·51 g.) on evaporation of the light petroleum eluate. Distillation at 120—130°/0·02 mm. gave 2 : 4 : 4′-trimethoxydiphenylmethane as a colourless viscous oil (Found: C, 74·5; H, 7·3. Calc. for $C_{16}H_{18}O_3$: C, 74·5; H, 7·0%). A comparison of b. p.s and infrared spectra proved the compound to be identical with a sample produced by hydrogenolysis of 2 : 4 : 4′-trimethoxybenzophenone.[11]

α-4-*Methoxyphenylphenethyl Methyl Ketone*.—Dry hydrogen chloride was passed for 5 min. through a solution of *p*-methoxydiphenylmethanol (0·50 g.) in ethyl acetoacetate (5·0 ml.), and the solution was kept at room temperature for 30 min. and then heated for 10 min. at 90°. The solution obtained by the addition of potassium hydroxide (5·0 g.) and ethanol (40 ml.) was boiled for 1 hr., then poured into excess of water. The precipitated yellow solid was crystallised twice from aqueous ethanol to yield the *ketone* (0·30 g.) as colourless prisms, m. p. 60—61°

---

[11] Brown and White, preceding paper.

[12] Strauss and Grindel, *Annalen*, 1924, **439**, 303.

(Found: C, 80·7; H, 7·2. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%). The 2 : 4-*dinitrophenylhydrazone* separated from methanol as yellow needles, m. p. 136—137° (Found: C, 63·55; H, 4·95. $C_{23}H_{22}O_5N_4$ requires C, 63·6; H, 5·05%).

4 : 4'-*Dimethoxytriphenylmethane*.—A solution of *p*-methoxydiphenylmethanol (1·0 g.) and phenol (1·0 g.) in ethanol (10 ml.) was treated with hydrogen chloride for 10 min. and kept at room temperature for 7 days. The mixture was poured into water (80 ml.) previously saturated with nitrogen, and the resulting white precipitate was extracted with ether, the ethereal layer washed with water to remove phenol, and the product removed by extraction with 10% aqueous sodium hydroxide (30 ml.). The alkaline solution was treated gradually with methyl sulphate (2·0 g.), methylation completed at 100° (20 min.), and the product extracted from the cold mixture with ether. Evaporation yielded a pale brown oil which was dissolved in benzene (2·0 ml.) and put on a column of alumina. Elution with light petroleum and evaporation yielded colourless crystals (0·47 g.). Recrystallisation from light petroleum gave 4 : 4'-dimethoxytriphenylmethane as colourless plates, m. p. and mixed m. p. 100·5—101·5° (Found: C, 83·05; H, 6·55. Calc. for $C_{21}H_{20}O_2$: C, 82·9; H, 6·6%).

2 : 4 : 4'-*Trimethoxytriphenylmethane*.—(a) *By condensation*. *p*-Methoxydiphenylmethanol (1·0 g.) and resorcinol (1·0 g.) in ethanol (10 ml.) was treated with hydrogen chloride for 10 min. and kept at room temperature for 2 days. The solution was poured into water (70 ml.; previously saturated with nitrogen) and the product isolated and methylated as previously described. The product in benzene (5·0 ml.) was put on a column of alumina and eluted with light petroleum (400 ml.) to yield a colourless oil (0·5 g.), which separated from light petroleum or alcohol as colourless crystals, m. p. 99—100° (Found: C, 79·6, 79·5; H, 6·6, 6·6. $C_{22}H_{22}O_3$ requires C, 79·05; H, 6·55%). Passage through a second column of alumina and crystallisation from light petroleum (b. p. 40—45°) yielded 2 : 4 : 4'-*trimethoxytriphenylmethane* as needles, m. p. 108—109° (Found: C, 78·9; H, 6·6%). The m. p. was unchanged on admixture of the compound with a specimen synthesised as described below.

(b) *By synthesis*. (i) 2 : 4 : 4'-Trimethoxytriphenylmethanol. The Grignard solution from bromobenzene (4·0 g.), magnesium (0·6 g.), and ether (15 ml.) was added at 0° to 2 : 4 : 4'-trimethoxybenzophenone (4·7 g.) in ether (150 ml.), and the reaction completed at 35° for 30 min. The usual method of isolation gave a red oil which was put on a column of alumina and eluted with 5 : 1 light petroleum–benzene to yield an oil (2·3 g.) which from light petroleum (b. p. 60—80°) gave 2 : 4 : 4'-*trimethoxytriphenylmethanol* as colourless needles, m. p. 109—110° (Found: C, 75·55; H, 6·25. $C_{22}H_{22}O_4$ requires C, 75·4; H, 6·3%). Elution of the column with 1 : 1 light petroleum–benzene gave unchanged 2 : 4 : 4'-trimethoxybenzophenone (2·2 g.), m. p. 69—71°.

(ii) 2 : 4 : 4'-Trimethoxytriphenylmethane. The above alcohol (0·4 g.) in ethanol (35 ml.) and concentrated hydrochloric acid (2·5 ml.) was boiled until the purple colour was discharged. Addition of water caused the triphenylmethane (0·2 g.) to separate, and recrystallisation from light petroleum gave colourless needles, m. p. 108—109° (Found: C, 79·4; H, 6·7%).

α-p-*Hydroxyphenylphenethyl Alcohol*.—To the Grignard solution from benzyl chloride (16·0 g.), magnesium (3·2 g.), and ether (70 ml.) was added a solution of *p*-hydroxybenzaldehyde (6·1 g.) in ether (125 ml.). The mixture was boiled under reflux for 20 min. and decomposed at 0° with dilute hydrochloric acid. The ether layer was washed with sodium hydrogen carbonate solution, sodium hydrogen sulphite solution, and finally water. Evaporation yielded the solid *alcohol* which separated from aqueous methanol as needles (2·2 g.), m. p. 157—158° (Found: C, 78·4; H, 6·6. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·55%). The *benzoate* separated from aqueous ethanol as hydrated needles, m. p. 87—88°, but from light petroleum (b. p. 60—80°) as colourless needles, m. p. 100—101° (Found: C, 79·8; H, 5·75. $C_{21}H_{18}O_3$ requires C, 79·3; H, 5·65%).

4-*Hydroxystilbene*.—A solution of the above alcohol in benzene was boiled for 5 min. in presence of a trace of hydrogen chloride. The cold solution deposited colourless plates which on recrystallisation from aqueous methanol had m. p. 187° (Found: C, 85·95; H, 6·2. Calc. for $C_{14}H_{12}O$: C, 85·7; H, 6·1%). Guss, Williams, and Jules [13] give m. p. 186—187·5°. The *benzoate* separated from acetone–ethanol as needles, m. p. 196° (Found: C, 83·6; H, 5·3. $C_{21}H_{16}O_2$ requires C, 84·0; H, 5·35%).

1-p-*Benzoyloxyphenyl*-1-(2 : 4-*dibenzoyloxyphenyl*)-2-*phenylethane*.—Dry hydrogen chloride was passed for 5 min. into a solution of α-*p*-hydroxyphenylphenethyl alcohol (0·40 g.) and resorcinol (0·25 g.) in ethanol (10 ml.). The solution was warmed to 70°, kept at room temperature for 3 days, and poured into water (60 ml.) to yield a sticky solid which was isolated by

---

[13] Guss, Williams, and Jules, *J. Amer. Chem. Soc.*, 1951, **73**, 1257.

means of ether, dissolved in aqueous sodium hydroxide, and shaken with excess of benzoyl chloride. The sticky solid which separated became a white solid on being boiled with ethanol, and two crystallisations from acetone–ethanol gave the *tribenzoate* (0·60 g.) as needles, m. p. 213—214·5° (Found: C, 79·95; H, 4·9. $C_{41}H_{30}O_6$ requires C, 79·6; H, 4·85%).

1-(2 : 4-*Dihydroxyphenyl*)-1-p-*methoxyphenyl*-2-*phenylethane*.—A solution of α-*p*-methoxyphenylphenethyl alcohol (0·7 g.) and resorcinol (0·4 g.) in ethanol (10 ml.) was treated with dry hydrogen chloride for 10 min. After a day at room temperature, the solution was poured into water, the resulting precipitate extracted with ether, and the ethereal layer washed with water to remove resorcinol. Evaporation of the ether yielded a pale orange, sticky solid which after several crystallisations from benzene gave the *ethane* (0·20 g.) as colourless prisms, m. p. 178—179° (Found, in material dried at 120°/0·1 mm. for 6 hr.: C, 78·7; H, 6·3. $C_{21}H_{20}O_3$ requires C, 78·8; H, 6·3%).

4-p-*Methoxyphenyl*-6-*phenylhexan*-2-*one*.—A solution of 1-*p*-methoxyphenyl-3-phenylpropan-1-ol (1·0 g.) in ethyl acetoacetate (10 ml.) was treated with dry hydrogen chloride for 30 min. After 15 min. at 100° the mixture was added to a solution of potassium hydroxide (10 g.) in ethanol (80 ml.) and boiled under reflux for 2 hr. The cold mixture was poured into excess of dilute hydrochloric acid, and the ketone extracted with ether. Evaporation yielded a brown oil which was dissolved in 4 : 1 light petroleum–benzene and put on a column of alumina. Elution with the same solvent mixture (350 ml.) and evaporation gave colourless crystals which were crystallised from light petroleum to yield 4-p-*methoxyphenyl*-6-*phenylhexan*-2-*one* (0·15 g.) as needles, m. p. 53—54° (Found: C, 80·8; H, 7·8. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·6%). The infrared spectrum showed a carbonyl band at 1709 cm.$^{-1}$. The dinitrophenylhydrazone was an oil.

1 : 1-*Di*-p-*methoxyphenyl*-3-*phenylpropane*.—A solution of 1-*p*-methoxyphenyl-3-phenylpropan-1-ol (1·0 g.) and phenol (1·0 g.) in ethanol (10 ml.) was treated with hydrogen chloride for 10 min. and kept at room temperature for 7 days. Isolation and methylation as usual yielded a brown oil which was dissolved in benzene (3·0 ml.), put on alumina, and eluted with light petroleum (500 ml.). Evaporation gave 1 : 1-*di*-p-*methoxyphenyl*-3-*phenylpropane* (0·89 g.) which separated from light petroleum as needles, m. p. 43—44·5° (Found: C, 83·5; H, 7·5. $C_{23}H_{24}O_2$ requires C, 83·1; H, 7·4%).

1-(2 : 4-*Dimethoxyphenyl*)-1-p-*methoxyphenyl*-3-*phenylpropane*.—An experiment identical with that described above but with resorcinol in place of phenol yielded, after methylation and chromatography, a pale yellow oil (0·175 g.). Distillation at 150—155°/0·01 mm. gave the *propane* as a colourless oil (Found: C, 80·0; H, 7·2. $C_{24}H_{26}O_3$ requires C, 79·6; H, 7·2%).

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.

[*Received, April* 23*rd*, 1957.]