The Synthesis of (±)-Pulvilloric Acid and of (±) Methyl Dihydropulvillorate *

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3,5-Dimethoxyphenylacetyl chloride has been converted into 1-(3,5-dimethoxyphenyl)heptan-2-one, and thence by demethylation into 1-(3,5-dihydroxyphenyl)heptan-2-one. Reduction of the latter with sodium borohydride, followed by carboxylation, gave (±)-1-(4-carboxy-3,5-dihydroxyphenyl)-heptan-2-ol. This reacted readily with ethyl orthoformate to give (±)-pulvilloric acid. Carboxylation of the (+)-heptan-2-ol followed by esterification with diazomethane and treatment with dimethoxymethane gave a very low yield of (±)-methyl dihydropulvillorate.

Several other compounds are described which were obtained during a study of alternative routes to the above heptan-2-one and heptan-2-ol.

THE structure (1), deduced for the mould metabolite pulvilloric acid on the basis of degradative studies[1] has now been confirmed by the synthetic work described below. Part of this work has been outlined in preliminary publications.[2,3]

The base-catalysed degradation of pullvilloric acid to the phenol (2; R = H) played an important role in the elucidation of the structure of the natural product and, as this phenol contains all but two of the carbon atoms of pulvilloric acid, its synthesis was a convenient intermediate objective for the synthesis of the acid itself. The first routes to the phenol (2; R = H) to be investigated all gave very low yields. These routes are described later in this Paper. Finally, a very satisfactory

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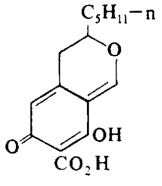
* This Paper is also regarded as Part LVII in the School of Pharmacy series on the Chemistry of Fungi. Part LVI, G. R. Birchall, K. Bowden, U. Weiss, and W. B. Whalley, *J. Chem. Soc.* (*C*), 1966, 2237.

[1] J. F. W. McOmie, A. B. Turner, and M. S. Tute, *J. Chem. Soc.* (*C*), 1966, 1608.

[2] B. K. Bullimore, J. F. W. McOmie, A. B. Turner, M. N. Galbraith, and W. B. Whalley, *Chem. Comm.*, 1966, 824.

[3] J. F. W. McOmie, M. S. Tute, A. B. Turner, and B. K. Bullimore, *Chem. and Ind.*, 1963, 1689.

synthesis of the phenol was devised. 3,5-Dimethoxyphenylacetic acid was treated with oxaloyl chloride and the resulting, unstable acid chloride was treated with the cadmium derivative of 1-bromopentane to give 1-(3,5-dimethoxyphenyl)-heptan-2-one (3; R = Me). This was demethylated in high yield by boiling it for 5 min., with pyridine hydrochloride. Reduction of the resorcinol (3; R = H) with sodium borohydride then gave the (±)-phenol (2; R = H) which had the same infrared spectrum as the (+)-phenol derived from pulvilloric acid. The phenol (2; R = H) was smoothly carboxylated by the Kolbe–Schmitt reaction to give the acid (2; R = CO_2H). This reaction is known to convert orcinol derivatives almost exclusively into the corresponding α-resorcylic acids.[4] The acid (2; R = CO_2H) reacted readily with ethyl orthoformate to yield (±)-pulvilloric acid (1) the infrared and ultraviolet spectra of which were identical with those of the natural product.



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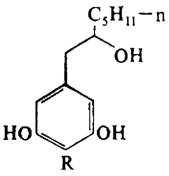

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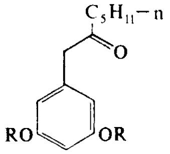

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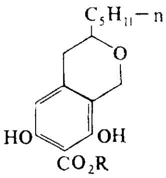

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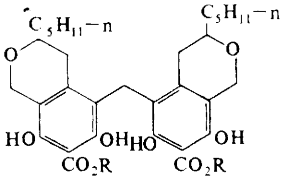

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Attempts to convert the acid (2; R = CO_2H) into dihydropulvilloric acid (4; R = H) by condensation with dimethoxymethane were unsuccessful, the diarylmethane (5; R = H) being formed instead (cf. ref. 5). In order to overcome the sparing solubility of the acid (2; R = CO_2H) in dimethoxymethane, the acid was esterified with diazomethane. The ester (2; R = CO_2Me) then condensed with dimethoxymethane to give a mixture of diarylmethane (5; R = Me) and methyl dihydropulvillorate (4; R = Me). The identity of this product with the material derived from natural pulvilloric acid by reduction and esterification was established by comparison of their infrared spectra and by mixed melting point. Owing to shortage of the synthetic phenol (2; R = H) this formal synthesis of methyl dihydropulvillorate was carried out using, as a relay, a sample of ester (2; R = CO_2Me) derived from the (+)-phenol (2; R = H). The conditions of the condensation with dimethoxymethane are such that racemisation would almost certainly have occurred [cf. the ready racemisation of the corresponding optically active phenol (6) derived from citrinin][6] and hence our product is considered to be (±)-methyl dihydropulvillorate.

As an alternate synthesis of the ketone (3; R = Me), 3,5-dimethoxybenzylcyanide was condensed with ethyl n-hexanoate to give 1-cyano-1-(3,5-dimethoxyphenyl)-heptan-2-one (67%) which, on acid hydrolysis, gave the desired ketone in only 17% yield; alkaline hydrolysis gave 3,5-dimethoxyphenylacetic acid.

Two routes for the preparation of 1-(3,5-dimethoxyphenyl)heptan-2-ol (7) were studied. In the first, 3,5-dimethoxybenzylmagnesium bromide was treated with n-hexanal and gave a mixture of orcinol dimethyl ether, the cyclic ether (8), 3,5,3′,5′-tetramethoxybibenzyl, and the alcohol (7) (12%). The formation of cyclic ethers by reaction of benzylmagnesium halides with aliphatic aldehydes has been observed previously.[7] When zinc was used in place of magnesium for this reaction (cf. ref. 8) the desired alcohol (7) was again the minor component (7%) of the mixture of products. The second route to the alcohol (7) involved the condensation of 3,5-dimethoxyphenylacetaldehyde with n-pentylmagnesium bromide. The phenylacetaldehyde was prepared by two methods after an attempt to reduce 3,5-dimethoxybenzyl cyanide with lithium triethoxyaluminohydride[9] had failed. In the first method, 3,5-dimethoxybenzyl cyanide was reduced by Stephen's method but the yield of aldehyde was only 8% although benzyl cyanide itself gives phenylacetaldehyde in 33% yield under the same conditions.[10] The second route to the phenylacetaldehyde proceeded *via* its lower homologue[11] which was made in 45% overall yield from 3,5-dimethoxybenzoic acid by the method of McFadyen and Stevens. 3,5-Dimethoxybenzaldehyde was condensed with ethyl chloroacetate in the presence of sodium ethoxide, to give the glycidic ester (9; R = Et) in 66% yield. Hydrolysis of this ester was conveniently achieved using sodium hydroxide in ethanol, and the sodium salt (9; R = Na) was isolated in 94% yield. When this salt was dissolved in dilute hydrochloric acid, and the resulting glycidic acid decarboxylated by warming the solution, the yield of 3,5-dimethoxyphenylacetaldehyde was 12—18%. The formation of an acidic by-product suggested that the yield of aldehyde was being reduced by some form of addition to the epoxide ring of the intermediate glycidic acid (9; R = H), rather than by dimerisation of the aldehyde itself.[12] While this work was in progress, Barash and Osbond[13] reported the formation of 3,4-dimethoxyphenyl acetaldehyde in 62% yield from sodium 3,4-dimethoxyphenylglycidate.

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[4] A. S. Lindsey and H. Jeskey, *Chem. Rev.*, 1957, **57**, 583.

[5] H. H. Warren, G. Dougherty, and E. S. Wallis, *J. Amer. Chem. Soc.*, 1949, **71**, 3422.

[6] N. J. Cartwright, A. Robinson, and W. B. Whalley, *J. Chem. Soc.*, 1949, 1563.

[7] S. Siegel, W. M. Boyer, and R. R. Jay, *J. Amer. Chem. Soc.*, 1951, **73**, 3237.

[8] M. Gaudemar, *Compt. rend.*, 1958, **246**, 1229.

[9] H. C. Brown, C. J. Shoaf, and C. P. Garg, *Tetrahedron Letters*, 1959, No. 3, 9.

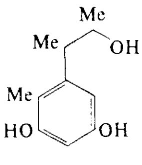
[10] J. W. Williams, *J. Amer. Chem. Soc.*, 1939, **61**, 2248.

[11] R. Adams, S. MacKenzie, and S. Loewe, *J. Amer. Chem. Soc.*, 1948, **70**, 664.

[12] W. A. Yarnall and E. S. Wallis, *J. Org. Chem.*, 1939, **4**, 270.

[13] M. Barash and J. M. Osbond, *J. Chem. Soc.*, 1959, 2157.

The salt was decomposed by heating it with aqueous oxalic acid in an atmosphere of nitrogen. This procedure was applied to the salt (9; R = Na) and resulted in a 37% yield of the phenylacetaldehyde. The latter was condensed with n-pentylmagnesium bromide, giving the alcohol (7) in 65% yield. The overall yield from 3,5-dimethoxybenzoic acid being 7%.



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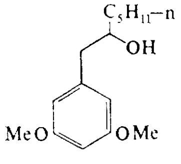

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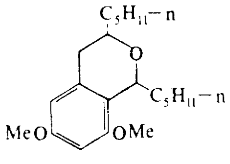

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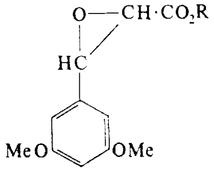

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Demethylation of the alcohol (7) was first achieved using the hydriodic acid method of Cartwright *et al.*[14] The yield of the phenol (2; R = H) was 11%, with 70% of the starting material being recovered. However, several repetitions of the demethylation under identical conditions, gave only a 0—10% yield of the phenol (2; R = H), and there was much decomposition. As any increase in the length of the reflux period was detrimental, other methods of demethylation were tried. Use of boron tribromide[15] likewise gave low and not always reproducible yields (see Experimental section) while the use of pyridine hydrochloride was completely unsuccessful.

EXPERIMENTAL

Spectra.—Infrared and u.v. spectra were measured for Nujol mulls and for ethanol solutions, respectively.

1-(3,5-*Dihydroxyphenyl*)*heptan*-2-*ol* (2; R = H).—Oxaloyl chloride (15 ml.) was added to a suspension of 3,5-dimethoxyphenylacetic acid (12·6 g.) in benzene (35 ml.). When evolution of gas had ceased the solution was heated under reflux for 1 hr. and the product purified by distillation to yield 3,5-dimethoxyphenylacetyl chloride (11·7 g.) as a pale yellow liquid, b. p. 122—124°/0·8 mm., having $\nu_{max.}$ (film), 2840 (methoxy), 1800 (acid $>$C=O), 1610, and 1595 cm.$^{-1}$ (aromatic). A solution of this chloride (11·7 g.) in benzene (50 ml.) was added dropwise (with stirring at 20°) to the cadmium derivative of 1-bromopentane (33·8 g.) (prepared by way of the corresponding Grignard reagent) in benzene (100 ml.). The mixture was then allowed to warm spontaneously during 1 hr., and then heated under reflux for a further hour. Isolated in the normal manner the product was purified by chromatography on alumina (450 g.) from methylene dichloride–light petroleum (b. p. 40—60°) and then by distillation to yield 1-(3,5-*dimethoxyphenyl*)*heptan*-2-*one* (9·2 g.) as an oil, b. p. 145°/0·5 mm. (Found: C, 71·8; H, 8·8. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·9%). The n.m.r. spectrum showed, *inter alia*, signals at τ 6·21 (2 × OCH_3, 6 protons).

A mixture of this ketone (2 g.) and pyridine hydrochloride (3 g.) was boiled for 5 min. After isolation with ether and 2N-sodium hydroxide, 1-(3,5-*dihydroxyphenyl*)*heptan*-2-*one* was purified by chromatography on silica from benzene followed by elution with benzene–light petroleum (2 : 1) and separated from benzene–light petroleum as plates (1 g.), m. p. 92° (Found: C, 70·0; H, 8·3. $C_{13}H_{18}O$ requires C, 70·2; H, 8·2%). The n.m.r. spectrum showed no peaks corresponding to methoxy groups.

A solution of this ketone (3·6 g.) in alcohol (8·0 ml.) containing sodium borohydride (1·8 g.) was heated under reflux for 20 min. The resultant solution was concentrated under reduced pressure, water (80 ml.) was added and the solution was acidified with 6N-sulphuric acid to yield (±)-1-(3,5-*dihydroxyphenyl*)*heptan*-2-*ol* which separated from benzene–methanol as plates (2·8 g.), m. p. 149° (Found: C, 70·0; H, 9·1. $C_{13}H_{20}O_3$ requires C, 69·6; H, 9·0%).

(±)-*Pulvilloric Acid* (1).—A mixture of the previous alcohol (2·7 g.), potassium hydrogen carbonate (5·8 g.), and glycerol (6 g.) was heated at 145—150° (stir) in an atmosphere of carbon dioxide during 5 hr. Isolated in the usual manner (±)-1-(4-*carboxy*-3,5-*dihydroxyphenyl*)-*heptan*-2-*ol* formed tiny prisms (1·5 g.) from chloroform, m. p. 146° (Found: C, 62·3; H, 7·2. $C_{14}H_{20}O_5$ requires C, 62·7; H, 7·5%). The acid gave an intense blue colour with ferric chloride solution.

This acid (0·3 g.) rapidly dissolved in ethyl orthoformate (1 ml.) to yield a yellow solution from which crystals separated after 2 min. Further ethyl orthoformate (1 ml.) was then added. After 5 min. the semisolid reaction mixture was diluted with ether (30 ml.) and the yellow solution extracted with 2% sodium hydrogen carbonate solution. This extract was acidified with 2N-sulphuric acid, extracted with ether to furnish a yellow gum (0·32 g.) which after solution in toluene (7 ml.) and ethanol (2 drops) was cooled to 0° when the colourless, crystalline alcohol adduct (150 mg.) of (±)-pulvilloric acid separated, m. p. 75—76°. This adduct rapidly became yellow on exposure to the air and was thus heated at 42°/0·01 mm., during 40 hr., to yield (±)-*pulvilloric acid* in a bright yellow microcrystalline form, m. p. 77—78° (Found: C, 64·3; H, 6·7. $C_{15}H_{18}O_5$ requires C, 64·7; H, 6·5%).

Reaction of 1-(3,5-*Dihydroxy*-4-*carboxyphenyl*)*heptan*-2-*ol with Dimethoxymethane.*—A suspension of the (±) acid (2; R = CO_2H) (0·12 g.) in dry benzene (2·5 ml.) and dimethoxymethane (0·3 ml.) was saturated with dry hydrogen chloride in a Carius tube. The sealed tube was heated at 60° for 6 hr., during which time a precipitate formed. This was collected (0·05 g.), m. p. 175—176°, and the pale yellow filtrate was evaporated to dryness under nitrogen. The green oil which remained was crystallised from aqueous ethanol, giving more of the same product (0·06 g.). The combined material was recrystallised from aqueous ethanol thereby giving the diarylmethane (5; R = H) as prisms (0·10 g.), m. p. 177—178°. The compound turned yellow at 170°, orange at 175°, and became deep

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[14] N. J. Cartwright, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1949, 1563.

[15] J. F. W. McOmie and M. L. Watts, *Chem. and Ind.*, 1963, 1658.

red and effervesced at its melting point (Found: C, 64·6; H, 7·5. $C_{31}H_{40}O_{10}$ requires C, 65·0; H, 7·0%), $\lambda_{max.}$ 227, 259, and 334 mμ (log ε 4·5, 4·2, and 3·7). It gave an intense green colour with ethanolic ferric chloride.

Methyl Dihydropulvillorate (*Methyl* 3,4-*Dihydro*-6,8-*dihydroxy*-3-*n*-*pentyl*-1*H*-2-*benzopyran*-7-*carboxylate*) (4; R = Me) (cf. ref. 16).—Carboxylation of (+) phenol (2; R = H) (derived from pulvilloric acid) gave the (+) carboxylic acid (2; R = CO_2H), m. p. 130—131° (Found: C, 62·6; H, 7·7. Calc. for $C_{14}H_{20}O_5$: C, 62·7; H, 7·5%), $\lambda_{max.}$ 220, 254, and 319 mμ (log ε 4·5, 4·2, and 3·6). This was esterified with diazomethane to give 1-(3,5-*dihydroxy*-4-*methoxycarboxyphenyl*)*heptan*-2-*ol*, m. p. 63° (from aqueous methanol) (Found: C, 63·8; H, 8·1; OMe, 11·5. $C_{15}H_{22}O_5$ requires C, 63·8; H, 7·8; OMe, 11·0%), $\nu_{max.}$ 1665 and 1645 cm.$^{-1}$.

A solution of this ester (0·12 g.) in benzene (1 ml.) and dioxan (1 ml.) was saturated with dry hydrogen chloride in a Carius tube. Dimethoxymethane (32 mg.) was added and the tube was sealed. It was heated at 60° for 4 hr. The pale yellow oil, which remained after evaporation of the solvent under reduced pressure, was chromatographed on silica gel. Elution with benzene–chloroform (2 : 1) gave a colourless oil, which ultimately crystallised. It was recrystallised from aqueous methanol (0·027 g.), m. p. 60—62°. Further recrystallisation gave the ester, m. p. 68·5—70°. A 1 : 1 mixture of this material and natural methyl dihydropulvillorate (m. p. 71·5—72·5°) had m. p. 70—71°. The i.r. spectra of the two specimens were identical. There was insufficient material for analysis or for measurement of optical rotation. Further elution of the silica gel with benzene–chloroform (3 : 2) gave a product [which is probably the diarylmethane (5; R = Me)] as plates (0·036 g.), m. p. 154—158° after recrystallisation from methanol

1-*Cyano*-1-(3,5-*dimethoxyphenyl*)*heptan*-2-*one*.—A mixture of 3,5-dimethoxybenzyl cyanide (20·0 g.) and ethyl n-hexanoate (22·4 g.) was added to a hot solution of sodium (3·5 g.) in absolute ethanol (40 ml.), and the resulting red solution was heated under reflux for 2 hr. Next morning, the solution was cooled to −10° for 2 hr., water (100 ml.) was then added, and the mixture was extracted with ether to remove unchanged nitrile. The aqueous solution was acidified with acetic acid (10 ml.) and extracted with ether. Distillation of these extracts gave *the cyano-ketone* as a yellow oil (20·9 g., 67%), b. p. 180—182°/1·0 mm. (Found: C, 69·95; H, 7·8. $C_{16}H_{21}NO_3$ requires C, 69·8; H, 7·6%). When methyl n-hexanoate was used, the yield of cyano-ketone was only 55%.

Hydrolysis of 1-*Cyano*-1-(3,5-*dihydroxyphenyl*)*heptan*-2-*one*.—(a) *With Sulphuric acid*. The above cyano-ketone (12·8 g.) was treated with sulphuric acid (13 ml.) in water (6 ml.) at 0°. The mixture was heated on a water-bath until complete dissolution was achieved (90 min.). Water (65 ml.) was added to the cooled solution, which was then heated at 100° for a further 2 hr. The mixture was extracted with ether and the extracts were washed with aqueous sodium hydrogen carbonate. The dark, yellow oil (9·8 g.) left after evaporation of the solvent was chromatographed on alumina. Elution with 1 : 1 benzene–light petroleum gave 1-(3,5-dimethoxyphenyl)heptan-2-one as a pale yellow oil (1·95 g.), which was identified by comparison of its i.r. spectrum with that of an authentic sample. A second yellow oil was eluted with benzene. This solidified and was recrystallised from light petroleum, giving 3,5-dimethoxyphenylacetonitrile as needles (2·3 g.), m. p. and mixed m. p. 53—54°. Elution with chloroform gave a brown oil, which on distillation gave a yellow oil (2·2 g.), b. p. 193—195°/0·4 mm.

(b) *With alkali*. The cyano-ketone (5·2 g.) and sodium hydroxide (12·0 g.) in methyl cellosolve (12 ml.) and water (36 ml.) were heated under reflux for 3 hr. The solution was extracted with ether, and the dried extracts yielded a brown, viscous oil (0·2 g.) on evaporation. The aqueous solution was acidified with 2N-hydrochloric acid, and the oil which separated was extracted into ether. The yellow oil (5·5 g.) remaining after evaporation of the dried extracts was crystallised from aqueous ethanol, giving 3,5-dimethoxyphenylacetic acid as needles (3·4 g.), m. p. 103—104°.

3,5-*Dimethoxybenzyl Bromide*.—This compound, m. p. 72—73°, was obtained in 84% yield from 3,5-dimethoxybenzoic acid by reduction of its ethyl ester [17] with lithium aluminium hydride followed by treatment with phosphorus tribromide. Its structure was confirmed by carboxylation of its Grignard reagent to give the corresponding phenylacetic acid. The bromide (m. p. 71—72°) has since been made by the action of hydrogen bromide on 3,5-dimethoxybenzyl alcohol.[18]

Condensation of 3,5-*Dimethoxybenzylmagnesium Bromide and n-Hexanal*.—n-Hexanal (6·5 g., 1 mol.) in dry ether (25 ml.) was slowly added to the Grignard reagent [from 3,5-dimethoxybenzyl bromide (15·0 g.) and magnesium (2·1 g.)] in ether (100 ml.). The pale yellow solution was heated under reflux for 6 hr., and left overnight, before addition of dilute acetic acid. The ethereal layer was separated, washed with aqueous sodium carbonate, dried ($MgSO_4$), and distilled, giving orcinol dimethyl ether (2·4 g.), b. p. 68—69°/0·5 mm. (lit.,[19] 102°/8 mm.). The residue (12·8 g.) was chromatographed on alumina, giving *the ether* (8) as a viscous oil (5·7 g.), b. p. 158—161°/0·05 mm. (Found: C, 75·8; H, 10·3; OMe, 18·0. $C_{21}H_{34}O_3$ requires C, 75·45; H, 10·2; OMe, 18·6%), 3,3′5,5′-tetramethoxybibenzyl as glistening plates from light petroleum (2·4 g.), m. p. 105—106°, and the alcohol (7) (2·3 g.), b. p. 125—140°/0·5 mm. as a yellow oil, which was crystallised from hexane as needles (2·0 g.), m. p. 48—50°, undepressed by admixture with the material prepared using zinc (Found: C, 71·1; H, 9·5. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·5%).

A similar yield of alcohol (7) was obtained using 0·75 mol. of aldehyde, and no better results followed from the use of the chloride in place of the bromide.

Condensation of 3,5-*Dimethoxybenzylzinc bromide and n-Hexanal*.—3,5-Dimethoxybenzyl bromide (22·8 g.) in dry tetrahydrofuran (150 ml.) was heated under reflux with granulated zinc (6·4 g.) for 11 hr. The cooled mixture was treated dropwise with n-hexanal (10·0 g.) in tetrahydrofuran (25 ml.) during 15 min. The mixture was heated under reflux for 5 hr., and the resulting complex was decomposed with water (25 ml.) followed by 2% hydrochloric acid (400 ml.). The product was a red oil (2·4 g.), which was isolated with ether, and chromatographed on alumina, giving orcinol dimethyl ether (5·0 g.), b. p. 118—

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[16] H. H. Warren, G. Dougherty, and E. S. Wallis, *J. Amer. Chem. Soc.*, 1949, **71**, 3422.

[17] R. Adams, M. Harfenist, and S. Loewe, *J. Amer. Chem. Soc.*, 1949, **71**, 1624.

[18] R. Huisgen, G. Seidl, and I. Wimmer, *Annalen*, 1964, **677**, 21.

[19] H. Walbaum and A. Rosenthal, *Ber.*, 1924, **57**, 771.

120°/25 mm., 3,3′5,5′-tetramethoxybibenzyl (4·9 g.) as needles from light petroleum, m. p. 107—108° (lit.,[20] 98—99°) (Found: C, 71·6; H, 7·5. Calc. for $C_{18}H_{22}O_4$: C, 71·5; H, 7·3%), and the alcohol (7) as an oil (b. p. 139—145°/0·5 mm.) which solidified, and was recrystallised from hexane as needles (2·4 g.), m. p. 49—50°.

Stephen Reduction of 3,5-*Dimethoxybenzyl Cyanide*.—The nitrile (4·5 g.) was shaken for 48 hr. with anhydrous stannous chloride (7·7 g.)[21] in dry ether, saturated at 0° with hydrogen chloride. After a few hr. the lower layer had set to a yellow crystalline mass. The solid was broken up, filtered off, and well washed with dry ether. It was suspended in water (200 ml.) and the solution was almost neutralised with potassium hydrogen carbonate. Steam distillation of the mixture gave the aldehyde as a yellow oil (0·35 g.) which was isolated with ether.

Ethyl 3,5-*Dimethoxyphenylglycidate* (cf. ref. 13).—A mixture of 3,5-dimethoxybenzaldehyde[11] (14·5 g.) and ethyl chloroacetate (9·1 ml.) was added, during 4 hr., to a stirred solution of sodium (2·1 g.) in absolute ethanol (30 ml.) at −5°. Stirring was continued at room temperature for a further 6 hr., and the mixture was left overnight before being poured on to ice (50 ml.) and acetic acid (1·2 ml.). The resulting mixture was extracted with ether, and the extracts were washed with aqueous sodium hydrogen carbonate. Distillation gave *the glycidic ester* (14·6 g.), b. p. 142—144°/0·05 mm. as a viscous oil (Found: C, 61·7; H, 6·5. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·35%).

Sodium 3,5-*Dimethoxyphenylglycidate*.—The glycidic ester (6·3 g.) in ether (50 ml.) was added during 15 min. to a solution of sodium (0·63 g.) in ethanol (12·5 ml.) and water (0·5 ml.) at 5°. The mixture was kept at 0—5° for 20 hr., ether (10 ml.) being added after 10 hr. The precipitated sodium salt was collected and washed with ether (5·8 g.), m. p. 232—235° (decomp.).

3,5-*Dimethoxyphenylacetaldehyde* (cf. ref. 22).—(*a*) The above sodium salt (1·6 g.) was added to warm, dilute hydrochloric acid. The stirred mixture was heated at 100° for 5 min. before being extracted with ether. The extracts were thoroughly washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated leaving the aldehyde (0·2 g.) as a yellow oil. This gave an orange 2,4-*dinitrophenylhydrazone* which had m. p. 189·5—190·5° after two recrystallisations from ethanol (Found: C, 52·9; H, 4·8; N, 15·3. $C_{16}H_{16}N_4O_6$ requires C, 53·3; H, 4·45; N, 15·55%).

(*b*) The sodium salt (5·7 g.) in water (23 ml.) was added, during 20 min., to oxalic acid (4·1 g.) in water (20 ml.) at 95—100°, under nitrogen. After a further 5 min. at the same temperature, the solution was cooled and extracted with chloroform. Distillation of the dried extracts gave the aldehyde as a yellow oil (1·55 g.), b. p. 99—103°/0·1 mm. (lit.,[23] b. p. 109—110°/0·5 mm.).

Condensation of 3,5-*Dimethoxyphenylacetaldehyde and n-Pentylmagnesium Bromide*.—The above aldehyde (3·1 g.) in ether (40 ml.) was added dropwise to a stirred, ethereal solution of the Grignard reagent (from 8·0 g. of 1-bromopentane) at 0°. After 1 hr., at room temperature, the complex was decomposed with dilute sulphuric acid. Distillation of the oil remaining after evaporation of the ethereal layer gave 1-(3,5-dimethoxyphenyl)heptan-2-ol (7) (2·8 g.), b. p. 135—140°/0·5 mm., as a pale yellow oil. The i.r. spectrum of this (±)compound was identical with that of the same alcohol prepared from 3,5-dimethoxybenzyl bromide and also with that of the dimethyl ether of the (+)phenol obtained by hydrolysis of pulvilloric acid.

Demethylation of the Alcohol (7).—(a) *With hydriodic acid* (cf. ref. 14). The alcohol (7) (2·0 g.) was gently heated under reflux with hydriodic acid (5 ml.; *d* 1·7), acetic anhydride (10 ml.), and red phosphorus (1·0 g.), for 3 min. The mixture was diluted with water (100 ml.), neutralised with sodium hydrogen carbonate, and extracted with ether. The ethereal extracts were extracted with 2N-sodium hydroxide, then the alkaline liquor was acidified with hydrochloric acid, and the phenolic material was isolated with ether. The ether was washed with aqueous sodium bisulphite, and evaporated, giving a brown gum (0·5 g.). Addition of benzene to this gum gave a buff precipitate, which was collected (0·2 g.), m. p. 141—142·5°. Recrystallisation from benzene gave 1-(3,5-dihydroxyphenyl)-heptan-2-ol as prisms, m. p. 145—146°.

(b) *With boron tribromide* (cf. ref. 15). The alcohol (7) (1·0 g.) in pentane (12 ml.) was added during 15 min., to boron tribromide (2·0 g.) at −80°. The mixture was left to warm up to −10° (18 hr.). The complex was decomposed by cautious addition of water and the mixture was extracted with ether. Phenolic material was removed from the ethereal extracts with 2N-sodium hydroxide, the alkaline liquor was acidified, and the resulting emulsion was extracted with ether. The brown oil (0·2 g.) remaining after evaporation of these extracts gave the phenol (2; R = H) as prisms (0·1 g., 11% conversion), m. p. 136—138°, from benzene. Recrystallisation raised the m. p. 145—146°. Starting material (0·8 g., 80%) was recovered as a yellow oil from the original ethereal solution.

Repetition of the reaction gave a further 10% conversion but subsequent repetitions gave little or none of the phenol. Use of methylene dichloride as solvent or alteration in the temperatures and durations of the experiments effected no improvement.

The i.r. spectra of the phenol prepared by both methods of demethylation were identical with the spectrum of the purer product described at the beginning of the Experimental section.

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