183. *The Chemistry of Fungi. Part IV. The Constitution of the Phenol, $C_{11}H_{16}O_3$, from Citrinin.*

By J. P. Brown, N. J. Cartwright, Alexander Robertson, and W. B. Whalley.

The isomeric phenols (A) and (B), $C_{11}H_{16}O_3$, obtained by the hydrolytic fission of citrinin with dilute alkalis as well as with dilute acids, form liquid dimethyl ethers which are readily characterised by the formation of *p*-nitrobenzoates and hydrogen phthalates. On resolution with the aid of strychnine or brucine the hydrogen phthalate of the dimethyl ether of (B) is separated into (+)- and (−)-forms, of which the latter is identical with the hydrogen phthalate derived from the dimethyl ether of (A). The phenol, $C_9H_{12}O_2$, formed by the fusion of (A) with alkalis is identical with synthetical 4-methyl-5-ethylresorcinol. Like the latter compound phenols (A) and (B) readily give bisphenylazo-derivatives. Reduction of (A) or (B) with hydriodic acid and red phosphorus yielded the phenol (XIV; R = Me), the structure of which was determined by two independent syntheses. Finally a synthesis of the *p*-nitrobenzoate of the dimethyl ether of (B) has been achieved, and thus the constitution of phenols (A) and (B) has been established.

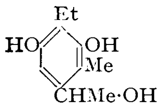
The lævo-rotatory, yellow, phenolic carboxylic acid, citrinin, $C_{13}H_{14}O_5$, a characteristic metabolic product of several strains of *Penicillium citrinum* grown on a Czapek–Dox glucose medium, and also produced by *Aspergillus* species, *A. terreus* and the *candidus* group, was first isolated by Hetherington and Raistrick (*Phil. Trans.*, 1931, *B*, **220**, 269) who, *inter alia*, described the general properties of this interesting compound and showed that on being boiled with dilute sulphuric acid it was decomposed :

$$C_{13}H_{14}O_5 \xrightarrow{2H_2O} C_{11}H_{16}O_3 + H{\cdot}CO_2H + CO_2.$$

The substance $C_{11}H_{16}O_3$ was found to be a mixture of two isomerides, one of which was optically active (lævo-rotatory), and was referred to as " product A," whilst the second substance was optically inactive, and was named " product B ; " the designations (A) and (B) have been retained for the present. Further, these authors concluded that (A) and (B) were dihydric phenols in which the third oxygen atom was present as an alcoholic-hydroxyl group, and they showed that on fusion with potassium hydroxide product (A) gave rise to a dihydric phenol, $C_9H_{12}O_2$, forming a dimethyl ether, $C_9H_{10}(OMe)_2$, which on oxidation with alkaline potassium permanganate yielded two acidic products, $C_{10}H_{12}O_4$ and $C_{11}H_{14}O_4$. From an examination of the phenol and of the oxidation products of its methyl ether, Coyne *et al.* (*Phil. Trans.*, 1931, *B*, **220**, 301) concluded that the compound was 4-methyl-2-ethylresorcinol and on this basis developed structural formulæ for (A) (I), and for citrinin. Subsequently Robinson and Shah (*J.*, 1934, 1491) synthesised 4-methyl-2-ethylresorcinol, but were unable to equate this compound with the phenolic degradation product from (A) (cf. Sprenger and Ruoff, *J. Org. Chem.*, 1946, **11**, 189). Of interest in this connexion are the results of Gore *et al.* (*Nature*, 1946, **157**, 333) who state that citrinin reacts with diazonium salts in the normal way to give monoazo-derivatives, and that this coupling is not accompanied by the displacement of any groups during the condensation. Further, the Indian authors found that, whilst (A) couples normally with the diazonium salt from 5-nitro-*o*-anisidine to give a bisazo-compound, with an excess of the salt from aniline the phenol behaves abnormally. On the basis of the foregoing results it appeared that phenol (A) and citrinin did not have the structures originally assigned to them.

Since citrinin has been shown to possess considerable antibiotic activity against Gram-positive organisms (Raistrick and Smith, *Chem. and Ind.*, 1941, **60**, 828 ; Oxford, *ibid.*, 1942, **61**, 48) an examination of its constitution was undertaken as part of a comprehensive investigation on chemical constitution and antibiotic activity. For the development of a rational structure for citrinin the determination of the orientation of the products (A) and (B) appeared to be an essential preliminary step, and accordingly the present communication deals with this topic. The compound (A) has now been obtained by the action of boiling dilute sodium hydroxide on citrinin, and under these conditions does not seem to be accompanied by appreciable amounts of phenol (B) which, however, can be obtained from (A) by the action of warm dilute sulphuric acid. The liquid dimethyl ether of (A), which can be prepared readily by the methyl iodide–potassium carbonate method, is conveniently characterised by the formation of a (—)-p-*nitrobenzoate* and a (—)-*hydrogen phthalate*. Similarly the liquid dimethyl ether of (B) affords an optically inactive p-*nitrobenzoate* and a *hydrogen phthalate*. Further, (A) and (B) react with warm alcoholic diazoaminobenzene, yielding isomeric *bisphenylazo*-derivatives, the compositions of which clearly indicate that the condensation is not preceded by the extrusion of an alkyl group, thus clearly establishing that there are not more than two side chains in (A) or (B). This result is supported by the fact that on oxidation with aqueous potassium permanganate the dimethyl ether of (A) gives rise to **3** : 5-dimethoxyphthalic acid (VIII).

In order to establish that (B) is the (±)-form of (A) as suggested by Hetherington and Raistrick (*loc. cit.*), and not a structural isomeride, the resolution of the optically inactive hydrogen phthalate of the dimethyl ether of (B) was undertaken. With (—)-strychnine and (—)-brucine, this derivative yields stable salts, and the (—)-*strychnine* and the (—)-*brucine* (+)-" *base* " *phthalate* separated from the acetone reaction mixtures in an almost pure state, whilst in both cases the comparatively pure salts of (—)-base (—)-acid remained in solution. Decomposition of the latter derivatives gave in each case the same (—)-hydrogen phthalate, identical in every way with the hydrogen phthalate of the dimethyl ether of phenol (A). Further, the decomposition of each of the " crossed salts " gave the same (+)-*hydrogen phthalate* of the dimethyl ether of (+)-(B), and a mixture of this ester with an equal amount of the (—)-isomeride gave rise, on recrystallisation, to an optically inactive hydrogen phthalate identical with the derivative prepared from the dimethyl ether of (B). Consequently it is clear that (A) and (B) are stereoisomerides and not structural isomerides.



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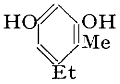

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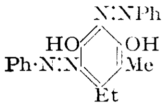

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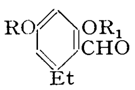

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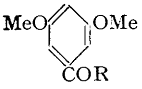

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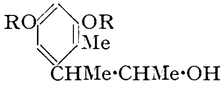

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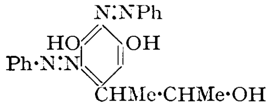
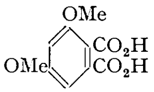


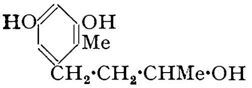
(VII.)



(VIII.)

The phenol, $C_9H_{12}O_2$, which is formed along with acetic acid by the fusion of (A) or (B) with potassium hydroxide appears to exist in hydrated and anhydrous forms, but is more conveniently characterised by the formation of a *di*-p-*nitrobenzoate*, and by conversion into the corresponding *aldehyde* according to Gattermann's procedure, a reaction which, in conjunction with the red-brown alcoholic ferric reaction of the product, clearly confirms the view that this phenol and therefore product (A) belong to the resorcinol series. Further, as would be expected from the behaviour of (A) the phenol, $C_9H_{12}O_2$, reacts readily with warm alcoholic diazoaminobenzene, forming a *bisphenylazo-derivative*. In order to establish the orientation of the phenol, $C_9H_{12}O_2$, the isomeric alkyl-resorcinols of the methyl-ethyl, *n*-propyl, and *iso*propyl series were synthesised, and it was ultimately found that the compound was identical with synthetical 4-methyl-5-ethylresorcinol (II) which was obtained by application of the Clemmensen reaction to 2 : 4-*dihydroxy*-6-*ethylbenzaldehyde* (IV; $R = R_1 = H$) prepared from 5-ethylresorcinol (the synthesis of the remaining alkyl-resorcinols will be described in a subsequent communication). Consequently the bisphenylazo-derivative of (II) must have formula (III). In preference to the route employed by Asahina and Ihara (*J. Pharm. Soc. Japan*, **1928**, **48**, 28) the ketone (V; $R = Me$), required for the preparation of 5-ethylresorcinol, was synthesised from 3 : 5-dimethoxybenzoic acid by way of the acid chloride (V; $R = Cl$) and the diazoketone (V; $R = CHN_2$). The reduction of the ketone (V; $R = Me$) with amalgamated zinc and boiling hydrochloric acid under the usual conditions gave mainly an intractable gum (compare Asahina and Ihara, *loc. cit.*, of whose work we have been able to consult only an abstract), but the use of benzene in the reduction mixture gave a satisfactory yield of 5-ethylresorcinol. The latter phenol was also obtained in good yield when the semicarbazone of the ketone was subjected to the Wolff–Kishner method of reduction. The orientation of the aldehyde (IV; $R = R_1 = H$) from 5-ethylresorcinol is established by the fact that two isomeric monomethyl ethers (IV; $R = Me$,

R_1 = H) and (IV; R = H, R_1 = Me) have been obtained from it. Of these one must be 2-*hydroxy*-4-*methoxy*-6-*ethylbenzaldehyde* (IV; R = Me, R_1 = H) since it gives an intense alcoholic ferric reaction, and readily condenses with acetophenone under standard conditions to give 7-*methoxy*-5-*ethylflavylium chloride*. The second *ether*, which does not give a ferric reaction or form a pyrylium salt, must have the orientation (IV; R = H, R_1 = Me). Although in spite of repeated efforts we were unable to effect a stepwise degradation of the dimethyl ether of (A) with oxidising agents, *e.g.*, potassium permanganate, chromic oxide, or the Oppenauer–Pondorff reaction, it seemed reasonably certain that, in view of the ready formation of acyl derivatives of the dimethyl ether of (A) and its resistance to dehydration (*e.g.* by hot Grignard reagents), the alcoholic-hydroxyl group in (A) was not tertiary. On this account and because (A) gives a bisphenylazo-derivative and can be degraded to 4-methyl-5-ethylresorcinol (II) by the loss of the group CHMe·OH as acetic acid it seemed probable that (A) was a secondary alcohol for which there are three possible formulæ (VI; R = H), (IX), and (X; R = H). Of these structures (VI; R = H) or (X; R = H) appeared to be the more likely.



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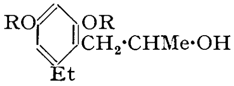

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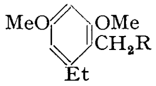
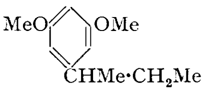


(XI.)

Accordingly syntheses of the methyl ethers (VI; R = Me) and (X; R = Me) were undertaken. In the preparation of the latter compound the *aldehyde* (IV; R = R_1 = Me) was converted into the *azlactone* by the standard method, and on hydrolysis this compound gave the phenylpyruvic acid (XI; R = $CO\cdot CO_2H$), the *oxime* of which [XI; R = $C(:NOH)\cdot CO_2H$] was converted into the *cyanide* (XI; R = CN). Reduction of the latter by the stannous chloride method gave a moderate yield of 2 : 4-*dimethoxy*-6-*ethylphenylacetaldehyde* (XI; R = CHO), and on treatment with methylmagnesium iodide this aldehyde gave the alcohol (X; R = Me) which was isolated as the p-*nitrobenzoate*, isomeric and not identical with the corresponding derivative of (B).

Before attempting the synthesis of the compounds having the remaining possible structures for the dimethyl ether of (B) it was decided to reduce the alcoholic-hydroxyl groups of (A) or (B), and then by synthesis to define the exact nature of the two alkyl groups in the product. By reduction of (A) or (B) with hydriodic acid and red phosphorus a dihydric *phenol*, containing all the carbon atoms present in (A), was obtained which was readily characterised by the formation of a *di*-p-*nitrobenzoate*, and was oriented by two independent syntheses.

(XII.)



(XIII.)

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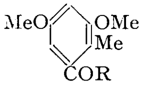

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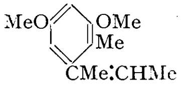

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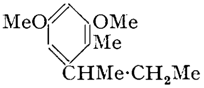
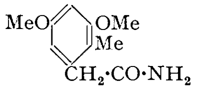


(XVII.)

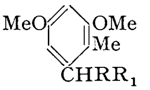
In the first synthesis interaction of 3 : 5-dimethoxyacetophenone (V; R = Me) with excess of warm ethylmagnesium iodide and simultaneous dehydration of the initial product yielded the *phenylbutene* (XII), and on hydrogenation this compound furnished the *phenylbutane* (XIII) which was demethylated giving 2-(3 : 5-*dihydroxyphenyl*)*butane* (XIV; R = H). Prepared from (XIV; R = H) by Gattermann's method, the *aldehyde* (XIV; R = CHO) was reduced by Clemmensen's method, giving 2-(3 : 5-*dihydroxy*-2-*methylphenyl*)*butane* (XIV; R = Me), identical in every way with the phenol obtained from (A) or (B). In the second procedure the *acid* (XV; R = OH), prepared by the methylation of 3 : 5-dihydroxy-2-methylbenzoic acid, was converted into the diazoketone (XV; R = CHN_2) by way of the acid chloride (XV; R = Cl) and on treatment with hydriodic acid the diazene gave rise to the *ketone* (XV; R = Me), the interaction of which with ethylmagnesium iodide furnished the phenylbutene (XVI). 2-(3 : 5-*Dimethoxy*-2-*methylphenyl*)*butane* (XVII) was then prepared by the hydrogenation of the butene, and on demethylation gave the phenol (XIV; R = Me) shown to be identical with the natural compound by comparison of the di-*p*-nitrobenzoates.

Having thus established the carbon skeleton of the substituent groups of (A) and (B) it seemed to us reasonably certain that these compounds had the constitution (VI; R = H) and accordingly a synthesis of the *p*-nitrobenzoate of the dimethyl ether of (B) was carried out as follows.

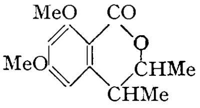
On being subjected to the Wolff rearrangement with ammoniacal silver nitrate the diazoketone (XV; R = CHN_2) furnished an excellent yield of the *amide* (XVIII) which was converted into 3 : 5-*dimethoxy*-2-*methylbenzyl cyanide* (XIX; R = H, R_1 = CN) by dehydration. The carbon methylation of this cyanide by the interaction of the sodio-derivative with methyl sulphate in benzene appeared to give a mixed product but, owing to the lack of material, it was distilled and used directly in the next stage. Reduction of this distillate by the stannous chloride method furnished aldehydic material, and on condensation with methylmagnesium iodide the latter yielded an alcoholic product which in the crude state was acylated with *p*-nitrobenzoyl chloride–pyridine mixture. Fractional crystallisation of the resulting mixed ester gave a small yield of a *p*-nitrobenzoate, identical in every respect with the *p*-nitrobenzoate of the dimethyl ether of (B). Along with this derivative there was isolated in larger amount a second p-*nitrobenzoate* which from its analytical results appeared to be derived from an alcohol containing a methylene residue more than the dimethyl ether of (B), *i.e.* arising in the synthesis owing to the required intermediate cyanide (XIX; R = Me, R_1 = CN) being contaminated with the αα-dimethyl homologue, with the result that the aldehyde (XIX; R = Me, R_1 = CHO) contained the corresponding higher homologue. In spite of the fact that we have not been able at present to define the intermediate stages in this synthesis it is clear that the production of a mixture containing the *p*-nitrobenzoate of the dimethyl ether of (B) from the cyanide (XIX; R = H, R_1 = CN) by the procedure employed, in conjunction with the conversion of (B) into (XIV; R = Me), affords conclusive proof that (B) and consequently (A) have the constitution (VI; R = H). Further, the bisphenylazo-derivative of (A) is represented by formula (VII), and the lactone, $C_{11}H_{10}O_2(OMe)_2$, formed by the oxidation of the dimethyl ether of (A) (Hetherington and Raistrick, *loc. cit.*) is represented by (XX). In connexion with the constitution (VI, R = H) assigned to (A) it may be noted that an alcohol of this structure, having two asymmetric carbon atoms, may exist in four optical isomerides, forming two pairs of (±)-forms capable of being separated by crystallisation. Since a derivative of (B) has been resolved to give the corresponding derivative of (A) it would seem that (B) is probably one of two possible (±)-forms and not a mixture of all four isomerides, but the elucidation of this problem must await the results of further synthetical investigations on the stereochemistry of (VI; R = H), which are in progress.



(XVIII.)



(XIX.)



(XX.)

The starting material (XV; R = OH) employed in the synthesis of the dimethyl ether of (B) was obtained from 3 : 5-dihydroxy-2-methylbenzoic acid, but we have encountered considerable difficulty in preparing this acid. As far as we are aware the only recorded preparation of the compound is that of Jacobsen and Wierss (*Ber.*, 1883, **16**, 1960) involving the sulphonation of *o*-toluic acid, and subsequent fusion of the resulting disulphonic acid with potassium hydroxide, for which insufficient details have been recorded (cf. Liebermann and Kostanecki, *Annalen*, 1887, **240**, 280). The application of the Clemmensen method of reduction to 3 : 5-dihydroxy-2-formylbenzoate as an alternative route to 3 : 5-dihydroxy-2-methylbenzoic acid gave only small yields of the required product accompanied by much resinous material. Consequently, in order to obtain a satisfactory source of 3 : 5-dihydroxy-2-methylbenzoic acid we are re-investigating its preparation from *o*-toluic acid.

After the completion of the work on the orientation of phenol (A) our attention was directed to an editorial communication by Cram (*J. Amer. Chem. Soc.*, 1948, **70**, 440) announcing the synthesis of 4-methyl-5-ethylresorcinol without giving experimental details (compare *Nature*, 1948, **162**, 72).

EXPERIMENTAL.

Derivatives of Phenols (A) *and* (B).—A solution of citrinin (1 g.) in 10% aqueous sodium hydroxide (50 ml.) was heated under reflux for 3½ hours in an atmosphere of nitrogen, and the cooled mixture saturated with carbon dioxide, and extracted several times with ether. Evaporation of the dried ethereal extracts gave the phenol (A) (0·5 g.), m. p. 128°, after recrystallisation from chloroform and subsequent de-solvation.

When boiling solutions of phenol (A) (0·5 g.) in alcohol (15 ml.) and diazoaminobenzene (2 g.) in alcohol (15 ml.) were mixed and kept at room temperature for several days the red *bisphenylazo*-derivative of (A) separated. Recrystallised from alcohol, the compound formed deep-red glistening needles, m. p. 204—205° (Found : C, 68·2; H, 6·0; N, 14·0. $C_{23}H_{24}O_3N_4$ requires C, 68·3; H, 5·9; N, 13·8%). When (B) was subjected to the same reaction a *bisazo*-derivative was obtained which separated from alcohol in deep-red needles, m. p. 222—223° (Found : N, 13·8%). A mixture of the two azo-derivatives from (A) and (B) melted at 204—206°, and after recrystallisation from alcohol at 204—207°.

The phenol (A) (5 g.) was methylated with excess of methyl iodide and potassium carbonate in boiling acetone during 16—20 hours, until a sample was completely insoluble in dilute aqueous sodium hydroxide. An ethereal solution of the product was washed with aqueous sodium hydroxide and then with water, dried, and evaporated, leaving an almost quantitative yield of the dimethyl ether of (A) which on distillation in a vacuum was obtained as a colourless oil, b.p. 146—148°/0·5 mm., and was characterised by the formation of a p-*nitrobenzoate* by the *p*-nitrobenzoyl chloride–pyridine method, forming characteristic yellow rhombic prisms, m. p. 92—93°, from alcohol; $[\alpha]_D^{18^\circ}$ −22·5° (*c*, 5·0 in chloroform [Found : C, 64·2; H, 5·9; N, 3·4; OMe, 17·0. $C_{18}H_{17}O_4N(OMe)_2$ requires C, 64·3; H, 6·2; N, 3·8; OMe, 16·6%].

Similarly, the phenol (B) was methylated and converted into the p-*nitrobenzoate* of the dimethyl ether which separated from alcohol in pale yellow lozenge-shaped prisms, m. p. 108—109° (Found : C, 64·2; H, 6·1; N, 3·7; OMe, 16·1%). A mixture of the dimethyl ether of (B) (2·8 g.), phthalic anhydride (2·0 g.), and pyridine (15 ml. was kept at 100° for 3 hours, the cooled solution was poured into dilute hydrochloric acid, and the *hydrogen phthalate*, which gradually solidified on being triturated with water, was crystallised from chloroform, forming colourless prisms (4 g.), m. p. 144° [Found : C, 67·5; H, 6·4; *M* (by titration), 376. $C_{21}H_{24}O_6$ requires C, 67·7; H, 6·5%; *M*, 372].

A suspension of the dimethyl ether of (A) in boiling water (1500 ml.) was vigorously agitated, and was treated with powdered potassium permanganate (40 g.) added gradually in portions of 1 g. during 1½ hours, the hot solution was filtered to remove manganese dioxide, and the filtrate evaporated under diminished pressure. On being kept, a solution of the residue in dilute hydrochloric acid slowly deposited 3 : 5-dimethoxyphthalic acid, m. p. 158° after recrystallisation from hot water, which gave the anhydride, m. p. 149°. This acid and its anhydride were identified by comparison with authentic specimens prepared according to Oxford and Raistrick's method (*Biochem. J.*, 1932, **26**, 1902).

Resolution of the Hydrogen Phthalate of the Dimethyl Ether of (B).—The phthalate (7 g.), dissolved in acetone (50 ml.), was added to a solution of strychnine (6·6 g.) in boiling acetone (1500 ml.), and 18 hours later the mixture was concentrated giving three crops of crystalline material which had almost identical melting points and specific rotations. The combined products (6·0 g.) were fractionally crystallised from alcohol, but each fraction of the *strychnine* salt was found to be identical, forming pearly plates, m. p. 213—214°, $[\alpha]_D^{18^\circ}$ −26·5° (*c*, 4·07 in chloroform) (Found : C, 71·1; H, 6·5; N, 4·1. $C_{21}H_{24}O_6,C_{21}H_{22}O_2N_2$ requires C, 71·4; H, 6·5; N, 4·0%). A solution of this salt in the minimum amount of acetone was added to water (100 ml.) and concentrated hydrochloric acid (20 ml.), and on being kept the oil thus precipitated slowly solidified. Recrystallised from chloroform–light petroleum, the (+)-*hydrogen phthalate* of the dimethyl ether of (+)- (B) formed dense, colourless prisms, m. p. 112—114°, $[\alpha]_D^{18^\circ}$ +31·0° (*c*, 5·0 in chloroform) (Found : C, 67·7; H, 6·4. $C_{21}H_{24}O_6$ requires C, 67·7; H, 6·5%).

On evaporation, the acetone liquors left after the separation of the crystalline strychnine salt gave a solid which could not be satisfactorily recrystallised, but which on treatment with acetone containing dilute hydrochloric acid gave the (−)-*hydrogen phthalate* of the dimethyl ether of (−)- (B) which formed colourless prisms, m. p. 112—114°, $[\alpha]_D^{18^\circ}$ −30·0° (*c*, 5·0 in chloroform), from chloroform–light petroleum (b. p. 80—100°); yield almost theoretical (Found : C, 67·5; H, 6·4. $C_{21}H_{24}O_6$ requires C, 67·7; H, 6·5%). This isomeride was identical in every way with a specimen of the hydrogen phthalate, m. p. 112—114°, $[\alpha]_D^{18^\circ}$ −30·0°, prepared directly from the dimethyl ether of (A). A mixture composed of equal weights of the (+)- and (−)-hydrogen phthalates was recrystallised from chloroform–light petroleum, and was obtained in colourless prisms, m. p. 144°, undepressed on admixture with an authentic specimen prepared from the dimethyl ether of inactive (B).

A mixture of the hydrogen phthalate of the dimethyl ether of (B) (7 g.) and brucine (7·0 g.) was dissolved in boiling acetone (150 ml.), and on being concentrated and cooled the mixture deposited the (−)-*brucine* salt (6·0 g.), m. p. 169—171°, which could not be further resolved by fractional crystallisation. This substance separated from acetone in tiny needles, m. p. 171°, $[\alpha]_D^{18^\circ}$ −25·6° (*c*, 4·07 in chloroform) (Found : C, 68·6; H, 6·7; N, 4·0. $C_{21}H_{24}O_6,C_{23}H_{26}O_4N_2$ requires C, 68·9; H, 6·6; N, 3·7%). Decomposition of this salt with dilute hydrochloric acid–acetone gave the (+)-hydrogen phthalate, m. p. 112—114°, $[\alpha]_D^{18^\circ}$ +32° (*c*, 5·0 in chloroform) after purification. Evaporation of the acetone liquor, left after the separation of the (−)-brucine salt, gave the isomeric salt of the (−)-base (+)-acid, which on decomposition yielded the (−)-hydrogen phthalate, m. p. 112—114°, $[\alpha]_D^{18^\circ}$ −29·4° (*c*, 5·0 in chloroform), after having been recrystallised from chloroform–light petroleum (b. p. 80—100°).

2 : 4-*Dimethoxy*-6-*ethylbenzaldehyde* (IV; $R = R_1 = H$).—3 : 5-Dimethoxybenzoyl chloride (9 g., prepared by the interaction of molecular proportions of the acid and phosphorus pentachloride), dissolved in ether (100 ml.), was slowly added to a well-agitated solution of diazomethane (from 25 g. of nitrosomethylurea), and after the vigorous evolution of nitrogen had subsided the mixture was kept for 1 hour, and the ether and excess of diazomethane removed by distillation. A solution of the residual crystalline diazoketone in chloroform (200 ml.) was vigorously agitated with hydriodic acid (30 ml.; *d* 1·7) for 10 minutes and, after the addition of water, the chloroform layer was separated, washed successively with aqueous sodium thiosulphate, aqueous sodium hydroxide, and water, and dried, and evaporated, leaving 3 : 5-dimethoxyacetophenone (V; R = Me) as a colourless oil (7·5 g.), b. p. 122°/0·5 mm., which gave a theoretical yield of the semicarbazone, m. p. 190° (Found : C, 55·4; H, 6·2. Calc. for $C_{11}H_{15}O_3N_3$: C, 55·7; H, 6·4%) (compare Asahina and Ihara, *loc. cit.*, who gave m. p. 187° for the semicarbazone). The ketone readily gave a 2 : 4-*dinitrophenylhydrazone*, forming orange prisms or red needles, m. p. 191°, from acetic acid (Found : C, 53·3; H, 4·5; N, 15·1. $C_{16}H_{16}O_6N_4$ requires C, 53·3; H, 4·5; N, 15·6%). The hydrazone of this ketone appeared to be a liquid, but when insufficient hydrazine

hydrate was employed in its preparation the *ketazine* was obtained, forming yellow prisms, m. p. 127·5°, from methanol (Found: C, 67·5; H, 7·0; N, 7·4. $C_{20}H_{24}O_4N_2$ requires C, 67·4; H, 6·8; N, 7·9%).

A mixture of the foregoing semicarbazone (7·5 g.), sodium methoxide (from 1·5 g. of sodium), and triethylene glycol (glycol bis-2-hydroxyethyl ether) (40 ml.) was kept at 200° for 1 hour, and then cooled, diluted with water (200 ml.), and extracted with ether. Evaporation of the dried extracts left 3 : 5-dimethoxyethylbenzene (4 g.), b. p. 123°/14 mm. (Asahina and Ihara, *loc. cit.*, gave b. p. 95—105°/10 mm.). The same compound was formed when 3 : 5-dimethoxyacetophenone (3·3 g.), benzene (100 ml.), concentrated hydrochloric acid (50 ml.), and amalgamated zinc (25 g.) were heated on the steam-bath for 2½ hours. After cooling, the benzene layer was separated, washed, dried, and evaporated, leaving 3 : 5-dimethoxyethylbenzene (2·1 g.), b. p. 135—140°/30 mm. Demethylation of this ether (3·5 g.) with boiling hydriodic acid (37 ml.; *d* 1·7) and acetic acid (from 25 ml. of anhydride) at 130° for 35 minutes gave an almost theoretical yield of 5-ethylresorcinol which was isolated with ether and purified by distillation in a high vacuum followed by recrystallisation from benzene, forming colourless prisms, b. p. 122°/0·1 mm., m. p. 96—97°, and giving a violet colouration with aqueous ferric chloride (compare Asahina and Ihara, *loc. cit.*, who gave m. p. 93°, and state that the phenol does not give a ferric reaction). The *di-*p*-nitrobenzoate* of this compound formed stout prisms, m. p. 175°, from acetic acid (Found: N, 6·6. $C_{22}H_{16}O_8N_2$ requires N, 6·5%). On being heated with alcoholic diazoaminobenzene 5-ethylresorcinol gave a *bisphenylazo*-derivative which separated from benzene–light petroleum (b. p. 80—100°) in small crimson prisms, m. p. 212° (decomp.) (Found: N, 16·2. $C_{20}H_{18}O_2N_4$ requires N, 16·2%).

A solution of 5-ethylresorcinol (3 g.) in ether (30 ml.), containing hydrogen cyanide (6 ml.), was saturated with hydrogen chloride at room temperature, and 18 hours later the crystalline aldimine was isolated, washed with ether, and hydrolysed with water (30 ml.) at 70—80° for ½ hour. The resulting 2 : 4-*dihydroxy*-6-*ethylbenzaldehyde* (2·5 g.) was purified by crystallisation from benzene, and then by sublimation in a high vacuum, being finally obtained in colourless prisms, m. p. 99—100° (Found: C, 64·7; H, 6·2. $C_9H_{10}O_3$ requires C, 65·1; H, 6·0%). It gave a 2 : 4-*dinitrophenylhydrazone*, separating from ethyl acetate in shining deep-crimson plates, m. p. 293° (decomp.) (Found: N, 16·5. $C_{15}H_{14}O_6N_4$ requires N, 16·2%). Prepared by the methyl iodide–potassium carbonate method, the *dimethyl ether* formed colourless prisms, m. p. 51—52°, from light petroleum (b. p. 40—60°) (Found: C, 68·0; H, 7·3. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·2%). The same ether was prepared directly as follows: Hydrogen chloride was led into a solution of 3 : 5-dimethoxyethylbenzene (12 g.) in ether (150 ml.), containing zinc cyanide (10 g.), for 4 hours, and 18 hours later the solid aldimine was washed by decantation with ether and hydrolysed with water (100ml.) at 80° for ½ hour. On being isolated by means of ether, and crystallised from light petroleum (b. p. 40—60°), the aldehyde (12·2 g.) was obtained in colourless prisms, m. p. 51—52°, and gave the *oxime*, forming colourless prisms, m. p. 111°, from light petroleum (b. p. 80—100°) (Found: C, 63·5; H, 7·3; N, 7·0. $C_{11}H_{15}O_3N$ requires C, 63·2; H, 7·2; N, 6·7%). The 2 : 4-*dinitrophenylhydrazone* separated from acetic acid in long deep-red needles, m. p. 217° (decomp.) (Found: N, 14·9. $C_{17}H_{18}O_6N_4$ requires N, 15·0%).

4-*Methyl*-5-*ethylresorcinol* (II).—Prepared by the fusion of (A) or (B) with potassium hydroxide according to the directions of Hetherington and Raistrick (*loc. cit.*), who gave m. p. 97—99°, this phenol was purified by sublimation in a vacuum, and then by crystallisation from anhydrous benzene, forming stout prisms, m. p. 95—96°, which did not change on further purification by sublimation and by crystallisation (Found: C, 71·3, 70·8; H, 7·8, 7·9. Calc. for $C_9H_{12}O_2$: C, 71·1; H, 7·9%). On being recrystallised from water the phenol separated as a hydrate in needles, m. p. 66—68°, which lost part of the solvent of crystallisation on being dried in a vacuum (Found, in material dried in a vacuum at room temperature over phosphoric oxide: C, 64·9; H, 7·8. Calc. for $C_9H_{12}O_2,H_2O$: C, 63·5; H, 8·3%). On being warmed on the steam-bath with pyridine (2 ml.) and *p*-nitrobenzoyl chloride (0·6 g.) for ½ hour, the anhydrous phenol gave rise to a *di-*p*-nitrobenzoate*, forming cream prismatic plates, m. p. 203° (Found: C, 61·1; H, 4·0; N, 6·2. $C_{23}H_{18}O_8N_2$ requires C, 61·3; H, 4·0; N, 6·2%). A solution of the phenol (0·3 g.) and diazoaminobenzene (1·5 g.) in alcohol (15 ml.) was warmed on the steam-bath for 1 hour, and on cooling deposited the *bisphenylazo*-derivative in long red needles, m. p. 169—173°. Recrystallised from light petroleum (b. p. 80—100°), this compound formed reddish-orange silky needles, m. p. 178—179° (Found: C, 69·7; H, 5·3; N, 15·1. $C_{21}H_{20}O_2N_4$ requires C, 70·0; H, 5·6; N, 15·6%). Condensation of the phenol (0·5 g.) with hydrogen cyanide (1 ml.) in ether (50 ml.) was effected by means of hydrogen chloride, and 18 hours later the crystalline aldimine was hydrolysed with water (25 ml.) at 60—70° for 5 minutes. On cooling the hydrolysate deposited 4 : 6-*dihydroxy*-3-*methyl*-2-*ethylbenzaldehyde* (0·4 g.), forming colourless glistening prisms, m. p. 157—158°, from benzene and having a red-brown ferric reaction in alcohol (Found: C, 66·4; H, 7·0. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%). Methylation of this compound by the methyl iodide–potassium carbonate method gave the dimethyl ether which separated from light petroleum (b. p. 60—80°) in colourless prisms, m. p. 92°, and gave a 2 : 4-*dinitrophenylhydrazone*, forming red needles, m. p. 236°, from acetic acid (Found: C, 55·6; H, 5·6; N, 14·4. $C_{18}H_{20}O_6N_4$ requires C, 55·7; H, 5·2; N, 14·4%).

Authentic 4-methyl-5-ethylresorcinol was prepared by the reduction of 2 : 4-dihydroxy-6-ethylbenzaldehyde (IV; $R = R_1 = H$) (0·5 g., added in small portions during 1 hour) with a boiling mixture of concentrated hydrochloric acid (9 ml.), water (75 ml.), and alcohol (9 ml.), containing amalgamated zinc (15 g.), in the course of 3 hours, with the addition of more acid (6 ml.) and alcohol (6 ml.) after 1 hour. On isolation with ether the phenol was purified by crystallisation from benzene followed by sublimation in a vacuum, and had m. p. 95—96° and a blue ferric reaction, identical in every way with a natural specimen (Found: C, 70·8; H, 7·9%). Like the natural phenol the synthetical compound separated from water as a hydrate in needles, m. p. 66—68°, which on being dried in a vacuum desiccator at room temperature appeared to be partially dehydrated (Found: C, 64·1; H, 7·9. Calc. for $C_9H_{12}O_2,H_2O$: C, 63·5; H, 8·3%). The bisphenylazo-derivative formed long, silky red needles, m. p. and mixed m. p. 178—179°, identical with a specimen prepared from the natural phenol. Similarly the di-*p*-nitrobenzoate and the aldehyde were identical with the corresponding derivatives of the natural phenol.

Monomethyl Ethers of 2 : 4-*Dihydroxy*-6-*ethylbenzaldehyde*.—A mixture of the aldehyde (2 g.), methyl iodide (2 g.), potassium carbonate (4 g.), and acetone (75 ml.) was heated under reflux for 1 hour, and the filtered liquor was evaporated. A solution of the residue in ether (150 ml.) was extracted with 2N-sodium hydroxide (50 ml., 3 times), the combined extracts acidified, and the product isolated with ether and distilled in a vacuum, giving the 2-*hydroxy*-4-*methoxy*-6-*ethylbenzaldehyde* (IV; R = Me, R_1 = H) as a colourless viscous oil which gradually solidified and then formed colourless rectangular prisms, m. p. 48°, from light petroleum–ethyl acetate, having a red-brown ferric reaction in alcohol (Found : C, 66·6; H, 6·5. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in bright-red flat prisms, m. p. 220° (decomp.) (Found : N, 15·8. $C_{16}H_{16}O_6N_4$ requires N, 15·6%). A solution of this monomethyl ether (0·5 g.) and acetophenone (0·5 g.) in ethyl acetate was saturated with hydrogen chloride, and in the course of 48 hours 7-*methoxy*-5-*ethylflavylium chloride* separated in golden-yellow needles (0·5 g.). Crystallised from dilute hydrochloric acid, the compound formed golden-brown flat prisms decomposing at 161° (Found : Cl, 11·6. $C_{18}H_{17}O_2Cl$ requires Cl, 11·5%).

Monobenzylation of 2 : 4-dihydroxy-6-ethylbenzaldehyde (1·6 g.) was effected with benzyl bromide (1·5 ml.) and potassium carbonate (5 g.) in boiling acetone (75 ml.) during 1 hour. On isolation 2-*hydroxy*-4-*benzyloxy*-6-*ethylbenzaldehyde* (IV; R = CH_2Ph, R_1 = H) was distilled in a high vacuum, and obtained as a colourless viscous oil (2·1 g.), b. p. 165—166°/0·1 mm., giving a red-brown ferric reaction in alcohol (Found : C, 75·2; H, 6·1. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%). The *oxime* of this ether formed colourless needles, m. p. 108°, from alcohol (Found : C, 70·7; H, 6·7; N, 5·3. $C_{16}H_{17}O_3N$ requires C, 70·9; H, 6·3; N, 5·2%), and the 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in shining scarlet plates, m. p. 237° (decomp.) (Found : N, 12·6. $C_{22}H_{20}O_6N_4$ requires N, 12·8%). Methylation of the monobenzyl ether with excess of methyl iodide and potassium carbonate during 12 hours gave 4-benzyloxy-2-methoxy-6-ethylbenzaldehyde (IV; R = CH_2Ph, R_1 = Me) which was purified by distillation in a high vacuum and obtained as a colourless oil (1·5 g.), b. p. 170°/0·1 mm., giving an *oxime* in colourless rectangular prisms, m. p. 133—134°, from alcohol (Found : C, 71·8; H, 6·4; N, 5·1. $C_{17}H_{19}O_3N$ requires C, 71·6; H, 6·7; N, 5·0%) and a 2 : 4-*dinitrophenylhydrazone*, in rosettes of scarlet needles, m. p. 179° (decomp.), from ethyl acetate (Found : N, 12·4. $C_{23}H_{22}O_6N_4$ requires N, 12·4%).

Debenzylation of the mixed ether (1·5 g.) was effected with a mixture of concentrated hydrochloric acid (10 ml.) and acetic acid (15 ml.) on the steam-bath for 10 minutes. The resulting deep-green solution was diluted with water, and on isolation with ether 4-*hydroxy*-2-*methoxy*-6-*ethylbenzaldehyde* (IV; R = H, R_1 = Me) was crystallised from benzene and then from benzene–methanol, forming colourless flat prisms, m. p. 199°, readily soluble in dilute aqueous sodium hydroxide and having a negative ferric reaction (Found : C, 66·6; H, 6·8. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* formed deep crimson plates, m. p. 279° (decomp.), from ethyl acetate (Found : N, 15·6. $C_{16}H_{16}O_6N_4$ requires N, 15·6%).

2-(3 : 5-*Dihydroxyphenyl*)*butane*.—Ethylmagnesium iodide (from 10 g. of magnesium) in ether (150 ml.) was added to a solution of 3 : 5-dimethoxyacetophenone (14 g.) in benzene (300 ml.), the ether was removed by distillation, the residual mixture was heated under reflux for 2 hours, the benzene was distilled off, and the residue was maintained at 100° for 2 hours, cooled, and decomposed with aqueous ammonium chloride at 0°. On isolation with ether the resulting 2-(3 : 5-*dimethoxyphenyl*)*but*-2-*ene* (XII) (12 g.) was purified by distillation in a vacuum, and obtained as a pale-yellow oil, b. p. 155°/14 mm., behaving as an unsaturated compound towards aqueous potassium permanganate and bromine water (Found : C, 75·0; H, 8·5. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%). Hydrogenation of this compound with hydrogen at 74 lb./sq. in. and a palladium–charcoal catalyst (from 1 g. of charcoal and 0·2 g. of palladium chloride) for 4 hours gave rise to a theoretical yield of 2-(3 : 5-dimethoxyphenyl)butane (XIII) as a colourless oil, b. p. 143°/13 mm. On being demethylated with boiling hydriodic acid (70 ml.; *d* 1·7) and acetic acid (from 45 ml. of anhydride) for 45 minutes this ether (10 g.) gave rise to 2-(3 : 5-dihydroxyphenyl)butane as a colourless viscous oil (7·3 g.), b. p. 143°/0·2 mm., which could not be induced to crystallise and gave a *di*-p-*nitrobenzoate*, forming slender cream prisms, m. p. 149°, from 80% acetic acid (Found : C, 61·9; H, 4·6; N, 6·3. $C_{24}H_{20}O_8N_2$ requires C, 62·1; H, 4·4; N, 6·0%).

2-(3 : 5-*Dihydroxy*-2-*methylphenyl*)*butane* (XIV; R = Me).—Interaction of the foregoing resorcinol derivative (7 g.) with zinc cyanide (8·0 g.) and excess of hydrogen chloride in ether (200 ml.) in the course of 72 hours, and subsequent hydrolysis of the oily aldimine salt with water (100 ml.) at 80° for ½ hour gave rise to 2-(3 : 5-dihydroxy-2-formylphenyl)butane (XIV; R = CHO) as an oil (7·0 g.) which was characterised by the formation of the *semicarbazone*, forming small prisms, m. p. 206°, from water (Found : C, 57·5; H, 6·7; N, 16·3. $C_{12}H_{17}O_3N_3$ requires C, 57·4; H, 6·8; N, 16·7%). Reduction of this aldehyde with a boiling mixture of concentrated hydrochloric acid (50 ml.) and alcohol (50 ml.) containing amalgamated zinc (50 g.) for 6 hours, with the addition of more acid (25 ml.) and alcohol (25 ml.) after 2 hours, furnished 2-(3 : 5-*dihydroxy*-2-*methylphenyl*)*butane* (XIV; R = Me) which was purified by distillation in a vacuum, and obtained as a viscous oil (4 g.), b. p. 135°/0·2 mm., giving a pale-blue colouration with aqueous ferric chloride and a yellow colouration with aqueous bleaching powder (Found : C, 73·6; H, 9·2. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·9%). The *di*-p-*nitrobenzoate* separated from 90% acetic acid in glistening, slender, cream prisms, m. p. 164° (Found : C, 62·5; H, 4·8; N, 5·8. $C_{25}H_{22}O_8N_2$ requires C, 62·8; H, 4·6; N, 5·9%).

3 : 5-*Dimethoxy*-2-*methylbenzoic acid* (XV; R = OH).—*o*-Toluic acid was converted into the barium salt of the 3 : 5-disulphonic acid, and this compound was fused with potassium hydroxide according to the directions of Jacobsen and Wierss (*loc. cit.*), giving 3 : 5-dihydroxy-2-methylbenzoic acid, but the yields in the latter process were very variable, and in a considerable number of experiments the only solid acid obtained was *m*-hydroxybenzoic acid. Methylation of 3 : 5-dihydroxy-2-methylbenzoic acid with methyl sulphate and 20% aqueous sodium hydroxide followed by hydrolysis of the resulting ester gave rise to an almost quantitative yield of 3 : 5-*dimethoxy*-2-*methylbenzoic acid* which separated from benzene in well-defined, stout, rectangular prisms, m. p. 161°, readily soluble in alcohol and sparingly soluble in water (Found : C, 61·1; H, 6·1. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%). On being cooled

quickly a warm saturated solution of the acid deposited slender needles, m. p. 161°, which in contact with the solvent changed to stout rectangular prisms.

In the course of numerous experiments on the reduction of methyl 3 : 5-dihydroxy-2-formylbenzoate by Clemmensen's method, as an alternative route to 3 : 5-dimethoxy-2-methylbenzoic acid, disappointing yields of the product were invariably obtained. The following appear to be the best conditions : a solution of the formyl ester (3 g.) in methanol (60 ml.) was slowly added to a mixture of concentrated hydrochloric acid (50 ml.), water (10 ml.), and amalgamated zinc (25 g.) which was then heated under reflux for 1 hour. On isolation with ether the product, which contained only traces of acidic material, was distilled in a high vacuum, giving *methyl* 3 : 5-*dihydroxy*-2-*methylbenzoate*, b. p. 170°/0·5 mm., along with a small amount of lower-boiling oil and much resin. Crystallised from benzene–light petroleum, this ester formed thick plates, m. p. 124°; yield, 10—15% of theoretical (Found : C, 59·2; H, 5·4. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%). Methylation of this ester with methyl sulphate and aqueous sodium hydroxide and subsequent hydrolysis of the methyl ester gave rise to 3 : 5-dimethoxy-2-methylbenzoic acid, m. p. and mixed m. p. 160—161° (Found : C, 61·2; H, 6·1%). A solution of 3 : 5-dimethoxy-2-methylbenzoyl chloride (10 g., prepared by the interaction of molecular proportions of the acid and phosphorus pentachloride) in ether (200 ml.) was added during 15 minutes to an excess of ethereal diazomethane (from 28 g. of nitrosomethylurea and 200 ml. of ether) maintained at 0° for 4 hours, and then the excess of diazomethane and the solvent were removed in a vacuum, leaving the diazoketone as a mass of pale yellow needles. To a solution of this product in chloroform (150 ml.) hydriodic acid (30 ml.; *d* 1·7) was slowly added (10 minutes), with agitation of the mixture, followed by water (150 ml.) 15 minutes later. The chloroform layer was separated, washed with aqueous sodium hydrogen carbonate and aqueous sodium hydrogen sulphite, dried, and evaporated, leaving the *ketone* as an oil which was distilled in a high vacuum and then crystallised from benzene–light petroleum (b. p. 60—80°), forming colourless prisms, m. p. 40° (Found : C, 67·9; H, 7·3. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·2%). This ketone, which reacted only slowly with carbonyl reagents, gave a 2 : 4-*dinitrophenylhydrazone* forming orange needles, m. p. 151°, from alcohol (Found : N, 15·2. $C_{17}H_{18}O_6N_4$ requires N, 15·0%). The *semicarbazone* crystallised from benzene in squat, colourless prisms, m. p. 166° (Found : N, 16·6. $C_{12}H_{17}O_3N_3$ requires N, 16·7%).

3 : 5-Dimethoxy-2-methylacetophenone (5 g.), dissolved in benzene (100 ml.), was slowly added to a well-stirred solution of ethylmagnesium iodide (from 4 g. of magnesium) in ether (125 ml.), the ether was distilled off, the benzene liquor was heated under reflux for 4 hours, the solvent was evaporated, and the residue was kept at 100° for 2 hours. Next day the product was decomposed with aqueous ammonium chloride, and the resulting 2-(3 : 5-dimethoxy-2-methylphenyl)but-2-ene (XVI) was isolated with ether and purified by distillation, being obtained as a colourless oil (5 g.), b. p. 125—135°/0·5 mm. Hydrogenation of this butene (3 g.), dissolved in alcohol (100 ml.), with a palladium–charcoal catalyst (from 1 g. of charcoal and 0·2 g. of palladium chloride) for 15 minutes gave rise to a quantitative yield of the *butane* (XVII) which on distillation was obtained as a colourless oil, b. p. 105°/0·1 mm. (Found : C, 74·8; H, 9·9. $C_{13}H_{20}O_2$ requires C, 75·0; H, 9·6%). On being demethylated with boiling concentrated hydriodic acid (15 ml.; *d* 1·7) for $\frac{1}{2}$ hour, this compound (2 g.) yielded 2-(3 : 5-dihydroxy-2-methylphenyl)butane (XIV; R = Me) (1·5 g.), b. p. 130—131°/0·1 mm., which gave the di-*p*-nitrobenzoate, m. p. and mixed m. p. 164° (Found : N, 5·6. Calc. for $C_{25}H_{22}O_8N_2$: N, 5·9%).

Reduction of (A) *and* (B) *with Hydriodic Acid and Phosphorus.*—(A) or (B) (5 g.) was heated under reflux with hydriodic acid (75 ml.; *d* 1·7) and red phosphorus (2·5 g.) for 3 hours, and the cooled solution was diluted with water (150 ml.), saturated with ammonium sulphate, and extracted with ether (100 ml. × 6). The phenolic fraction was separated from the combined ethereal extracts by means of 2N-sodium hydroxide, and the alkaline liquor was saturated with carbon dioxide, and extracted with ether. Distillation of the residue left on evaporation of the ethereal extracts gave 2-(3 : 5-dihydroxy-2-methylphenyl)butane as a colourless oil (2·5 g.), b. p. 132—135°/0·2 mm., giving the same ferric reaction as the synthetical material (Found : C, 73·6; H, 9·2%). The di-*p*-nitrobenzoate separated from 90% acetic acid in glistening cream prisms, m. p. 164°, undepressed on admixture with a specimen from the synthetical phenol (Found : C, 62·7; H, 4·2; N, 5·8%).

(WITH F. M. DEAN.) 3 : 5-*Dimethoxy*-2-*methylbenzyl Cyanide* (XIX; R = H, R_1 = CN).—The diazoketone [from 3 : 5-dimethoxy-2-methylbenzoyl chloride (5 g.) and excess of ethereal diazomethane] was dissolved in dioxan (20 ml.), and treated with 2N-ammonia (25 ml.) in dioxan (25 ml.) containing silver nitrate (0·2 g.), and the mixture kept (agitate) at 80° for $1\frac{1}{2}$ hours. The liquid, which became red and deposited a silver mirror, was filtered, and evaporated in a vacuum, leaving a residue of almost pure 3 : 5-*dimethoxy*-2-*methylphenylacetamide* (XVIII) which formed colourless needles (4·6 g.), m. p. 149°, from alcohol (Found : N, 6·5. $C_{11}H_{15}O_3N$ requires N, 6·7%). The amide (3 g.) was dehydrated in boiling chloroform (100 ml.) with phosphoric oxide (2 g.) during 3 hours, and the resulting *cyanide* crystallised from light petroleum (b. p. 60—80°) in colourless needles, (1·8 g.), m. p. 66° (Found : C, 68·9; H, 6·8; N, 7·2. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·9; N, 7·3%). From the residues unchanged amide (0·5—0·7 g.) was recovered.

A solution of this cyanide (6 g.) in benzene (150 ml.) was added to benzene (50 ml.) containing finely-powdered sodamide (1·5 g.) in an atmosphere of nitrogen, and the mixture gently heated under reflux. The sodio-derivative of the cyanide separated, and 25 minutes later the pasty mixture was cooled, treated with methyl sulphate (4·8 g.) in benzene (25 ml.), and heated on the steam-bath for 1 hour. On cooling the benzene liquor was washed with water, dried, and evaporated, and the residue distilled in a high vacuum, giving a product (4 g.), b. p. 135°/0·5 mm., which partly solidified. Ether (35 ml.), containing anhydrous stannous chloride (2 g.), was saturated at 0° with hydrogen chloride, and the methylated cyanide (1·5 g.) was introduced followed by more hydrogen chloride. On being kept the aldimine stannichloride separated as an oil which slowly crystallised, and 48 hours later the ethereal layer was decanted, and the residue repeatedly washed with fresh ether. A solution of the solid in water (30 ml.) was almost neutralised with 2N-aqueous sodium hydroxide, heated on the water-bath for 30 minutes, and a further small amount of aqueous sodium hydroxide added to render the reaction mixture neutral. The resulting aldehyde was isolated with ether, and on distillation obtained as a colourless oil,

b. p. 112—115°/0·2 mm., which, on treatment with semicarbazide acetate, gave an almost quantitative yield of a condensation product during 72 hours. This product formed rosettes of colourless prisms, m. p. 138°, from benzene–light petroleum (Found : C, 58·8; H, 7·2; N, 15·8. Calc. for $C_{13}H_{19}O_3N_3$: C, 58·9; H, 7·2; N, 15·9%).

A solution of the aldehydic product (0·4 g.) in ether (20 ml.) was treated with methylmagnesium iodide (from 0·2 g. of magnesium) in ether (20 ml.), and next day the mixture was heated under reflux for ½ hour, cooled, and treated with aqueous ammonium chloride. The ethereal layer was separated, washed, dried, and distilled, leaving the product as an oil which was acylated with pyridine and *p*-nitrobenzoyl chloride. Crystallised from alcohol, the resulting solid gave a p-*nitrobenzoate* in cream needles, m. p. 150—151° [Found (mean of 3 analyses) : C, 65·3; H, 6·2; N, 3·9. $C_{21}H_{25}O_6N$ requires C, 65·1; H, 6·5; N, 3·6. $C_{20}H_{23}O_6N$ requires C, 64·3; H, 6·2; N, 3·8%]. The alcoholic liquors from the crystallisation of this substance were evaporated by a current of air, and the residue extracted with boiling light petroleum (b. p. 60—80°), leaving a small amount of the derivative m. p. 150—151°. On cooling, the light-petroleum extract deposited pale yellow plates, and on repeated crystallisation from alcohol this material gave the *p*-nitrobenzoate of (B) in characteristic prisms, m. p. 108—109° alone or mixed with a natural specimen (Found : C, 64·5; H, 6·3; N, 3·9. $C_{20}H_{23}O_6N$ requires C, 64·3; H, 6·2; N, 3·8%).

2 : 4-*Dimethoxy*-6-*ethylbenzyl Cyanide* (XI; R = CN).—To an intimate mixture of 2 : 4-dimethoxy-6-ethylbenzaldehyde (1 mol.), hippuric acid (4 mols.), and sodium acetate (4 mols.) sufficient acetic anhydride was added to form a stiff paste which was then heated on the steam-bath for 3 hours, and treated with alcohol and water to decompose the excess of anhydride. On being kept the mixture deposited the *azlactone* in long silky, yellow needles, m. p. 148—149°, after having been recrystallised from alcohol; the yield was variable, the optimum being 6 g. of azlactone from 6 g. of aldehyde (Found : C, 71·0; H, 5·8; N, 4·0. $C_{20}H_{19}O_4N$ requires C, 71·2; H, 5·7; N, 4·2%). The azlactone (3 g.) was hydrolysed with 10% aqueous sodium hydroxide for 8 hours, and the cooled solution saturated with sulphur dioxide, kept for 24 hours, filtered to remove benzoic acid, treated with concentrated hydrochloric acid, and heated on the steam-bath for 30 minutes. The phenylpyruvic acid (XI; R = $CO{\cdot}CO_2H$) was isolated with ether, and converted into the *oxime* (1·6 g.). Crystallised from alcohol, this derivative formed white fluffy needles, m. p. 155° (Found : C, 58·2; H, 6·6; N, 5·4. $C_{13}H_{17}O_5N$ requires C, 58·4; H, 6·4; N, 5·2%). Decomposition of the oxime (1·3 g.) with acetic anhydride (5 ml.) on the steam-bath for 15 minutes gave rise to 2 : 4-*dimethoxy*-6-*ethylbenzyl cyanide* which was purified by distillation in a high vacuum, and then by crystallisation from light petroleum (b. p. 60—80°), forming colourless prisms (1·2 g.), m. p. 76° (Found : C, 70·0; H, 7·2; N, 7·0. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·3; N, 6·8%).

2 : 4-*Dimethoxy*-6-*ethylphenylacetaldehyde* (XI; R = CHO).—The foregoing cyanide (2 g.) was added with vigorous agitation to a mixture of ether (40 ml.) and stannous chloride (3 g.) which had been saturated at 0° with hydrogen chloride. 48 Hours later the crystals and viscous oil left on decanting the ethereal layer were washed with ether, and dissolved in water (50 ml.), the solution was almost neutralised with sodium carbonate, and the mixture warmed on the steam-bath for ½ hour. On isolation the *aldehyde* was obtained as a colourless oil (1·2 g.), b. p. 150°/3 mm. (Found : C, 69·0; H, 7·9. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%).

1-(2 : 4-*Dimethoxy*-6-*ethylphenyl*)*propan*-2-*ol* (X; R = Me).—An ethereal solution of magnesium-methyl iodide (from 0·12 g. of magnesium) in ether (20 ml.) at below 0° was gradually added to the foregoing aldehyde (0·75 g.) in ether (20 ml.) cooled by an ice–salt mixture, and after having been kept at room temperature for ½ hour the mixture was treated with aqueous ammonium chloride. The ethereal layer was separated, dried, and distilled, leaving the alcohol as a colourless oil which was converted into the p-*nitrobenzoate*. This substance crystallised from alcohol in stout, bright yellow prisms (0·6 g.), m. p. 82° (Found : C, 64·4; H, 6·5; N, 3·6. $C_{20}H_{23}O_6N$ requires C, 64·3; H, 6·2; N, 3·8%).

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