

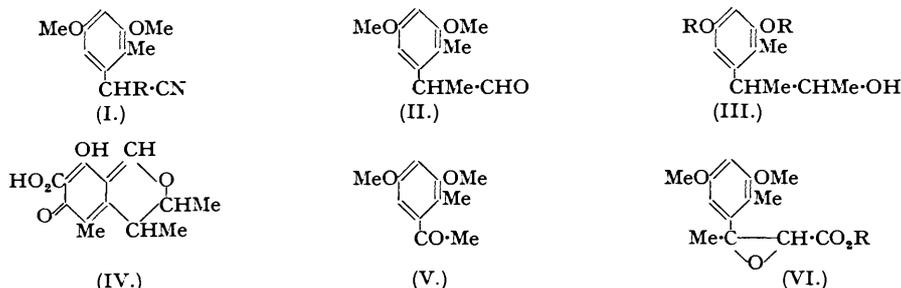
580. The Chemistry of Fungi. Part XIII. Citrinin.

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By means of its brucine salt optically inactive citrinin, obtained from the optically inactive phenol (B) [3-(4 : 6-dihydroxy-*o*-tolyl)butan-2-ol], has been resolved into the (+)- and (-)-isomerides of which the latter is identical with natural citrinin (cf. Part VII, *J.*, 1949, 1563). Degradation of these (+)- and (-)-isomerides furnished respectively (+)- and (-)-phenol (A) which on admixture in equal amounts gave phenol (B).

New syntheses of α -(4 : 6-dimethoxy-*o*-tolyl)propionaldehyde (II) and 2-(3 : 5-dimethoxy-2 : 4-dimethylphenyl)butane have been described.

In Part VII (*J.*, 1949, 1563) it was indicated that to complete the synthesis of natural citrinin (IV) it was necessary either to obtain the optically active phenol (A) by the resolution of the optically inactive phenol (B) [which is one of the two racemates having formula (III; R = H)], or to resolve the racemic form of citrinin synthesised from this compound. Further, in the synthesis of phenol (B) dimethyl ether* (III; R = Me) from 4 : 6-dimethoxy-*o*-toluic acid by the stages (I; R = H), (I; R = Me), and (II), it was not clear whether the last two intermediates



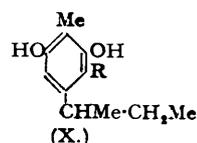
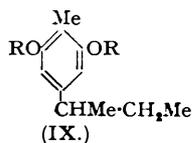
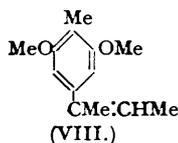
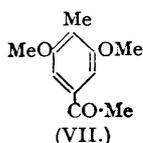
had been obtained pure (Part IV, *J.*, 1949, 859). The present communication deals with these outstanding problems and also with an alternative rational synthesis of the butane (X; R = Me)

* In the partial ethers thus designated, the phenolic hydroxyl groups are methylated and the alcoholic hydroxyl group is unaffected.

employed in the orientation of a degradation product from methylated citrinin (Part V, *J.*, 1949, 867).

The difficulties encountered in the preparation of 4 : 6-dihydroxy-*o*-toluic acid (Part IV, *loc. cit.*) have now been overcome and the acid obtained in fairly satisfactory yield. Prepared from this compound, 3 : 5-dimethoxy-2-methylbenzyl cyanide (I; R = H) was methylated in the α -position by use of sodamide prepared *in situ*, and the product (I; R = Me) converted by Stephen's method into the aldehyde (II), which with methylmagnesium iodide gave a mixture of the two racemates having formula (III; R = Me); this was separated by fractional crystallisation of the mixed *p*-nitrobenzoates. That the aldehyde (II) now obtained and hence the butanol (III; R = Me) were not contaminated with small amounts of a higher homologue arising from the bis-methylation of the nitrile (I; R = H) (cf. Part IV, *loc. cit.*) is shown by the independent synthesis of (II) by way of the glycidic ester (VI; R = Et). The compound (VI; R = Et) was prepared by the condensation of 3 : 5-dimethoxy-2-methylacetophenone and ethyl chloroacetate with sodium ethoxide and on hydrolysis followed by decomposition of the resulting acid (VI; R = H) furnished the aldehyde (II).

Since the demethylation of phenol (A) dimethyl ether is accompanied by racemisation giving phenol (B) (Part VII, *loc. cit.*) and attempts to resolve phenol (B) were unsuccessful, the resolution of optically inactive citrinin derived from phenol (B) was undertaken. By means of its brucine salt this compound has been separated into a (+)- and a (-)-citrinin of which the latter is identical with the natural citrinin and with the specimen synthesised from phenol (A). Hydrolytic decomposition of (+)- and (-)-citrinin with aqueous sodium hydroxide gave respectively (+)- and (-)-phenol (A), a mixture of which furnished phenol (B). This result in conjunction with the resolution of the hydrogen phthalate of phenol (B) dimethyl ether clearly confirms that phenol (B) is one of the two possible racemates having formula (III; R = H) (Part IV, *loc. cit.*) (cf. Cram, *J. Amer. Chem. Soc.*, 1948, 70, 4244; 1950, 72, 1001).



In Part V (*loc. cit.*) the structure of 3-(3 : 5-dihydroxy-2 : 4-dimethylphenyl)butan-2-ol, a degradation product of methylated citrinin, was derived from its conversion into 2-(3 : 5-dihydroxy-2 : 4-dimethylphenyl)butane (X; R = Me), the orientation of which was established by an indirect method. The following more rational synthesis of the butane (X; R = Me) has now been achieved. On dehydration the product formed by the condensation of 3 : 5-dimethoxy-4-methylacetophenone (VII) with ethylmagnesium iodide gave 2-(3 : 5-dimethoxy-4-methylphenyl)but-2-ene (VIII) which on hydrogenation furnished 2-(3 : 5-dimethoxy-4-methylphenyl)butane (IX; R = Me). Demethylation of (IX; R = Me) yielded the resorcinol (IX; R = H) which by Gattermann's method gave an aldehyde which can only have the structure (X; R = CHO). Reduction of this product by Clemmensen's method furnished 2-(3 : 5-dihydroxy-2 : 4-dimethylphenyl)butane (X; R = Me), characterised by the formation of the di-*p*-nitrobenzoate which was identical with the derivative from natural sources.

EXPERIMENTAL.

4 : 6-Dihydroxy-*o*-toluic Acid.—*o*-Toluic acid (50 g.) was sulphonated with 61% oleum (100 ml.) at 160—170° during 6 hours and next day the viscous reaction mixture was gradually added to ice (600 g.). The crystalline sodium salt of the resulting disulphonic acid was prepared by way of the barium salt in the usual manner and was added gradually to a well-stirred melt of potassium hydroxide (450 g., containing 15 ml. of water) at 160°. The mixture was then heated at 190—200° for $\frac{1}{2}$ hour and at 180° for 2 hours, cooled to about 100—110°, and added to ice (1 kg.). From this solution which had been acidified with concentrated hydrochloric acid 4 : 6-dihydroxy-*o*-toluic acid was isolated with ether (100 ml. \times 6) and then crystallised from water, forming colourless needles (10—11 g.), m. p. 245° (slight decomp.). Esterification with diazomethane gave the methyl ester, m. p. 124°, which on methylation by the methyl iodide-potassium carbonate method, followed by hydrolysis, furnished 4 : 6-dimethoxy-*o*-toluic acid, m. p. 160—161° after purification (cf. Part IV, *loc. cit.*).

α -(4 : 6-Dimethoxy-*o*-tolyl)propionitrile (I; R = Me).—3 : 5-Dimethoxy-2-methylphenylacetamide (Part IV, *loc. cit.*) (5 g.) was dehydrated with phosphoryl chloride (3.1 ml.) on the steam-bath for 45 minutes; the resulting 3 : 5-dimethoxy-2-methylbenzyl cyanide (I; R = H) (4.3 g.), purified by distillation, had m. p. 66° (cf. Part IV, *loc. cit.*, where phosphoric oxide was employed).

3 : 5-Dimethoxy-2-methylphenylacetamide (2.3 g.) was hydrolysed with boiling 20% aqueous potassium hydroxide (40 ml.) during 10 hours and the resulting 3 : 5-dimethoxy-2-methylphenylacetic acid

isolated from the acidified hydrolysate with ether. Crystallised from water and then sublimed at 140—150°/0.05 mm., this acid formed colourless needles, m. p. 130—132° (Found: C, 62.8; H, 6.9. $C_{11}H_{14}O_4$ requires C, 62.9; H, 6.7%).

Sodium (0.3 g.) was added to liquid ammonia containing ferric nitrate (0.1 g.) and a gentle current of dry air aspirated through the liquid until the sodium began to dissolve. When the initial blue colour of the solution had faded more sodium (2 g.) was added in portions and the mixture vigorously stirred for 10—15 minutes; the blue colour had then disappeared and a grey sludge of sodamide had separated. A solution of 3 : 5-dimethoxy-2-methylbenzyl cyanide (17.1 g.) in benzene (70 ml.) containing ether (20 ml.) was then introduced dropwise and the mixture stirred until the ammonia had evaporated. The residual liquor, which contained the finely divided sodio-derivative of 3 : 5-dimethoxy-2-methylbenzyl cyanide, was treated with methyl iodide (20 ml.) and ether (20 ml.) and simultaneously heated under reflux (with stirring) for 1 hour, cooled, treated with water (125 ml.), acidified, and extracted several times with ether. The combined extracts were washed with aqueous sodium hydrogen sulphite, dried, and evaporated, leaving α -(4 : 6-dimethoxy-*o*-tolyl)propionitrile (I; R = Me) which, on distillation, was obtained as a colourless oil (13 g.), b. p. 117—119°/0.2 mm. (Found: C, 70.3; H, 7.1. $C_{12}H_{15}O_2N$ requires C, 70.2; H, 7.3%). A solution of this nitrile (1 g.) in concentrated sulphuric acid (5 ml.) was kept for 1 hour and poured on ice, giving a precipitate of the α -(4 : 6-dimethoxy-*o*-tolyl)propionamide (1.05 g.) which formed colourless prisms, m. p. 113°, from benzene—light petroleum (b. p. 60—80°) (Found: C, 64.6; H, 7.0; N, 6.1. $C_{12}H_{17}O_3N$ requires C, 64.6; H, 7.3; N, 6.0%).

3-(4 : 6-Dimethoxy-*o*-tolyl)butan-2-ol.—(a) Prepared from the foregoing nitrile (6 g.) by Stephen's method, α -(4 : 6-dimethoxy-*o*-tolyl)propionaldehyde (II) was obtained as a colourless mobile liquid (2 g.), b. p. 103—105°/0.01 mm. (Found: C, 69.4; H, 8.0. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%), which gave the semicarbazone, m. p. 138°, identical with the derivative described in Part IV (*loc. cit.*). The oxime formed tufts of colourless slender prisms, m. p. 134°, from dilute methanol (Found: C, 46.7; H, 7.7; N, 6.1. $C_{12}H_{17}O_3N$ requires C, 64.6; H, 7.6; N, 6.3%).

Condensation of this aldehyde (3.7 g.) with methylmagnesium iodide as described in Part IV (*loc. cit.*) gave the mixed racemates of 3-(4 : 6-dimethoxy-*o*-tolyl)butan-2-ol (III; R = Me) as a colourless viscous liquid (3.5 g.), b. p. 109—110°/0.03 mm. (Found: C, 69.9; H, 9.3. Calc. for $C_{13}H_{20}O_3$: C, 69.7; H, 8.9%), which gave a mixture of the *p*-nitrobenzoates (5.5 g.). This was resolved by fractional crystallisation from alcohol and acetic acid. A less soluble ester (2.2 g.) separated from alcohol in rosettes of pale greenish-yellow needles, m. p. 153—154°, unchanged on sublimation in a high vacuum (Found: C, 64.4; H, 6.4; N, 4.4; OMe, 16.3. Calc. for $C_{20}H_{23}O_6N$: C, 64.3; H, 6.2; N, 3.8; OMe, 16.6%) (cf. Part IV, *loc. cit.*); the corresponding product, m. p. 150—151°, obtained previously gave high analytical results for carbon. The more soluble *p*-nitrobenzoate (0.5 g.) of phenol (B) dimethyl ether had m. p. and mixed m. p. 108—109° (Part IV, *loc. cit.*). This compound, m. p. 108—109° (0.2 g.), was hydrolysed with 20% methanolic potassium hydroxide (10 ml.) during 3 hours and the resulting dimethyl ether of phenol (B) converted into the hydrogen phthalate which formed colourless prisms, m. p. 144°, from chloroform, identical with the derivative obtained by degradation, of natural citrinin (Part IV, *loc. cit.*) (Found: C, 67.7; H, 6.7. Calc. for $C_{21}H_{24}O_6$: C, 67.7; H, 6.5%).

(b) On the addition of powdered sodium ethoxide (5 g.) to a well stirred mixture of 3 : 5-dimethoxy-2-methylacetophenone (Part IV, *loc. cit.*) (13.7 g.) and ethyl chloroacetate (8.5 ml.) at 5° a vigorous reaction ensued. The resulting orange-red mixture was stirred at 5° for 2½ hours and then at room temperature for 24 hours, heated on the steam-bath for 2 hours, cooled, treated with ice-water (150 ml.), and extracted with ether (75 ml. \times 4). The combined extracts were washed with 5% aqueous sodium carbonate (100 ml. \times 2) and then water (50 ml. \times 3), dried, and evaporated, leaving an oil which on distillation in a vacuum furnished unchanged ketone (6.8 g.), b. p. 122—130°/0.4 mm., and a pale green viscous oil (5 g.), b. p. 155—163°/0.5 mm. Repeated distillation of the latter fraction gave ethyl β -(4 : 6-dimethoxy-*o*-tolyl)- β -methylglycidate as a colourless oil (5.5 g.), b. p. 156—158°/0.6 mm. A mixture of this ester (5.5 g.), methanol (35 ml.), and 12.5% aqueous potassium hydroxide (20 ml.) was boiled for 4 hours, cooled, and acidified with 2*N*-hydrochloric acid. On isolation with ether the resulting acid (orange-red oil) was heated with copper bronze (1 g.) in a vacuum until the evolution of carbon dioxide had ceased and the residue then distilled, giving α -(4 : 6-dimethoxy-*o*-tolyl)propionaldehyde (II) (2.6 g.), b. p. 105—106°/0.01 mm., identified by conversion into the semicarbazone, m. p. 138°, and the oxime, m. p. 134° (Found: C, 64.8; H, 7.6; N, 6.5%). From this aldehyde (2 g.) 3-(4 : 6-dimethoxy-*o*-tolyl)butan-2-ol (mixed racemates) was prepared with methylmagnesium iodide and converted into the mixture of *p*-nitrobenzoates which was separated by fractional crystallisation as in (a). The *p*-nitrobenzoate (0.2 g.) of phenol (B) dimethyl ether had m. p. and mixed m. p. 108—109° (Found: C, 64.6; H, 6.0; N, 3.9%). The second *p*-nitrobenzoate had m. p. and mixed m. p. 153—154° (Found: C, 64.5; H, 6.1; N, 3.6%).

3-(4 : 6-Dibenzoyloxy-*o*-tolyl)butan-2-ol [Dibenzyl Ether of Phenol (B)].—Benzylation of phenol (B) (5 g.) with benzyl bromide (7.7 ml.) and potassium carbonate (7.1 g.) in boiling acetone (80 ml.) appeared to be complete in about 50 hours. A solution of the product in ether (200 ml.) was washed with 2*N*-aqueous sodium hydroxide (20 ml. \times 3) and then water (20 ml. \times 2), dried, and evaporated, leaving an oil. On distillation in a vacuum this gave the dibenzyl ether as a pale yellow glass (7.5 g.), b. p. 194—196°/0.03 mm., which could not be induced to crystallise (Found: C, 79.5; H, 7.4. $C_{25}H_{28}O_3$ requires C, 79.8; H, 7.5%). In an attempt to resolve phenol (B) the phthalate of this ether was prepared but as this derivative could not be obtained crystalline the project was abandoned.

Resolution of Optically Inactive Citrinin.—Brucine (1.9 g. of the tetrahydrate) dissolved in acetone—methanol (15 ml.; 1 : 3) was added to a warm solution of (\pm)-citrinin (Part VII, *loc. cit.*) (1 g.) in the same solvent (40 ml.), and the crystalline product (2.1 g.), m. p. 167—168° (decomp.), was collected 1 hour later. Recrystallisation of this solid from methanol gave 3 fractions, (a) (0.5 g.), m. p. 178° (decomp.), (b) (0.3 g.), m. p. 178° (decomp.), and (c) (0.3 g.), m. p. 176—178° (decomp.). Of these (a) and (b) were combined and recrystallised several times from much methanol, giving the brucine salt of (–)-citrinin as

a hydrate in irregular hexagonal prisms, m. p. 182—183° (decomp.) (alone or on admixture with the salt from natural citrinin) (Found : C, 65.0; H, 6.3; N, 4.6. $C_{13}H_{14}O_5 \cdot C_{23}H_{26}O_4 \cdot N_2 \cdot H_2O$ requires C, 65.3; H, 6.4; N, 4.2%. $C_{13}H_{14}O_5 \cdot C_{23}H_{26}O_4 \cdot N_2$ requires C, 67.1; H, 6.2; N, 4.4%). Because of its low solubility in the usual organic solvents the rotation of this salt was not determined. Decomposition of the compound (0.5 g.) in acetone (15 ml.) with 2*N*-hydrochloric acid, followed by the addition of water (50 ml.), gave (–)-citrinin which was isolated with ether and crystallised from ethanol, forming characteristic long yellow prisms, m. p. 179° (decomp.) (alone or admixed with a natural specimen), $[\alpha]_D^{20} -34.5^\circ$ (c, 0.600 in alcohol) (Found : C, 62.3; H, 5.4. Calc. for $C_{13}H_{14}O_5$: C, 62.4; H, 5.6%). A specimen of the hydrated brucine salt of natural citrinin was prepared by mixing warm solutions of (–)-brucine (1.9 g. of tetrahydrate) in acetone–methanol (20 ml. of 1 : 3) and the natural acid (1 g.) in the same solvent (25 ml.). Recrystallised from methanol this salt formed irregular hexagonal prisms, m. p. 182—183° (decomp.) (Found : C, 65.4; H, 6.7; N, 4.7%).

The combined mother-liquors left after the separation of the foregoing brucine salt of (–)-citrinin were concentrated in a vacuum and on being kept the residue deposited a crystalline solid (0.4 g.), m. p. 171° (decomp.), consisting mainly of the brucine salt of (–)-citrinin. Treatment of the residual liquor with dilute hydrochloric acid regenerated crude (+)-citrinin which was recrystallised from alcohol and then converted into a brucine salt. Recrystallised from much methanol, this product gave the brucine salt of (+)-citrinin in colourless needles, m. p. 167—168° (decomp.) (Found : C, 64.3; H, 6.5; N, 4.7%). Decomposition of this compound (0.4 g.) with 2*N*-hydrochloric acid furnished (+)-citrinin (0.15 g.) which separated from alcohol in long yellow needles, m. p. 179° (decomp.), $[\alpha]_D^{20} +33.0^\circ$ (c, 0.600 in alcohol) (Found : C, 62.5; H, 5.6%). The chemical properties of (+)-citrinin were identical with those of natural (–)-isomeride.

Degradation of Synthetical (–) and (+)-Citrinin with Alkali.—(a) A solution of (–)-citrinin (0.4 g.) was heated under reflux with 10% aqueous sodium hydroxide (20 ml.) in an atmosphere of nitrogen for 3½ hours, cooled, saturated with carbon dioxide, and extracted with ether (20 ml. × 6). The residue left on evaporation of the combined, dried, ethereal extracts was sublimed in a vacuum at 150—160°/0.1 mm., giving (–)-phenol (A) in almost colourless needles, m. p. 128°, alone or admixed with a specimen derived from the natural compound, $[\alpha]_D^{20} -36.4^\circ$ (c, 0.79 in alcohol) (Found : C, 67.3; H, 8.2. Calc. for $C_{11}H_{16}O_3$: C, 67.3; H, 8.2%).

(b) Hydrolytic decomposition of (+)-citrinin under the same conditions gave (+)-phenol (A) which on sublimation in a high vacuum was obtained in rosettes of almost colourless needles, m. p. 122°, $[\alpha]_D^{20} +35.9^\circ$ (c, 0.79 in alcohol) (Found : C, 67.5; H, 8.3%). A mixture of equal amounts of (+)- and (–)-phenol (A) had a zero rotation and separated from chloroform in colourless needles, m. p. 168—169°, alone or admixed with a specimen of phenol (B) from natural citrinin.

Phenol (B) has been prepared from the dimethyl ether (Part IV, *loc. cit.*) by the demethylation procedure employed for phenol (A) dimethyl ether (Part VII, *loc. cit.*) and had m. p. and mixed m. p. 169° after purification.

3 : 5-Dimethoxy-4-methylacetophenone (VII).—When a solution of 4-methyl-3 : 5-dinitrobenzoyl chloride (Frye *et al.*, *J. Org. Chem.*, 1949, 14, 397) (5 g.) in ether (100 ml.) was added to ethereal diazomethane (from 10 g. of nitrosomethylurea and 150 ml. of ether) kept at 0°, ω-diazo-4-methyl-3 : 5-dinitroacetophenone separated in pale yellow needles and was isolated 24 hours later. Hydriodic acid (15 ml.; *d* 1.7) was added during 15 minutes to a well stirred solution of this product in chloroform (150 ml.), followed by water (150 ml.) 15 minutes later. The chloroform solution was separated, washed with aqueous sodium hydrogen sulphite, aqueous sodium hydrogen carbonate, and then water, dried, and evaporated, leaving 4-methyl-3 : 5-dinitroacetophenone (3.5 g.). This ketone separated from aqueous alcohol in almost colourless needles which in contact with the mother-liquor changed into pale yellow plates, m. p. 70—71° (Found : C, 48.4; H, 3.8; N, 12.7. Calc. for $C_9H_8O_5N_2$: C, 48.2; H, 3.6; N, 12.5%) (cf. Frye *et al.*, *loc. cit.*, who give m. p. 68—69° for a specimen prepared by an alternative process). The *oxime* formed long, colourless silky needles, m. p. 152—153°, from dilute alcohol (Found : C, 45.3; H, 3.9; N, 17.9. $C_9H_8O_5N_3$ requires C, 45.2; H, 3.8; N, 17.6%). The 2 : 4-dinitrophenylhydrazone separated from acetic acid in tiny orange needles, m. p. 257—258° (decomp.) (Found : C, 44.7; H, 3.3; N, 21.0. $C_{13}H_{12}O_8N_6$ requires C, 44.6; H, 3.0; N, 20.8%).

3-Amino-4-methyl-5-nitroacetophenone (Frye *et al.*, *loc. cit.*) gave an *oxime* which separated from dilute alcohol in slender bright yellow needles, m. p. 199° (Found : C, 51.9; H, 5.2; N, 20.3. $C_9H_{11}O_2N_3$ requires C, 51.9; H, 5.3; N, 20.1%), and an *acetyl* derivative, clusters of colourless needles, m. p. 196°, from the same solvent (Found : C, 56.2; H, 5.2; N, 11.6. $C_{11}H_{12}O_4N_2$ requires C, 55.9; H, 5.1; N, 11.9%).

The *oxime* of 3-hydroxy-4-methyl-5-nitroacetophenone (Frye *et al.*, *loc. cit.*) formed greenish-yellow needles, m. p. 188°, from water (Found : N, 13.6. $C_9H_{10}O_4N_2$ requires N, 13.3%). The *p*-nitrobenzoate of the same phenol separated from dilute alcohol in tiny buff-coloured needles, m. p. 173° (Found : N, 8.1. $C_{16}H_{12}O_7N_2$ requires N, 8.1%).

3 : 5-Dihydroxy-4-methylacetophenone (Frye *et al.*, *loc. cit.*) formed a *di-p*-nitrobenzoate, colourless needles, m. p. 220—221°, from alcohol (Found : N, 5.3. $C_{23}H_{16}O_9N_2$ requires N, 6.0%) and on methylation by the methyl iodide–potassium carbonate method gave 3 : 5-dimethoxy-4-methylacetophenone which separated from aqueous alcohol or benzene–light petroleum (b. p. 60—80°) in colourless rhombic prisms, m. p. 104° (Found : C, 68.1; H, 7.4. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.2%). The *oxime* of this ketone crystallised from dilute alcohol in colourless needles, m. p. 130° after sintering at 120° (Found : N, 7.3. $C_{11}H_{15}O_3N$ requires N, 6.7%).

2-(3 : 5-Dihydroxy-4-methylphenyl)butane (IX; R = H).—A solution of 3 : 5-dimethoxy-4-methylacetophenone (5.5 g.) in benzene (100 ml.) was added to cooled ethereal ethylmagnesium iodide (from 4.5 g. of magnesium and 100 ml. of ether), the ether was evaporated, the residual benzene solution was

heated under reflux for 4 hours and evaporated, and the viscous syrup heated on the steam-bath for 2 hours. After the addition of ice and aqueous ammonium chloride (150 ml.) to the cooled reaction mixture the product was isolated with ether and twice distilled over sodium, giving 2-(3 : 5-dimethoxy-4-methylphenyl)but-2-ene (VIII) as a colourless oil (3 g.), b. p. 115—117°/0.3 mm., which on hydrogenation with a palladium-charcoal catalyst furnished 2-(3 : 5-dimethoxy-4-methylphenyl)butane (IX; R = Me) (2.5 g.), b. p. 105°/1 mm. Demethylation of this ether (2.5 g.) with a mixture of boiling hydriodic acid (15 ml.; *d* 1.7) and acetic acid (from 10 ml. of acetic anhydride) containing red phosphorus (0.5 g.) during $\frac{1}{2}$ hour gave rise to 2-(3 : 5-dihydroxy-4-methylphenyl)butane which on distillation in a high vacuum was obtained as a mass of almost colourless needles (0.6 g.), m. p. 95°, having a negative ferric reaction (Found : C, 73.3; H, 9.1. $C_{11}H_{14}O_2$ requires C, 73.3; H, 8.9%). The *di-p*-nitrobenzoate of this phenol formed glistening, pale cream-coloured plates, m. p. 194°, from much alcohol (Found : N, 5.5. $C_{25}H_{22}O_8N_2$ requires N, 5.9%).

2-(2-Formyl-3 : 5-dihydroxy-4-methylphenyl)butane (X; R = CHO).—The interaction of 2-(3 : 5-dihydroxy-4-methylphenyl)butane (0.3 g.), hydrogen cyanide (1 ml.), and zinc cyanide (0.2 g.) in ether (25 ml.), saturated with hydrogen chloride, during 48 hours gave a crystalline aldimine salt which on hydrolysis with water (15 ml.) on the steam-bath for 15 minutes yielded 2-(2-formyl-3 : 5-dihydroxy-4-methylphenyl)butane (X; R = CHO). Purified by sublimation in a high vacuum, this aldehyde was obtained in colourless plates, m. p. 78°, having a violet-brown ferric reaction in alcohol (Found : C, 69.7; H, 7.8. $C_{12}H_{14}O_3$ requires C, 69.2; H, 7.7%). The 2 : 4-dinitrophenylhydrazones formed crimson needles, m. p. 280—281° (decomp.), from alcohol (Found : N, 14.8. $C_{18}H_{20}O_6N_4$ requires N, 14.4%).

2-(3 : 5-Dihydroxy-2 : 4-dimethylphenyl)butane (X; R = Me).—A mixture of the foregoing aldehyde (150 mg., dissolved in 10 ml. of methanol), zinc amalgam (5 g.), and concentrated hydrochloric acid (10 ml.) was kept at room temperature for 20 minutes and then heated under reflux for $\frac{1}{2}$ hour. On isolation with ether the resulting 2-(3 : 5-dihydroxy-2 : 4-dimethylphenyl)butane (100 mg.) was converted into the *di-p*-nitrobenzoate which formed colourless prisms, m. p. 146°, from much alcohol, identical with a specimen from methylated citrinin (Part V, *loc. cit.*) (Found : C, 63.2; H, 4.6; N, 5.5. Calc. for $C_{24}H_{24}O_8N_2$: C, 63.4; H, 4.9; N, 5.7%).

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