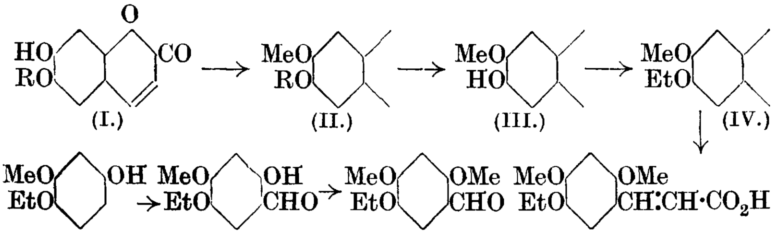
CCCXIX.—*Natural Glucosides. Part II. The Constitution of Æsculin.*

By Frank S. H. Head and Alexander Robertson.

The glucoside æsculin was first isolated in the pure state from the bark of *Æsculus hippocastanum* by Minor (*Arch. Pharm.*, 1831, **38**, 130). Rochleder and Schwartz (*Annalen*, 1853, **87**, 186; **88**, 356) showed that the substance was a monoglucoside of æsculetin and that it was hydrolysed by emulsin as well as by mineral acids. Æsculetin was synthesised by Gattermann and Köbner (*Ber.*, 1899, **32**, 287), but they did not determine the orientation of the intermediate hydroxyquinol aldehyde. The conversion of æsculetin into 2 : 4 : 5-trimethoxycinnamic acid by Tiemann and Will (*Ber.*, 1882, **15**, 2072) and the oxidation of this acid to asarylaldehyde and asaronic acid by Moore (J., 1911, **99**, 1047), together with the orientation of asaronic acid by Luff, Perkin, and Robinson (J., 1910, **97**, 1131), serve to confirm the conclusions of Gattermann and Köbner. That glucose is the sugar derived from æsculin was proved by Schunck and Marchlewski (*Annalen*, 1893, **278**, 349) and by ter Meulen (*Rec. trav. chim.*, 1905, **24**, 446). The hydrolysis by emulsin indicated that the glucoside belongs to the β-series. Glaser and Kraus (*Biochem. Z.*, 1923, **138**, 183) obtained a synthetic glucoside which appeared to be identical with the natural substance but did not exhibit in alcoholic solution the fluorescence characteristic of the natural substance. They suggested that æsculin was 7-glucosidoxy-6-hydroxycoumarin, but definite evidence of the position of the glucose residue was lacking.

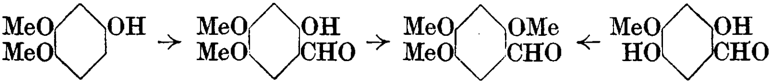


(I.) (II.) (III.) (IV.) (VI.) (VII.) (VIII.) (V.)

[R = $C_6H_{11}O_5$·]

Methylation of æsculin by Robinson's procedure (J., 1928, 1457) afforded the *O*-methyl ether (II), which on hydrolysis gave glucose and *O*-monomethylæsculetin (III) identical with that described by Tiemann and Will (*Ber.*, 1882, **15**, 2072) and by Bargellini and Monti (*Gazzetta*, 1915, **45**, 90). 7-*Methoxy*-6-*ethoxycoumarin* (IV), prepared by ethylation of (III), was converted into the *methyl* ester (pale yellow) of (V) by means of methyl sulphate and sodium hydroxide. Hydrolysis of this ester gave rise to a colourless form (A) of 2 : 4-*dimethoxy*-5-*ethoxycinnamic acid* (V), which was converted into a bright yellow, unstable form on heating. A synthesis of (V) through the stages (VI), (VII), and (VIII) afforded a pale yellow form (B). Although the experimental conditions necessary for the interconversion of (A) and (B) could not be determined, both forms on oxidation gave rise to 2 : 4-*dimethoxy*-5-*ethoxybenzaldehyde* (VIII), which was further oxidised to 2 : 4-*dimethoxy*-5-*ethoxybenzoic acid*. Attempts to prepare the coumarin (IV) from the aldehyde (VII) failed.

The preparation of 4 : 5-*dimethoxysalicylaldehyde* (X) was undertaken in the first instance in order to determine the orientation of aldehydes derived from phenols of the type (IX) by Gattermann's procedure. The orientation of (X) follows from its methylation to asarylaldehyde (XI), which was oxidised to asaronic acid.

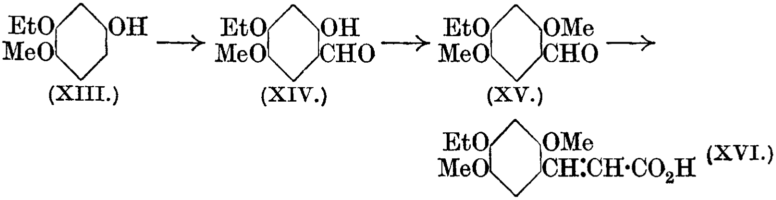


(IX.) (X.) (XI.) (XII.)

Application of Gattermann's reaction to methoxyquinol (Dakin, *Amer. Chem. J.*, 1909, **42**, 492) gave 2 : 5-*dihydroxy*-4-*methoxy*-

benzaldehyde (XII), the orientation of which depends on the production of (XI) by methylation. A Perkin reaction on (X) gave only a small yield of the coumarin (III).

The constitutions assigned to (VIII) and consequently to (V) were independently confirmed by the synthesis of 2 : 5-*dimethoxy-4-ethoxybenzaldehyde* (XV) through the stages (XIII) and (XIV).



(XIII.) (XIV.) (XV.) (XVI.)

The oxidation of (XV) gave 2 : 5-*dimethoxy-4-ethoxybenzoic acid.*

The formula of æsculin (I), therefore, is definitely established and the suggestion of Glaser and Kraus (*loc. cit.*) is disproved.

It may be noted in connexion with the cinnamic acid (V) that Will (*Ber.*, 1883, **16**, 2106) isolated two forms of 2 : 4 : 5-triethoxycinnamic acid.

EXPERIMENTAL.

Methylation of Æsculin. 7-O-*Methylæsculin* (II).—A suspension of æsculin (5 g.) and well-ground potassium carbonate (7 g.) in a mixture of methyl iodide (20 c.c.) and acetone (150 c.c.) was heated under reflux on the steam-bath for 85 hours; after 50 hours, more methyl iodide (10 c.c.) and methyl alcohol (50 c.c.) were added to the mixture. The æsculin slowly dissolved and was replaced by a bulky white precipitate; the bright yellow colour which the mixture had assumed during the first hour gradually disappeared. The acetone, methyl alcohol, and unchanged methyl iodide were removed by distillation and the residual solid mixture was extracted with dilute acetic acid. 7-O-*Methylæsculin* remained as a white solid, which was collected, washed with water, and crystallised from methyl alcohol, separating in colourless slender needles, m. p. 230° (decomp.), apparently of a *dihydrate* [Found in air-dried material: C, 49·5; H, 5·9. $C_{16}H_{18}O_9,2H_2O$ requires C, 49·2; H, 5·6%. Found in a specimen dried at 110° for 2 hours: C, 54·0; H, 5·3; OMe, 8·6. $C_{15}H_{15}O_8(OMe)$ requires C, 54·2; H, 5·1; OMe, 8·8%]. The glucoside is insoluble in cold 10% aqueous sodium hydroxide and benzene, sparingly soluble in water and acetone, and moderately easily soluble in alcohol. Aqueous and alcoholic solutions are non-fluorescent. Addition of ammonia to a nitric acid solution of the substance does not give a coloration; æsculin gives a blood-red coloration (compare Sonnenschein, *Ber.*, 1876, **9**, 1184).

Hydrolysis of 7-O-*Methylæsculin.*—The glucoside (3·8 g.), heated under reflux in 5% sulphuric acid (36 c.c.) for ½ hour, rapidly passed into solution, and after 20 minutes pale yellow needles of 7-*O*-methylæsculetin (III) separated. The coumarin crystallised from methyl alcohol in almost colourless needles, and from 40% acetic acid in tiny plates, m. p. 185° (Found : C, 62·2; H, 4·4. Calc. for $C_{10}H_8O_4$: C, 62·5; H, 4·2%). It is readily soluble in warm alcohol and in acetone, and does not give a ferric chloride reaction. The yellow solution in sodium hydroxide darkens on keeping. A solution of the coumarin in alcohol is non-fluorescent in daylight, but one in concentrated sulphuric acid is slightly fluorescent. In the light of the carbon arc both alcoholic and sulphuric acid solutions exhibit a striking blue fluorescence (compare Tiemann and Will, *loc. cit.*; Bargellini and Monti, *loc. cit.*).

The acid filtrate from the coumarin was neutralised with an excess of barium carbonate and the barium salts were removed by filtration. Concentration of the solution gave a syrup which on treatment with phenylhydrazine yielded phenylglucosazone, identified by comparison with an authentic specimen.

7-*Methoxy*-6-*ethoxycoumarin* (IV).—An attempt to ethylate 7-*O*-methylæsculetin by means of ethyl iodide and silver oxide in acetone gave a resinous product from which a definite compound could not be isolated. A mixture of 7-*O*-methylæsculetin (5·5 g.), ethyl iodide (10 c.c.), acetone (100 c.c.), and potassium carbonate was refluxed for 20 hours. The end-point of the reaction was indicated by the disappearance of the bright yellow colour which had developed when the reagents were mixed. After filtration, the solution was evaporated, and the solid residue washed with water. 7-*Methoxy*-6-*ethoxycoumarin*, thus obtained in almost theoretical yield, was crystallised from benzene–ligroin and then from dilute alcohol, from which it separated in hexagonal prisms, m. p. 120° (Found : C, 65·3; H, 5·5. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%). A solution of the coumarin in alcohol exhibits a blue fluorescence.

5-*Nitro*-2-*ethoxyanisole*.—Powdered potassium carbonate (70 g.) was suspended in a solution of 4-nitroguaiacol (Pollecoff and Robinson, J., 1918, **113**, 647) (63 g.) in acetone (200 c.c.) and ethyl iodide (70 c.c.), and the mixture refluxed for 70 hours. After filtration from potassium salts the acetone and the excess of ethyl iodide were removed by distillation and the product was washed with dilute sodium hydroxide solution and then with water. Crystallisation from dilute alcohol gave 5-nitro-2-ethoxyanisole (62 g.), m. p. 85° (Allan and Robinson, J., 1926, 376).

3-*Methoxy*-4-*ethoxyaniline Sulphate*.—The nitro-compound (58 g.) was added to a solution of sodium sulphide (200 g. of the hydrate in 500 c.c. of water), and the mixture refluxed for 8 hours. The cooled reaction mixture was extracted with chloroform and the gradual addition of concentrated sulphuric acid to the dried chloroform solution precipitated the sulphate (60 g.), which crystallised from water in almost colourless plates. The salt gave with aqueous ferric chloride a brown coloration, changing to wine-red and finally violet. The acetyl compound crystallised from water in rhombic plates, m. p. 146° (compare Freyss, *Bull. Soc. Ind. Mulhouse*, 1900, **70**, 375; Heidelberger and Jacobs, *J. Amer. Chem. Soc.*, 1919, **41**, 1450).

3-*Methoxy*-4-*ethoxyphenol* (VI).—A solution of the foregoing sulphate (25 g.) in concentrated sulphuric acid (27 c.c.) and water (250 c.c.) was diazotised at below 0° with sodium nitrite (8 g.) dissolved in water (50 c.c.). The diazonium solution was heated on the steam-bath for 2 hours, cooled, saturated with ammonium sulphate, and extracted with ether. After drying and removal of the ether, the oily residue (17 g.), which partly solidified, was distilled three times in a vacuum. The *phenol*, obtained as an almost colourless oil which solidified, crystallised from ether–ligroin in elongated prisms, m. p. 58° (Found: C, 64·5; H, 7·4. $C_9H_{12}O_3$ requires C, 64·3; H, 7·1%). The compound is readily soluble in alcohol, acetone, and chloroform and sparingly soluble in ligroin. It gives with alcoholic ferric chloride a brownish-violet coloration which does not change on dilution with water. The phenol dissolves in concentrated sulphuric acid to a brownish-purple solution and on the addition of a few drops of water an intense magenta colour is produced which on further dilution changes to bright blue. The blue colour disappears on addition of an excess of alkali but returns on acidification with mineral acid.

2-*Hydroxy*-4-*methoxy*-5-*ethoxybenzaldehyde* (VII).—Powdered zinc cyanide (10 g.) was suspended in a solution of 3-methoxy-4-ethoxyphenol (12 g.) in ether (250 c.c.), anhydrous hydrogen cyanide (10 c.c.) introduced, and the mixture saturated with hydrogen chloride. After 4 hours, the copious yellow solid was collected, washed with ether, dissolved in water (250 c.c.), and heated on the steam-bath for 20 minutes. The *aldehyde*, which separated as an oil and crystallised on cooling, was recrystallised from a small volume of methyl alcohol, forming almost colourless, hexagonal prisms (10 g.), m. p. 112—113° (Found: C, 60·9; H, 6·2. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%). It is readily soluble in warm alcohol, ether, and acetone, and sparingly soluble in warm water. The colour of the solution in aqueous sodium hydroxide is yellow, and in alcohol or water the ferric chloride reaction is dark green.

2 : 4-*Dimethoxy*-5-*ethoxybenzaldehyde* (VIII).—The foregoing alde-

hyde (VII) (4 g.) was dissolved in acetone (60 c.c.) and methylated by means of methyl iodide (8 c.c.) and potassium carbonate (6 g.) during 2 hours on the steam-bath. On isolation, 2 : 4-*dimethoxy*-5-*ethoxybenzaldehyde* crystallised from methyl alcohol in clusters of elongated silky needles (3·5 g.), m. p. 110° (Found : C, 62·8; H, 6·8. $C_{11}H_{14}O_4$ requires C, 62·9; H, 6·7%). The substance is insoluble in alkali and does not give a ferric chloride reaction.

2 : 4-*Dimethoxy*-5-*ethoxybenzoic Acid*.—Potassium permanganate (0·8 g.), dissolved in water (45 c.c.), was gradually added to a solution of 2 : 4-dimethoxy-5-ethoxybenzaldehyde (1 g.) in acetone (30 c.c.) maintained at 40°. After 20 minutes the cooled reaction mixture was cleared with sulphur dioxide, and on slow evaporation of the solvent a colourless solid separated. A solution of the product in 5% aqueous sodium carbonate (20 c.c.) was filtered from unchanged aldehyde and, on acidification with concentrated hydrochloric acid, gave 2 : 4-*dimethoxy*-5-*ethoxybenzoic acid*, which crystallised from hot water in elongated silky needles (0·5 g.), m. p. 137° (Found : C, 58·2; H, 6·4. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%). The substance is readily soluble in alcohol and acetone and sparingly soluble in cold water. Crystallised from benzene, it formed elongated prisms.

2 : 4-*Dimethoxy*-5-*ethoxycinnamic Acid* (V).—(A) A suspension of 7-methoxy-6-ethoxycoumarin (4·5 g.) in a mixture of methyl alcohol (20 c.c.) and 20% aqueous sodium hydroxide (50 c.c.) was heated on the water-bath until the solid dissolved. After cooling to 50°, the solution was mechanically agitated, and methyl sulphate (32 g.) gradually introduced. 20% Aqueous sodium hydroxide (50 c.c.) and a further quantity of methyl sulphate (20 g.) were then added. *Methyl* 2 : 4-*dimethoxy*-5-*ethoxycinnamate* separated as an oil which crystallised on cooling. Recrystallised from ligroin and then from methyl alcohol (charcoal), it formed clusters of pale yellow, hexagonal prisms (3·5 g.), m. p. 80° (Found : C, 63·1; H, 6·9. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%). Hydrolysis of this ester (1 g.) by means of warm 5% aqueous methyl-alcoholic sodium hydroxide (30 c.c.) gave the *acid*, which crystallised from benzene in colourless prismatic needles (Found : C, 62·0; H, 6·5. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·3%). On being heated, the substance sintered and was transformed at 117—118° into a bright yellow solid which then melted at 128°. The yellow solid crystallised from warm benzene in bright yellow needles, m. p. 128°, which on standing in contact with the solvent reverted to the colourless form. This acid is easily soluble in alcohol and sparingly soluble in warm water.

The colourless cinnamic acid (0·5 g.) was dissolved in warm acetone (20 c.c. at 45°) and oxidised by the addition of a 1·4% aqueous solution of potassium permanganate (50 c.c.). The cooled reaction mixture was cleared with sulphur dioxide, and, after the addition of 20% sulphuric acid (10 c.c.), was heated to boiling. On cooling, 2 : 4-dimethoxy-5-ethoxybenzaldehyde separated, m. p. and mixed m. p. 110° after crystallisation from methyl alcohol (Found : C, 63·0; H, 6·8%). The aldehyde thus obtained, on oxidation by means of potassium permanganate, gave 2 : 4-dimethoxy-5-ethoxybenzoic acid, m. p. and mixed m. p. 137° after crystallisation from water.

(B) A mixture of 2 : 4-dimethoxy-5-ethoxybenzaldehyde (2 g.), malonic acid (4 g.), pyridine (8 c.c.), and piperidine (0·25 c.c.) was heated on the steam-bath for 4 hours and then under reflux for 5 minutes. After dilution with water (30 c.c.) and acidification with concentrated hydrochloric acid (50 c.c.), it deposited 2 : 4-dimethoxy-5-ethoxycinnamic acid as a pale yellow solid (2·2 g.). The substance crystallised from benzene in pale yellow needles containing solvent of crystallisation. After drying at 100° for 4 hours, it melted at 132—133° (Found : C, 61·9; H, 6·3%). A mixture of the pale yellow and the colourless form melted at 75—80°.

The pale yellow cinnamic acid on oxidation in acetone solution with aqueous potassium permanganate gave 2 : 4-dimethoxy-5-ethoxybenzaldehyde, m. p. and mixed m. p. 110°, which was further oxidised to 2 : 4-dimethoxy-5-ethoxybenzoic acid, m. p. and mixed m. p. 137°.

3 : 4-*Dimethoxyphenol* (IX).—4-Aminoveratrole (35 g.) (Fargher, J., 1920, **117**, 869) was dissolved in water (450 c.c.) and concentrated sulphuric acid (53 c.c.) cooled to below 0°, and diazotised by the addition of 16% sodium nitrite solution (100 c.c.). After filtering, the diazonium solution was heated on the steam-bath for 2 hours, the cooled reaction mixture saturated with ammonium sulphate, and the product isolated by five extractions with ether. On distillation under diminished pressure, the phenol was obtained as a pale yellow oil, b. p. 168—170°/12 mm., which solidified. Crystallisation from water gave a *hydrate* in almost colourless, rhombic plates, m. p. 46° (Found in air-dried specimen : C, 56·1; H, 7·1. $C_8H_{10}O_3,H_2O$ requires C, 55·8; H, 7·0%). The phenol is readily soluble in ether, alcohol, and acetone. The ferric chloride reaction in alcohol is pale green and in water is bluish-green, instantly changing to reddish-brown. The sulphuric acid reaction is the same as that of (VI).

2-*Hydroxy*-4 : 5-*dimethoxybenzaldehyde* (X).—Hydrogen chloride was led into a solution of 3 : 4-dimethoxyphenol (15 g.) and hydrogen cyanide (20 c.c.) in ether (300 c.c.) containing powdered zinc cyanide (15 g.) in suspension. The double zinc salt began to separate after 15 minutes and the passage of hydrogen chloride was continued until the liquid was saturated. After 12 hours the solid was collected, washed with ether, and dissolved in cold water (300 c.c.). Hydrolysis was effected during ½ hour on the steam-bath and the *aldehyde* (15 g.) separated as a brown oil which solidified on cooling. Crystallised from aqueous alcohol (charcoal) and then from methyl alcohol, it formed almost colourless, thick, rhombic plates, m. p. 105° (Found: C, 59·2; H, 5·6. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%). The substance is sparingly soluble in hot water, from which it separates in glistening needles on cooling. The ferric chloride reaction is dark green, changing to brownish-purple on dilution with water. Added to 10% aqueous sodium hydroxide, the aldehyde dissolves, and the pale yellow sodium salt is precipitated almost immediately; with 10% potassium hydroxide a yellow potassium salt is obtained.

Methylation of this aldehyde (X) by means of methyl iodide and potassium carbonate in boiling acetone gave a quantitative yield of asarylaldehyde (XI), which crystallised from water in colourless needles, m. p. 114° after slight sintering at 93—95°. Asarylaldehyde (1 g.) was dissolved in warm acetone (30 c.c. at 40°) and oxidised by the addition of a solution of potassium permanganate (0·7 g.) in water (40 c.c.). After isolation, asaronic acid crystallised from water in colourless needles, m. p. 143—144° (Found in specimen dried at 105°: C, 56·3; H, 5·6. Calc. for $C_{10}H_{12}O_5$: C, 56·6; H, 5·7%).

2 : 5-*Dihydroxy*-4-*methoxybenzaldehyde* (XII).—Methoxyquinol was repeatedly crystallised from benzene and obtained in colourless leaflets, m. p. 89° (Will, *Ber.*, 1888, **21**, 606, gives m. p. 84°; Dakin, *loc. cit.*, gives m. p. 82—83°). It behaves with sulphuric acid in the same way as (VI).

Zinc cyanide (10 g.) and hydrogen cyanide (10 c.c.) were added to a solution of methoxyquinol (13 g.) in ether (250 c.c.), and the mixture was saturated with hydrogen chloride. Next day, the solid was collected, washed with ether, and dissolved in water (250 c.c.). The solution was heated on the steam-bath for 20 minutes, a part of the *aldehyde* crystallising; the remainder separated on cooling. The substance was recrystallised from acetic acid and then from alcohol (charcoal), giving almost colourless, hexagonal prisms (6 g.), m. p. 209° (slight decomp.) (Found: C, 56·8; H, 4·9. $C_8H_8O_4$ requires C, 57·1; H, 4·8%). It is sparingly soluble in hot alcohol or acetic acid and moderately easily soluble in acetone. It gives with alcoholic ferric chloride a bluish-green coloration which fades on addition of water. The compound dissolves in aqueous sodium hydroxide to a yellow solution. On methylation in acetone solution with methyl iodide and potassium carbonate, 2 : 5-dihydroxy-4-methoxybenzaldehyde gave a theoretical yield of asarylaldehyde (XI), m. p. and mixed m. p. 115°.

Synthesis of 7-O-*Methylæsculetin* (III).—A mixture of 2 : 5-dihydroxy-4-methoxybenzaldehyde (5 g.), acetic anhydride (25 c.c.), and sodium acetate (8 g.) was heated on the steam-bath for 3 hours, at 120° for 2 hours, and finally at 180° for 8 hours. Water (200 c.c.) was added to the cooled mixture and 12 hours later the solid was collected. A solution of the product in a mixture of methyl alcohol (30 c.c.) and 10% aqueous sodium hydroxide (25 c.c.) was kept at room temperature for 2 hours and then acidified with concentrated hydrochloric acid. The coumarin gradually separated and after 24 hours was collected. On crystallisation from 40% acetic acid and then from alcohol, the substance was obtained in colourless needles, m. p. and mixed m. p. 185° (Found : C, 62·3; H, 4·2%). The synthetic compound was identical in every way with a specimen prepared by the hydrolysis of 7-*O*-methylæsculin (p. 2437). Acetylation with acetic anhydride and pyridine gave the acetyl derivative, which crystallised from 80% alcohol in prismatic needles, m. p. 164° (compare Bargellini and Monti, *loc. cit.*).

4-*Nitro*-2-*ethoxyanisole.*—5-Nitroguaiacol (Paul, *Ber.*, 1906, **39**, 2779; Cardwell and Robinson, J., 1915, **107**, 255) (50 g.) was dissolved in acetone (300 c.c.) and ethylated by means of ethyl bromide (40 g.) and potassium carbonate (50 g.) during 16 hours on the steam-bath. On isolation, the product crystallised from dilute alcohol in pale yellow needles (58 g.), m. p. 101—102° (compare Wisinger, *Monatsh.*, 1900, **21**, 1007; Allan and Robinson, *loc. cit.*).

4-*Methoxy*-3-*ethoxyaniline.*—Of the following methods of reduction the first (A) proved to be the most convenient (compare Wisinger, *loc. cit.*; Heidelberger and Jacobs, *loc. cit.*).

(A) A mixture of 4-nitro-2-ethoxyanisole (75 g.), hydrated sodium sulphide (250 g.), and water (600 c.c.) was refluxed for 8 hours. The chloroform extract of the reaction mixture was washed with water and then agitated with dilute hydrochloric acid. After separation, the acid solution was made alkaline with sodium hydroxide, the amine being liberated as an oil which solidified. Crystallisation from warm water (charcoal) gave almost colourless, rhombic plates (51 g.), m. p. 81°. The acetyl derivative melted at 144—145° after crystallisation from toluene.

(B) The nitro-compound (50 g.), dissolved in boiling alcohol, was reduced with iron powder (40 g.) and concentrated hydrochloric acid (5 c.c.). After filtration, the alcohol was distilled, and the residue extracted with ether. The gradual addition of concentrated sulphuric acid to the dried ethereal extract precipitated the aniline sulphate, which crystallised from water in rhombic plates (59 g.).

(C) Sufficient water was added to a mixture of the nitro-compound (56 g.) and iron powder (50 g.) to form a stiff paste. The mixture was heated on the water-bath for 5 minutes, and acetic acid (10 c.c.) added. A vigorous reaction ensued and after 4 hours the warm mass was extracted with alcohol and the aniline sulphate (55 g.) isolated as described under (B).

4-*Methoxy*-3-*ethoxyphenol* (XIII).—The foregoing amine (45 g.) in water (600 c.c.) and concentrated sulphuric acid (68 c.c.) cooled to below 0° was diazotised with a solution of sodium nitrite (18·6 g.) in water (100 c.c.). After 30 minutes the diazonium solution was heated on the water-bath until the evolution of nitrogen had ceased. On cooling, part of the product separated and was collected; the remainder was isolated by five extractions with ether, the total yield of crude product being 20 g. Crystallisation from water (charcoal) gave a *hydrate* in colourless needles, which showed slight sintering at 85° and melted at 92—93° (Found: C, 57·7; H, 7·4. $C_9H_{12}O_3,H_2O$ requires C, 58·1; H, 7·5%). After drying at 100°, the *phenol* was distilled under diminished pressure and obtained as a colourless oil which solidified, b. p. 175°/12 mm. (Found: C, 64·1; H, 7·3. $C_9H_{12}O_3$ requires C, 64·3; H, 7·1%). The substance is readily soluble in alcohol, ether, and benzene. It gives with alcoholic ferric chloride an unstable greenish-blue coloration which is unchanged on the addition of water. The sulphuric acid reaction is the same as that of (VI).

2-*Hydroxy*-5-*methoxy*-4-*ethoxybenzaldehyde* (XIV).—The condensation of 4-methoxy-3-ethoxyphenol (4·5 g.) and hydrogen cyanide (6 c.c.) in ethereal solution was effected by means of zinc cyanide (3 g.) and excess of hydrogen chloride. On hydrolysis of the aldimine–zinc chloride double compound, the *aldehyde* (4·5 g.) separated as an oil which solidified. Crystallised from aqueous alcohol and then from methyl alcohol, it was obtained in almost colourless, squat prisms, m. p. 91° (Found in material dried at 100°: C, 61·0; H, 6·0. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%). The substance is readily soluble in warm alcohol or acetone and sparingly soluble in warm water. Addition of ferric chloride to an alcoholic solution gives a thin bluish-green coloration which is unchanged on addition of water. The phenylhydrazone crystallised from 80% methyl alcohol in pale yellow plates, m. p. 157—158°.

2 : 5-*Dimethoxy*-4-*ethoxybenzaldehyde* (XV).—The foregoing aldehyde (6 g.) was dissolved in acetone (90 c.c.) and methylated by means of methyl iodide (12 c.c.) and potassium carbonate (10 g.)

during 2 hours on the steam-bath. The *product* (6 g.) crystallised from methyl alcohol in short thick prisms, m. p. 110° (Found : C, 62·7; H, 6·6. $C_{11}H_{14}O_4$ requires C, 62·9; H, 6·7%). A mixture of this substance and the isomeric aldehyde (VIII), m. p. 110°, melted at 85—90°. On oxidation with potassium permanganate in aqueous-acetone solution at 50—55°, this aldehyde gave 2 : 5-*dimethoxy*-4-*ethoxybenzoic acid*, which crystallised from water in rectangular prisms, m. p. 130° (Found : C, 58·5; H, 6·4. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%). The acid is readily soluble in alcohol and in hot benzene.

2 : 5-*Dimethoxy*-4-*ethoxycinnamic Acid* (XVI).—A mixture of 2 : 5-dimethoxy-4-ethoxybenzaldehyde (1 g.), malonic acid (2 g.), pyridine (6 c.c.), and piperidine (0·25 c.c.) was heated on the steam-bath for 3 hours and then under reflux for 5 minutes. After dilution with water and acidification with concentrated hydrochloric acid, it deposited the *acid* (1·3 g.), which crystallised from dilute acetic acid in pale yellow, slender needles, m. p. 178—179° after sintering at 170° (Found : C, 61·9; H, 6·1. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·3%). The compound is insoluble in water and sparingly soluble in hot benzene.

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