168. *Synthesis of Aurantiogliocladin.*

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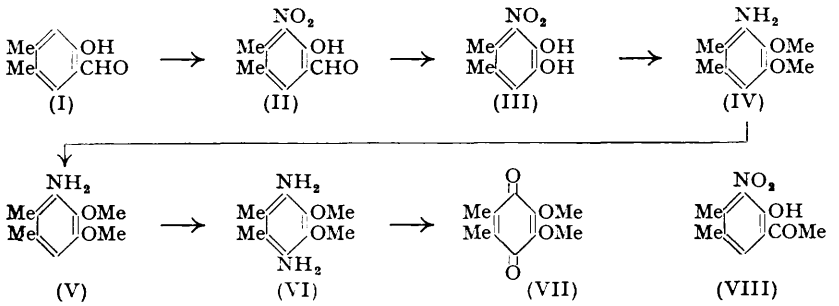
The paper describes an unambiguous synthesis of aurantiogliocladin, 2 : 3-dimethoxy-5 : 6-dimethyl-*p*-benzoquinone (VII), from *o*-4-xylenol.

Aurantiogliocladin, 2 : 3-dimethoxy-5 : 6-dimethyl-*p*-benzoquinone (Vischer, preceding paper), has been synthesised, and is identical with the material isolated from a species of *Gliocladium*.

o-4-Xylenol and hexamine in acetic acid gave 2-hydroxy-4 : 5-dimethylbenzaldehyde (I) (aldehyde synthesis of Duff and Bills, *J.*, 1932, 1987; 1934, 1305), which was nitrated to 2-hydroxy-4 : 5-dimethyl-3-nitrobenzaldehyde (II). Oxidation of (II) by alkaline hydrogen peroxide (Dakin reaction) gave 4 : 5-dimethyl-3-nitrocatechol (III), which was dimethylated and reduced, giving 3-amino-1 : 2-dimethoxy-4 : 5-dimethylbenzene (V), characterised as its *N*-benzoyl derivative. The amine (V) was coupled in acid solution with diazotised sulphanilic acid, and the azo-compound, without isolation, was reduced to the diamine (VI) by alkaline sodium dithionite (hydrosulphite). The crude diamine (VI) was finally oxidised by ferric chloride in cold aqueous solution under a layer of light petroleum (cf. synthesis of fumigatin, 3-hydroxy-4-methoxy-2 : 5-toluquinone, Baker and Raistrick, *J.*, 1941, 670), giving 2 : 3-dimethoxy-5 : 6-dimethyl-*p*-benzoquinone (VII), identical with natural aurantiogliocladin.



The synthesis of aurantiogliocladin was first attempted from 2-hydroxy-4 : 5-dimethylacetophenone which is much more easily prepared than the related aldehyde (I). Nitration of this ketone readily gave 2-hydroxy-4 : 5-dimethyl-3-nitroacetophenone (VIII), but, unlike the nitro-aldehyde (II), the nitro-ketone was unattacked by alkaline hydrogen peroxide even on heating. The inaccessibility of 4 : 5-dimethylcatechol rendered it unsuitable as a starting-point in the synthesis.

Experimental

M. p.s are uncorrected.

2-Hydroxy-4 : 5-dimethylbenzaldehyde (I).—*o*-4-Xylenol (20 g.), hexamine (140 g., 6 mols.), and glacial acetic acid (300 c.c.) were heated on a steam-bath for 5 hours, and, while still hot, treated with a boiling mixture of water (150 c.c.) and concentrated hydrochloric acid (150 c.c.),

then cooled, and poured into water. The product was steam-distilled, and the solid in the distillate was crystallised from light petroleum (b. p. 40—60°) (charcoal), giving nacreous plates, m. p. 67—68° (8 g., 32·5%). This aldehyde (I) was first prepared by Clayton (*J.*, 1910. **97**, 1404) in unstated yield along with 2-hydroxy-3 : 4-dimethylbenzaldehyde from 3 : 4-dimethylphenol by the Tiemann–Reimer reaction; a mixture of the isomerides was also obtained by the entirely different preparation used by Marvel and Higgins (*J. Amer. Chem. Soc.*, 1948, **70**, 2219).

4 : 5-*Dimethyl*-3-*nitrocatechol* (III).—Nitration of the aldehyde (I) (11 g.) according to Clayton (*loc. cit.*) gave a 77% yield of 2-hydroxy-4 : 5-dimethyl-3-nitrobenzaldehyde (II), m. p. 146—147°. This (5 g., 1 mol.) was dissolved at 80° in 5% aqueous sodium hydroxide (58 c.c., 3·5 mols.), the whole cooled rapidly with shaking, and to the suspension of the sparingly-soluble sodium salt was added 3% aqueous hydrogen peroxide (62 c.c., 1·25 mol.); a spontaneous rise of temperature from 20° to 48° occurred (20 min.). After the mixture had cooled it was acidified with concentrated hydrochloric acid, and the dark precipitate extracted with boiling light petroleum (2 × 100 c.c.; b. p. 40—60°), giving 4 : 5-*dimethyl*-3-*nitrocatechol* (III); a further amount of (III) separated from the aqueous liquor on saturation with sodium chloride (total yield, 1·58 g.). The pure phenol separates from water in yellow plates, m. p. 123—124° (Found : C, 52·4; H, 4·6; N, 7·6. $C_8H_9O_4N$ requires C, 53·0; H, 4·9; N, 7·7%).

1 : 2-*Dimethoxy*-4 : 5-*dimethyl*-3-*nitrobenzene* (IV).—The nitro-compound (III) (1 g.), acetone (20 c.c.), methyl sulphate (4·7 c.c.), and anhydrous potassium carbonate (3 g.) were boiled for 10 hours, the mixture was filtered, the acetone filtrate and washings were boiled with water (¼ hour), and the solid *ether* was collected after cooling to 0°. Crystallisation from ethanol gave colourless plates (0·83 g.), m. p. 77—78° [Found : C, 56·9; H, 6·1; N, 6·7; OMe, 29·3. $C_8H_7O_2N(OMe)_2$ requires C, 57·1; H, 6·2; N, 6·6 ; OMe, 29·4%].

3-*Amino*-1 : 2-*dimethoxy*-4 : 5-*dimethylbenzene* (V).—The nitro-ether (IV) (1 g.) in ethanol (100 c.c.) was shaken at atmospheric pressure with hydrogen in presence of Raney nickel (0·5 g.) for 2 hours. The filtrate yielded the crude amino-compound (V) which solidified. It was characterised as 3-*benzamido*-1 : 2-*dimethoxy*-4 : 5-*dimethylbenzene* by treatment (1 g.) in pyridine at room temperature for 18 hours with benzoyl chloride (1·5 mols.), pouring on to ice, and crystallisation from ethanol; this formed thin prisms (0·9 g.), m. p. 171—172° [Found : C, 71·4; H, 6·6; N, 5·0; OMe, 22·7. $C_{15}H_{13}ON(OMe)_2$ requires C, 71·6; H, 6·7; N, 4·9; OMe, 21·8%].

2 : 3-*Dimethoxy*-4 : 5-*dimethyl*-p-*benzoquinone* (*Aurantiogliocladin*) (VII).—A solution of the crude amino-compound (V) (1·47 g.) in concentrated hydrochloric acid (2 c.c.) and water (5 c.c.) at 0° was added slowly to the diazonium solution prepared from sulphanilic acid (1·8 g.), 6% aqueous sodium carbonate (30 c.c.), 12% aqueous sodium nitrite (5 c.c.), and 11% aqueous hydrochloric acid (6 c.c.). After ½ hour a 10% aqueous solution of sodium hydroxide was added, and to the dark red solution was added sodium dithionite (15 g.) in portions with shaking at 60°, and the resulting orange solution was extracted while hot with ethyl acetate (3 × 50 c.c.). The extracts yielded a dark, viscous material (0·9 g.) containing the diamine (VI), and this was dissolved in 8% aqueous hydrochloric acid (35 c.c.), covered with a layer of light petroleum (b. p. 60—80°) and shaken for 2 hours with a 20% aqueous solution of ferric chloride (15 c.c.). The orange-yellow petroleum layer was separated, and the aqueous layer extracted similarly 3 times; evaporation of the combined extracts at room temperature under diminished pressure gave orange crystals (0·25 g.). After several recrystallisations from light petroleum (b. p. 60—80°) *aurantiogliocladin* (VII) was obtained as bright orange plates, m. p. 62·0°, mixed m. p. with the natural compound (m. p. 62·5°), 62·0—62·5° [Found : C, 61·5; H, 6·4; OMe, 30·8. $C_8H_6O_2(OMe)_2$ requires C, 61·2; H, 6·2; OMe, 31·6%]. Like the natural compound this material dissolved in concentrated sulphuric acid with a pure violet colour.

Both natural and synthetical material gave the same (mixed m. p.) *mono*-2 : 4-*dinitrophenylhydrazone* when treated with hot ethanolic 2 : 4-dinitrophenylhydrazine containing some concentrated hydrochloric acid. After 4 crystallisations from ethyl acetate, this derivative from both sources formed small red needles, m. p. (oil-bath) 228—229° (decomp.), m. p. 243—244° (Kofler block) [Found : C, 51·4; H, 4·1; N, 14·9; OMe, 17·3. $C_{14}H_{10}O_5N_4(OMe)_2$ requires C, 51·1; H, 4·3; N, 14·9; OMe, 16·5%].

2-*Hydroxy*-4 : 5-*dimethylacetophenone*.—To *o*-4-xylyl acetate (1 mol.) was added in portions aluminium chloride (1·5 mols.), and the mixture kept at 120° for 10 minutes. After addition of dilute hydrochloric acid, heating, and cooling, the product was crushed, washed, and crystallised from dilute alcohol, giving the hydroxy-ketone as plates, m. p. 70—71° (72%). The conditions used by Auwers, Bundesmann, and Wiener (*Annalen*, 1926, **447**, 176) gave a ketone, m. p. 71°, in unspecified yield.

2-Hydroxy-4 : 5-dimethyl-3-nitroacetophenone (VIII).—A solution of the preceding ketone (10 g.) in acetic acid (40 c.c.) was treated with a solution of nitric acid (12 c.c.; *d* 1·42) in acetic acid (12 c.c.). After 18 hours much water was added, and the solid washed and crystallised from ethanol, giving *2-hydroxy-4 : 5-dimethyl-3-nitroacetophenone* (VIII) as faintly yellow prisms, m. p. 143—144° (9·0 g.) (Found : C, 56·7; H, 5·4; N, 6·9. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3; N, 6·7%).

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