

122. *Derivatives of 1 : 2 : 3 : 4-Tetrahydroxybenzene. Part VII.
The Synthesis of Fumigatin.*

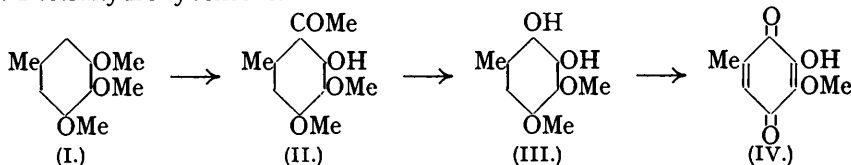
By WILSON BAKER and H. RAISTRICK.

The mould metabolic product fumigatin, 3-hydroxy-4-methoxy-2 : 5-toluquinone (IV), has been synthesised from 3 : 4 : 5-trimethoxytoluene (I) *via* the intermediates (II) and (III), the oxidation of (III) to fumigatin being effected by aqueous ferric chloride at room temperature.

THE observation, described in the preceding paper, that 1 : 2-dihydroxy-3 : 4 : 6-trimethoxybenzene is oxidised by aqueous ferric chloride at room temperature to 2-hydroxy-3 : 6-dimethoxy-1 : 4-benzoquinone (formulæ III and XI of that paper), suggested the possibility of synthesising the mould metabolic product fumigatin by an application of the same method.

Fumigatin was isolated by Anslow and Raistrick (*Biochem. J.*, 1938, **32**, 687) from the

metabolism solution of *Aspergillus fumigatus* Fresenius, as maroon-coloured needles, which possessed the property of dissolving in alkaline solutions with an intense permanganate colour. The substance was proved to be 3-hydroxy-4-methoxy-2:5-toluquinone (IV), and it is thus the first known example of a naturally occurring quinone derived from 1:2:3:4-tetrahydroxybenzene.



The synthesis of fumigatin has now been effected in the following way. 3:4:5-Trimethoxytoluene (I) was treated with a solution of acetyl chloride and aluminium chloride in dry ether, giving 3-hydroxy-4:5-dimethoxy-2-acetyltoluene (II) (cf. the similar production of 2-hydroxy-3:4:6-trimethoxyacetophenone from 1:2:3:5-tetramethoxybenzene and acetyl chloride described in the preceding paper). The hydroxy-ketone (II) when oxidised under the conditions of the Dakin reaction with hydrogen peroxide in dilute alkaline solution gave 2:3-dihydroxy-4:5-dimethoxytoluene (III). The oxidation of (III) to give fumigatin (IV) did not proceed so readily as the corresponding reaction mentioned in the first paragraph, probably owing to the instability of fumigatin towards ferric chloride. The method finally adopted, however, gave a 44% yield of purified fumigatin. This consisted in oxidising in very dilute solution at room temperature with 2 molecules of ferric chloride under a layer of benzene-light petroleum, in which the dihydroxy-derivative is almost insoluble but the fumigatin is easily soluble, so that the danger of further destructive oxidation is largely excluded.

The synthetical fumigatin showed all the very characteristic colour reactions of the natural product (see experimental section), and a mixed melting-point determination showed no depression of the melting point.

The synthetical fumigatin was also converted into its bright yellow acetyl derivative, and a mixed melting point with the acetyl derivative of natural fumigatin again showed the complete identity of the products.

EXPERIMENTAL.

3-Hydroxy-4:5-dimethoxy-2-acetyltoluene (II).—3:4:5-Trimethoxybenzaldehyde (25.4 g.; Baker and Robinson, J., 1929, 156) gave 3:4:5-trimethoxytoluene (I) (18.7 g.; b. p. 137°/20 mm.) by the method of Asahina and Yasue (*Ber.*, 1936, 69, 2327). 3:4:5-Trimethoxytoluene (5 g.) was added to a solution of anhydrous aluminium chloride (5 g.) in absolute ether (25 c.c.), and then acetyl chloride (2.5 g.) added with shaking and cooling in water. After 24 hours with occasional shaking, a mixture of water (50 c.c.) and concentrated hydrochloric acid (10 c.c.) was cautiously added, and the whole heated on the water-bath for $\frac{1}{2}$ hour, the ether being allowed to distil away; the oily product (which solidified on cooling) was extracted with ether, and the extract washed with water and then with excess of dilute sodium hydroxide solution. Acidification of the alkaline solution caused the separation of a crystalline solid (3.1 g.), which separated from light petroleum (b. p. 60—80°) in large, branching, rhombic crystals, m. p. 92° (Found: C, 62.8; H, 6.7. $C_{11}H_{14}O_4$ requires C, 62.9; H, 6.7%). It gave a dull violet-brown solution with alcoholic ferric chloride.

2:3-Dihydroxy-4:5-dimethoxytoluene (III).—3-Hydroxy-4:5-dimethoxy-2-acetyltoluene (4.2 g.) was dissolved in a solution of sodium hydroxide (1.6 g.) in water (32 c.c.), and a 3% aqueous solution of perhydrol (28.4 c.c.; 1.25 mol.) added. After warming to about 45° an exothermic reaction set in, accompanied by darkening of the solution, and after 2 hours the solution was acidified with sulphuric acid, unchanged ketone (1.2 g.) removed by filtration, and the filtrate saturated with salt and extracted four times with ether. The extracts were shaken with aqueous sodium bicarbonate to remove acetic acid, dried over sodium sulphate, and distilled, leaving an oil which rapidly solidified (1.9 g.). It crystallised from light petroleum (b. p. 60—80°) in long, faintly brownish, branching crystals, m. p. 101° (Found: C, 58.7; H, 6.4. $C_9H_{12}O_4$ requires C, 58.7; H, 6.5%). Its solution in alkali rapidly turned reddish-brown on exposure to the air.

The *diacetyl* derivative, prepared by heating on the water-bath with excess of acetic anhydride and a drop of pyridine for 2 hours and then shaking with water, was crystallised twice from alcohol and obtained in colourless, rhombic plates, m. p. 108° (Found: C, 58.3; H, 5.8. $C_{12}H_{16}O_6$ requires C, 58.2; H, 5.9%).

3-Hydroxy-4-methoxy-2:5-toluquinone. Fumigatin (IV).—Pure 2:3-dihydroxy-4:5-dimethoxytoluene (III) (0.55 g.) was dissolved in cold water (50 c.c.), and pure benzene (50 c.c.) and light petroleum (b. p. 60—80°; 50 c.c.) added, followed by concentrated hydrochloric acid (5 drops); after addition of a solution of anhydrous ferric chloride (0.98 g.; 2 mols.) in water (12 c.c.) the mixture was shaken for 2 hours. The solution, at first dark, was now orange-red, and the upper layer was separated, dried over sodium sulphate, and distilled to dryness at a low temperature under diminished pressure, leaving a dark red crystalline deposit of fumigatin (0.22 g.), m. p. about 108° with previous softening. The aqueous layer was again shaken with benzene (50 c.c.) for 1 hour, and yielded as before slightly less pure fumigatin (0.06 g.), and a third extraction with benzene gave a further quantity (0.04 g.) of a similar product. The combined specimens were crystallised from carbon tetrachloride (10 c.c.), which appears to be the best solvent for fumigatin, and in which it is quite stable and easily soluble on heating. The fumigatin (0.21 g.) separated in maroon-coloured needles (rapid crystallisation), or dark maroon, frequently branching prisms or sometimes hexagonal plates (slow crystallisation), m. p. 112° with some previous softening. A further rapid crystallisation from light petroleum (b. p. 60—80°) gave maroon-coloured, glistening, prismatic needles (0.16 g.), m. p. 114° (Found: C, 57.3; H, 5.0. Calc. for $C_8H_8O_4$: C, 57.1; H, 4.8%). The m. p. varies slightly with the rate of heating owing to slight decomposition, and is lowered by previous fusion. A specimen of natural fumigatin which had been kept for some years and had deteriorated slightly was sublimed in a high vacuum at 80° and then had m. p. 114° when heated slowly but melted at 115—116° when heated moderately quickly. A mixture of the natural and the synthetical specimen when slowly heated had m. p. 114°.

The synthetical fumigatin showed all the properties of the natural material. The specimens were directly compared side by side, and no divergences in behaviour could be detected. In particular may be mentioned (*a*) the purple-black colour with alcoholic ferric chloride, turning to light brown on the addition of water; (*b*) the permanent permanganate colour of solutions in dilute sodium bicarbonate; and (*c*) the brown solution in concentrated sulphuric acid which becomes cherry-red in a few minutes, and then, rather more slowly, a very intense permanganate colour.

The acetyl derivative of fumigatin was prepared by the addition of a drop of pyridine to a solution of fumigatin in acetic anhydride, warming to 30°, when the red solution rapidly faded to yellow, and then shaking with water. The solid was collected, washed, and dried (m. p. 94—95°), and then crystallised from light petroleum, from which it separated in canary-yellow crystalline aggregates, m. p. 96—97° (Found: C, 57.3; H, 4.9. Calc. for $C_{10}H_{10}O_5$: C, 57.1; H, 4.8%). A specimen of fumigatin acetate prepared from natural fumigatin and purified by sublimation in a high vacuum at 70° had m. p. 95—96°, and a mixture of the synthetical and the natural product had m. p. 96°.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.

THE DIVISION OF BIOCHEMISTRY, LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE,
UNIVERSITY OF LONDON.

[Received, August 6th, 1941.]