329. *New Synthesis of Fumigatin, Spinulosin Monomethyl Ethers, and Aurantiogliocladin.*

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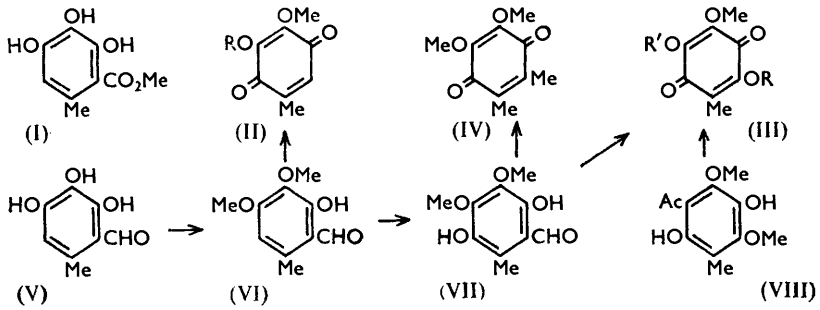
Fumigatin, spinulosin 3-methyl ether, and aurantiogliocladin have been prepared by using 3-hydroxyorcylaldehyde as the common C_8 intermediate. The hitherto unknown 6-monomethyl ether of spinulosin has also been made by the Dakin oxidation of 2 : 5-dihydroxy-4 : 6-dimethoxy-3-methylacetophenone.

AGHORAMURTHY and SESHADRI [1] outlined a theory of biosynthesis of mould products involving C_8 units. As a typical example of toluquinones, fumigatin methyl ether (II; R = Me) was synthesised [2] starting from methyl 3-hydroxyorsellinate (I). We have now prepared fumigatin [3] (II; R = H), spinulosin 3-methyl ether [4] (III; R = H, R′ = Me) and aurantiogliocladin [5] (IV), employing 3-hydroxyorcylaldehyde (V) as common C_8 intermediate and simple reactions. These syntheses emphasise, not only the close relation among these compounds, but also their common origin; the methods involved are quite convenient.

Atranol is best prepared from lecanoric acid by a Gattermann reaction and decarboxylation.[6] By Dakin oxidation to 5-methylpyrogallol [7] and then a Gattermann reaction [8] this



gives the aldehyde (V). Partial methylation of (V) gives 2-hydroxy-3 : 4-dimethoxy-6-methylbenzaldehyde (VI), which is obtained in a better yield from the trimethyl ether of (V) by partial demethylation with anhydrous aluminium chloride in ether. The dimethyl ether (VI) was converted by successive Dakin oxidation and oxidation with ferric chloride into fumigatin (II; R = H). Alkaline persulphate oxidation of the dimethyl ether gave the quinol aldehyde (VII) which by Dakin oxidation yielded spinulosin 3-methyl ether (III; R = H, R′ = OMe). Clemmensen reduction of the quinol aldehyde (VII) yielded the quinol of aurantiogliocladin which was oxidised to aurantiogliocladin (IV) by ferric chloride as described by Vischer.[9]

In the above reactions Dakin oxidation of the quinol aldehyde (VII) gives the quinone (III; R = H, R′ = Me) directly. Examples of this type have been recorded previously.[10] By using this general reaction the hitherto unknown spinulosin 6-methyl ether (III; R′ = H, R = Me) has now been prepared from 2 : 5-dihydroxy-4 : 6-dimethoxy-3-methylacetophenone [11] (VIII) which however does not fall into the C_8 scheme.

[1] Aghoramurthy and Seshadri, *J. Sci. Ind. Res., India*, 1954, **13**, *A*, 114.
[2] *Idem, Chem. and Ind.*, 1954, 1327.
[3] Baker and Raistrick, *J.*, 1941, 670.
[4] Anslow and Raistrick, *J.*, 1939, 1446.
[5] Baker, *J.*, 1953, 824.
[6] Seshadri and Venkatasubramanian, preceding paper.
[7] Pfau, *Helv. Chim. Acta*, 1926, **9**, 650.
[8] Asahina and Yasue, *Ber.*, 1936, **69**, 2327.
[9] Vischer, *J.*, 1953, 815.
[10] Hassel and Todd, *J.*, 1947, 611; Jain and Seshadri, *Proc. Indian Acad. Sci.*, 1952, **35**, *A*, 233.

Experimental

2-Hydroxy-3 : 4-dimethoxy-6-methylbenzaldehyde (VI).—Atranol, obtained from lecanoric acid,[6] was converted by Dakin reaction into 5-methylpyrogallol [7] which by Gattermann synthesis yielded 2 : 3 : 4-trihydroxy-6-methylbenzaldehyde.[8] This with an excess of dimethyl sulphate and potassium carbonate in acetone gave the trimethyl ether (negative ferric reaction) as an oil which was partially demethylated as follows. A solution of it (1·5 g.) in ether (500 c.c.) was treated at 0° with a solution of anhydrous aluminium chloride (3 g.) in ether (20 c.c.). After 48 hr. at room temperature, the complex was decomposed with ice and dilute hydrochloric acid, warmed at 100° for ½ hr., and shaken with ether. The ether layer was extracted with 1% aqueous sodium hydroxide. Acidification of the alkaline extract gave a precipitate of the *dimethoxy-aldehyde* which crystallised from light petroleum (b. p. 60—80°) as needles (yield quantitative), m. p. 110° (Found: C, 61·1; H, 6·7. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%). It gave a violet-brown colour with alcoholic ferric chloride and a yellow solution in alkali.

The dimethoxy-aldehyde was obtained in poorer yield by partial methylation of the trihydroxy-aldehyde by 2 mols. of dimethyl sulphate and potassium carbonate (boiling for 3 hr.).

3 : 4-Dimethoxy-6-methylpyrocatechol.—A solution of the above dimethoxy-aldehyde (0·8 g.) in 4% aqueous sodium hydroxide (4 c.c.) was treated at 10° with a 6% solution (2 c.c.) of hydrogen peroxide and after 1 hr. acidification and extraction with ether gave the catechol (0·5 g.) which crystallised from light petroleum (b. p. 60—80°) as colourless aggregates of prisms, m. p. 101°. A mixed m. p. with a sample prepared according to the method of Baker and Raistrick [3] showed no depression.

Fumigatin (II; R = H).—The preceding ether was converted as described by Baker and Raistrick [3] into fumigatin, which crystallised from light petroleum as maroon-coloured needles, m. p. 112°. It exhibited all the colour reactions reported.

2 : 5-Dihydroxy-3 : 4-dimethoxy-6-methylbenzaldehyde (VII).—A solution of the above-mentioned dimethoxy-aldehyde (2·8 g.) in 10% aqueous sodium hydroxide (28 c.c.) was treated during 2 hr. at 10° with a saturated aqueous solution of potassium persulphate (4·4 g.). After 24 hr. at room temperature, the mixture was acidified to Congo Red with concentrated hydrochloric acid and extracted with ether to remove the unchanged aldehyde. The aqueous layer was treated with more concentrated hydrochloric acid (20 c.c.) and heated at 80° for ½ hr. The solution was then cooled, saturated with salt, and extracted with ether. The ether extract was dried and the solvent removed. The residual *quinol-aldehyde* crystallised from benzene–light petroleum (b. p. 60—80°) as pale yellow clusters of long, thin plates (1·3 g.), m. p. 130° (Found: C, 56·5; H, 5·9. $C_{10}H_{12}O_5$ requires C, 56·6; H, 5·7%). It gave a transient green colour with alcoholic ferric chloride.

Spinulosin 3-Methyl Ether (*6-Hydroxy-3 : 4-dimethoxytoluquinone*) (III; R = H, R′ = Me).—A solution of the quinol-aldehyde (VII) (0·4 g.) in 4% aqueous sodium hydroxide (3 c.c.) was treated with 6% hydrogen peroxide (2 c.c.) and left at 10° for ½ hr. The solution gradually became deep purple. It was acidified, filtered (deep red), saturated with sodium chloride, and continuously extracted with light petroleum (b. p. 60—80°). The extract was dried (Na_2SO_4) and the solvent removed. The residue crystallised from light petroleum as orange-red needles (0·2 g.), m. p. 108° (Found: C, 54·5; H, 5·4. Calc. for $C_9H_{10}O_5$: C, 54·5; H, 5·1%). Anslow and Raistrick [4] reported m. p. 105°.

On methylation with methyl sulphate–acetone–potassium carbonate, spinulosin dimethyl ether was obtained (m. p. 80°) agreeing in m. p. and colour reactions with the sample described by the above authors.

2 : 3-Dimethoxy-5 : 6-dimethylquinol.—A solution of 2 : 5-dihydroxy-3 : 4-dimethoxy-6-methylbenzaldehyde (0·4 g.) in alcohol (5 c.c.), concentrated hydrochloric acid (2 c.c.), and water (5 c.c.) was added to zinc amalgam (2 g.), and the mixture kept at 80° for ½ hr. The solution, initially yellow, slowly became colourless. The zinc was separated and the solution saturated with sodium chloride and repeatedly extracted with ether. The combined ether extracts were dried (Na_2SO_4) and the solvent was removed. The colourless oily residue was taken up in hot light petroleum (b. p. 60—80°) from which it crystallised as prisms (0·25 g.), m. p. 84° (Found: C, 60·8; H, 7·6. Calc. for $C_{10}H_{14}O_4$: C, 60·6; H, 7·1%). Brian *et al.*[12] who obtained it from aurantiogliocladin reported the same m. p.

[11] Murti, Seshadri, Sundaresan, and Venkataramani, *Proc. Indian Acad. Sci.*, 1957, **46**, *A*, 265.
[12] Brian, Curtis, Howland, Jefferys, and Raudnitz, *Experientia*, 1951, **7**, 266.

Aurantiogliocladin (IV).—Oxidation of the above quinol under the conditions described by Vischer [9] gave aurantiogliocladin, m. p. 63° (Found: C, 61·8; H, 5·8. Calc. for $C_{10}H_{12}O_4$: C, 61·2; H, 6·2%).

Spinulosin 6-Methyl Ether (*3-Hydroxy-4 : 6-dimethoxytoluquinone*) (III; R = Me, R′ = H).—Dakin oxidation of 2 : 5-dihydroxy-4 : 6-dimethoxy-3-methylacetophenone [11] (1 g.) under the conditions described earlier gave the *quinone methyl ether* which crystallised from light petroleum as broad, maroon-coloured, rectangular plates (0·5 g.), m. p. 75° (Found: C, 54·9; H, 5·0. $C_9H_{10}O_5$ requires C, 54·5; H, 5·1%). It gave a deep blue solution with concentrated sulphuric acid, a permanent pink colour with a trace of alkali, and a bluish-black colour with alcoholic ferric chloride. The identity was further confirmed by methylation to spinulosin dimethyl ether, m. p. and mixed m. p. 80°.

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