984. *Constituents of the Higher Fungi. Part II.*[1] *The Synthesis of Hispidin.*

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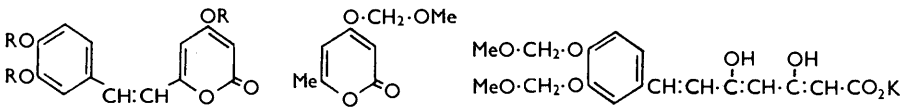
Hispidin has been synthesised by two methods. Methoxymethyl groups have been used to protect the phenolic hydroxyl groups of the starting materials.

In Part I [1] the isolation and elucidation of the structure of a new 4-hydroxy-6-styryl-2-pyrone (I) from the basidiomycete *Polyporus hispidus* (Bull.) Fr. was described. We now report its synthesis.

6-Styryl-2-pyrones have been synthesised by condensing an acid chloride with acetonedicarboxylic acid and cyclising the product,[2] and by condensing an aromatic aldehyde with 4-methoxy-6-methyl-2-pyrone in the presence of magnesium methoxide.[1,3] The latter method failed to yield a condensation product from protocatechualdehyde, doubtless because the phenolic hydroxyl groups prevent aldol condensation.[4] In the protection of hydroxyl groups, methoxymethyl ethers are readily cleaved by acids [5] and they have been



used for the preparation of hydroxycinnamaldehydes.[6] 4-Hydroxy-6-methyl-2-pyrone readily formed the 4-methoxymethyl ether (III) on reaction with chloromethyl ether in the presence of anhydrous potassium carbonate, the identity of the product being established from its ultraviolet spectrum; the 2-methoxymethyl ether was not detected. Protocatechualdehyde dimethoxymethyl ether was prepared in 50% yield from chloromethyl ether and the sodium salt of the aldehyde suspended in dry toluene: condensation of these two protected compounds in the presence of magnesium methoxide gave only a low yield of the required 6-[3,4-di(methoxymethoxy)styryl]-4-methoxymethoxy-2-pyrone (II) which was difficult to separate from the accompanying yellow oil but hydrolysis with boiling 2N-acid gave hispidin in quantitative yield.

An alternative procedure giving a much higher overall yield involved condensation of protocatechualdehyde dimethoxymethyl ether with the 4-methyl instead of the methoxymethyl ether. The styrylpyrone, obtained in good yield, was hydrolysed to the potassium salt (IV) by ethanolic potassium hydroxide; the free acid gave tri-*O*-acetylhispidin in refluxing acetic anhydride and thence hispidin on acid hydrolysis.

Experimental

4-Methoxymethoxy-6-methyl-2-pyrone.—Chloromethyl ether [7] (16 ml.) was added during 15 min. to a stirred, refluxing solution of 4-hydroxy-6-methyl-2-pyrone (triacetic lactone) [8] (10 g.) in dry acetone (200 ml.) containing anhydrous potassium carbonate (30 g.). The

[1] Part I, Edwards, Lewis, and Wilson, preceding paper.
[2] Borsche and Bodenstein, *Ber.*, 1929, **62**, 2513; Zdzistaw and Macierewiez, *Roczniki Chem.*, 1950, **24**, 144.
[3] Bu'Lock and Smith, *J.*, 1960, 502.
[4] Tiemann, *Ber.*, 1885, **18**, 3482.
[5] Hoering and Baum, G.P. 209,608.
[6] Pauly and Wascher, *Ber.*, 1923, **56**, 603; Pauly and Strassberger, *Ber.*, 1929, **62**, 2277.
[7] *Org. Synth.*, 1929, **9**, 58.
[8] Collie, *J.*, 1891, **59**, 607.

mixture was allowed to cool and filtered, the solid being washed with acetone. Evaporation gave an oil which was washed in ether (30 ml.) with 2N-sodium hydroxide, then with water (30 ml.), dried (Na_2SO_4), and evaporated. The residue was repeatedly extracted with hot light petroleum (b. p. 40—60°), which afforded needles of 4-*methoxymethoxy*-6-*methyl*-2-*pyrone* (6·3 g.), m. p. 57° (from light petroleum) (Found: C, 56·5; H, 6·2. $C_8H_{10}O_4$ requires C, 56·5; H, 5·9%), $\lambda_{max.}$ 280 mμ.

3,4-*Di*(*methoxymethoxy*)*benzaldehyde*.—To protocatechualdehyde (69 g.) in stirred boiling toluene (600 ml.), sodium ethoxide [from sodium (23 g.) and absolute alcohol (300 ml.)] was added during 30 min., alcohol being meanwhile removed in a stream of nitrogen. The remaining alcohol was distilled off and the residue was cooled to 0° and treated with chloromethyl ether (81 g.) during 3 hr., stirred at room temperature for 4 hr., and shaken with 2N-sodium hydroxide (100 ml.). The toluene layer was separated, washed with water, dried (Na_2SO_4), and evaporated. The residue brown oil was distilled at 3 mm.; the fraction boiling up to 160° was collected: it solidified. A small quantity of contaminant insoluble in acid and alkali was removed by dissolving the distilled product in alcohol (60 ml.) and adding water until an oil separated. The colourless suspended solid was filtered off and the filtrate vigorously shaken; the oil rapidly solidified to yield 3,4-*di*(*methoxymethoxy*)*benzaldehyde*, which after recrystallising twice from light petroleum (b. p. 80—100°) formed needles, m. p. 60° (Found: C, 58·1; H, 6·2. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·15%).

6-[3,4-*Di*(*methoxymethoxy*)*styryl*]-4-*methoxymethoxy*-2-*pyrone*.—3,4-Di(methoxymethoxy)-benzaldehyde (1·07 g.), 6-methyl-4-methoxymethoxy-2-pyrone (0·85 g.), and magnesium methoxide (from magnesium, 0·4 g., and methyl alcohol, 20 ml.) were refluxed for 4 hr., then filtered and evaporated on the water bath. The residue was extracted with light petroleum (100 ml.; b. p. 80—100°); cooling this gave a yellow oil which at low temperature slowly deposited 6-[3,4-*di*(*methoxymethoxy*)*styryl*]-4-*methoxymethoxy*-2-*pyrone* (3 mg.), which recrystallised from light petroleum–ether as pale yellow cubes, m. p. 59—60° (Found: C, 60·1; H, 5·9. $C_{19}H_{22}O_8$ requires C, 60·3; H, 5·8%).

6-(3,4-*Dihydroxystyryl*)-4-*hydroxy*-2-*pyrone* (*Hispidin*).—The foregoing ether (30 mg.) was boiled in water (10 ml.) containing 2N-sulphuric acid (3 drops) for 3 min. On cooling, hispidin was precipitated (19 mg.), with m. p. and mixed m. p. 259° (decomp.) (correct ultraviolet and infrared spectrum).

6-[3,4-*Di*(*methoxymethoxy*)*styryl*]-4-*methoxy*-2-*pyrone*.—3,4-Di(methoxymethoxy)benzaldehyde (2·15 g.) and 4-methoxy-6-methyl-2-pyrone were condensed as described above. The methanol solution was evaporated and the residue washed in chloroform with 2N-sulphuric acid (20 ml.) and water, dried (Na_2SO_4), and placed on magnesium oxide; evaporation of the eluate gave the solid *pyrone* (0·76 g.), pale yellow needles, softening at 107°, m. p. 116° (from methanol) (Found: C, 61·9; H, 5·8. $C_{18}H_{20}O_7$ requires C, 62·1; H, 5·75%).

This ether (0·5 g.) was hydrolysed by boiling 2N-sulphuric acid in 5 min. to *O*-methylhispidin, orange-yellow needles, m. p. and mixed m. p. 257° (decomp) (from glacial acetic acid) (Found: C, 64·5; H, 4·9. Calculated for $C_{14}H_{12}O_5$: C, 64·6; H, 4·6%).

The triether (0·65 g.) in ethanol (50 ml.) at 5° was treated with potassium hydroxide (8 g.) in ethanol (180 ml.). The mixture was set aside at room temperature in a stream of nitrogen for 48 hr. The precipitated potassium 7-[3,4-di(methoxymethoxy)phenyl]-3,5-dihydroxy-hepta-2,4,6-trienoate (0·4 g.) was separated, washed with absolute alcohol, and dissolved in water (10 ml.). Acidification of the solution with dilute sulphuric acid yielded the free acid with spontaneous removal of the methoxymethyl groups. The yellow acid was air-dried and refluxed with acetic anhydride (3 ml.) for 3 min.; pouring the mixture into water gave orange-yellow tri-*O*-acetylhispidin (135 mg.) which after recrystallisation twice from alcohol had m. p. 143° (Found: C, 61·3; H, 4·4. Calc. for $C_{19}H_{16}O_8$: C, 61·3; H, 4·3%). Hydrolysis of this acetate as described in Part I [1] yielded hispidin, m. p. and mixed m. p. 259° (decomp.).

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