The Chemistry of Fungi. Part LXVII.[1] Synthesis of Di-*O*-methylcitromycinone and Related Pyrano[3,2-*c*][1]benzopyran-4,5-diones

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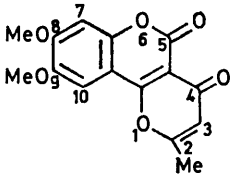
Novel, general routes to 2-methylpyrano[3,2-*c*][1]benzopyran-4,5-diones are reported. Di-*O*-methylcitromycinone, a major degradation product of the fungal metabolite, citromycetin, has been synthesised.

DURING our investigations concerning the fungal metabolite, citromycetin, a major degradation product, di-*O*-methylcitromycinone was assigned the structure (1).[2] Our previous attempts [3] to synthesise this pyrano[3,2-*c*]-[1]benzopyran-4,5-dione (1) furnished only the isomeric 2,5-dione (2). The condensation of 4-hydroxycoumarins (or of 3-acetyl-4-hydroxycoumarins) with acetic anhydride in the presence of perchloric acid was later reported [4] to yield compounds of type (1). However, using a variety of reaction conditions, we have been unable to substantiate this report.[4] In our hands, the only products were the parent 4-hydroxycoumarin or its 4-*O*-acetate. Consequently we have devised alternative routes to compounds of type (1) in general, and to di-*O*-methylcitromycinone in particular.

In the most efficient process, 4-hydroxy-6,7-dimethoxycoumarin was condensed with crotonyl chloride, with titanium tetrachloride as a catalyst, to yield 2,3-dihydro-8,9-dimethoxy-2-methylpyrano[3,2-*c*][1]-benzopyran-4,5-dione (3; R = H), τ 2·82 (s, 7-H), 3·2



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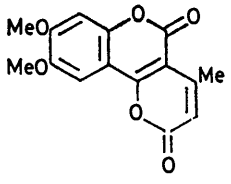

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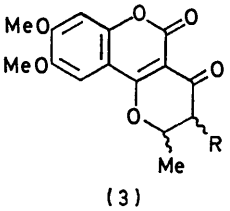

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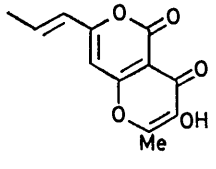

(4)

(s, 10-H), 5·1 (m, 2-H), 6·05 (6H, s, 2 × OMe), 7·26 (m, 3-H), and 8·32 (3H, d, CMe). This coumarin (3; R = H) was dehydrogenated to di-*O*-methylcitromycinone (1) by two processes. In the first it was oxidised with lead tetra-acetate to a readily separable mixture of compound (1), τ 2·70 (s, 7-H), 3·12 (s, 10-H), 3·70 (s, 3-H), 6·0 (6H, s, 2 × OMe), and 7·55 (3H, s, CMe), and the 3-acetoxy-derivative (3; R = OAc), τ 4·0 (m, 3-H), 5·1 (m, 2-H), 6·01 (6H, s, 2 × OMe), 7·8 (3H, s, OAc), and 8·32 (3H, s, CMe). During the course of our work a similar sequence of reactions was described [5] by Kato and Hirata, in their synthesis of radicinin (4), and of its dihydro-derivative.

In our second oxidation method compound (3; R = H) was brominated with phenyltrimethylammonium tribromide to give the unstable (epimeric?) 3-bromo-compounds (3; R = Br) which were converted by base into di-*O*-methylcitromycinone (1). Alternative, but less satisfactory, syntheses of (1) were achieved by (*a*) the condensation of tetrolyl chloride with 4-hydroxy-6,7-dimethoxycoumarin, and (*b*) the interaction of keten dimer with the morpholine enamine of 4-hydroxy-6,7-dimethoxycoumarin.

The generality of these methods is illustrated by their application to 4-hydroxycoumarin, 4-hydroxy-7-methoxycoumarin, 4-hydroxy-6-methoxycoumarin, and 4-hydroxy-5,7-dimethoxycoumarin.

EXPERIMENTAL

Di-O-methylcitromycinone.—(*a*) To a cooled (0°), stirred solution of crotonyl chloride (1 g) in tetrachloroethane (10 ml) containing titanium tetrachloride (3 g) was added 4-hydroxy-6,7-dimethoxycoumarin (1 g). After 8 h at room temperature the resultant deep red solution was added to ice–water (100 ml) and the product was extracted with methylene chloride. Preparative t.l.c. on silica [ethyl acetate–methanol (95 : 5)] gave 2,3-*dihydro*-8,9-*dimethoxy*-2-*methylpyrano*[3,2-c][1]*benzopyran*-4,5-*dione* (3; R = H), which formed pale yellow needles (1·2 g), m.p. 228° (from ethyl acetate) (Found: C, 61·6; H, 4·8%; M^+, 290. $C_{15}H_{14}O_6$ requires C, 62·0; H, 4·8%; *M*, 290).

A solution of this coumarin (0·5 g) in acetic acid (10 ml) containing lead tetra-acetate (0·75 g) was kept at 100° for 2 h. Excess of oxidising agent was then destroyed by the addition of ethylene glycol (0·5 g). After isolation with methylene chloride the product was purified by chromatography on silica from ethyl acetate–methanol (95 : 5). Elution with methylene chloride gave (i) di-*O*-methylcitromycinone (0·02 g), which formed buff coloured needles, m.p. and mixed m.p. (with the natural product) 314°, and having the requisite spectral properties (Found: C, 62·5; H, 4·6%; M^+, 288. Calc. for $C_{15}H_{12}O_6$: C, 62·5; H, 4·2%; *M*, 288), and (ii) 3-*acetoxy*-2,3-*dihydro*-8,9-*dimethoxy*-2-*methylpyrano*[3,2-c][1]*benzopyran*-4,5-*dione* (3; R = OAc) (0·03 g), which formed needles, m.p. 210° (from ethanol) (Found: C, 58·2; H, 4·6%; M^+, 348. $C_{17}H_{16}O_8$ requires C, 58·5; H, 4·6%; *M*, 348). Unchanged starting material (0·05 g) was recovered.

(*b*) A solution of the dihydro-compound (3; R = H) (0·5 g) in tetrahydrofuran (50 ml) containing phenyltrimethylammonium tribromide (1·8 g) was stirred at 0° for 2 h. The product was isolated with methylene chloride, to

[1] Part LXVI, S. Ahmad, W. B. Whalley, and D. F. Jones, *J. Chem. Soc.* (*C*), 1971, 3590.

[2] G. W. K. Cavill, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1950, 1031.

[3] G. G. Badcock, F. M. Dean, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1950, 903.

[4] P. F. G. Praill, and A. L. Whitear, *Proc. Chem. Soc.*, 1961, 112.

[5] K. Kato, Y. Hirate, and S. Yamamura, *J. Chem. Soc.* (*C*), 1969, 1997.

yield the unstable 3-bromo-2,3-dihydro-8,9-dimethoxy-2-methylpyrano[3,2-*c*][1]benzopyran-4,5-dione in needles from methanol. Dehydrobromination of this derivative (0·1 g) dissolved in dimethylformamide (2 ml) containing sodium hydrogen carbonate (0·12 g) at 125° for 0·5 h gave di-*O*-methylcitromycinone (0·03 g), identical with the natural product and with that prepared by method (*a*).

(*c*) A solution of tetrolic acid (220 mg) in benzene (5 ml) and oxalyl chloride (0·8 ml) was warmed for 2 h at 100°. The solvent and excess of oxalyl chloride were removed under reduced pressure, to furnish tetrolyl chloride as a viscous oil, $\nu_{max.}$ 1870 cm^{-1}. A solution of this acid chloride (150 mg) in tetrachloroethane (5 ml) was added to 4-hydroxy-6,7-dimethoxycoumarin (100 mg) dissolved in the same solvent (5 ml). Five days later, isolation of the product in the usual manner gave di-*O*-methylcitromycinone (25 mg), identical with the natural product and with that prepared by methods (*a*) and (*b*).

(*d*) (with M. M. E. Badran). Prepared by the interaction of 4-hydroxy-6,7-dimethoxycoumarin (0·3 g) with morpholine (1·5 ml) in benzene (10 ml) during 5 h at 100°, the *morpholine enamine* (0·3 g) formed needles (from methanol), m.p. 198° [Found: C, 61·9; H, 6·0; N, 4·9; OMe, 23·3. $C_{15}H_{17}NO_5(OMe)_2$ requires C, 61·8; H, 5·8; N, 4·7; OMe, 21·3%].

A solution of this enamine (150 mg) in methylene chloride (7 ml) was added to keten dimer (0·25 g) in methylene chloride (2 ml) at 0°. After isolation 5 days later the product was purified from ethanol to yield di-*O*-methylcitromycinone (10 mg).

Analogous Syntheses.—(i) *From 4-hydroxycoumarin.* Prepared from crotonyl chloride and 4-hydroxycoumarin (1 g), *2,3-dihydro-2-methylpyrano*[3,2-c][1]*benzopyran-4,5-dione* (0·8 g) formed needles, m.p. 201° (from ethanol) (Found: C, 67·3; H, 4·3%; M^+, 230. $C_{13}H_{10}O_4$ requires C, 67·8; H, 4·3%; *M*, 230).

Oxidation of this coumarin (0·5 g) with lead tetra-acetate gave *2-methylpyrano*[3,2-c][1]*benzopyran-4,5-dione* (20 mg) in pale yellow needles, m.p. 258° (from ethanol) (Found: C, 68·2; H, 3·5%; M^+, 228. $C_{13}H_8O_4$ requires C, 68·4; H, 3·5%; *M*, 228), together with *3-acetoxy-2,3-dihydro-2-methylpyrano*[3,2-c][1]*benzopyran-4,5-dione* (25 mg) in needles, m.p. 190° (from ethyl acetate) (Found: M^+, 288. $C_{15}H_{12}O_6$ requires *M*, 288).

(ii) *From 4-hydroxy-7-methoxycoumarin.* Prepared from crotonyl chloride (0·5 g) and 4-hydroxy-7-methoxycoumarin, *2,3-dihydro-8-methoxy-2-methylpyrano*[3,2-c][1]*benzopyran-4,5-dione* (0·4 g) formed yellow needles, m.p. 188° (from ethanol) (Found: C, 64·2; H, 4·5%; M^+, 260. $C_{14}H_{12}O_5$ requires C, 64·6; H, 4·6%; *M*, 260).

Prepared from this γ-pyrone (150 mg) by the bromination process, *8-methoxy-2-methylpyrano*[3,2-c][1]*benzopyran-4,5-dione* (45 mg) formed yellow needles, m.p. 222° (from chloroform) (Found: C, 65·1; H, 4·3%; M^+, 258. $C_{14}H_{10}O_5$ requires C, 65·1; H, 3·9%; *M*, 258). The same product (20 mg) resulted from the condensation of tetrolyl chloride with 4-hydroxy-7-methoxycoumarin (100 mg).

(iii) *From 4-hydroxy-6-methoxycoumarin.* Prepared from crotonyl chloride (0·5 g) and 4-hydroxy-6-methoxycoumarin (0·5 g), *2,3-dihydro-9-methoxy-2-methylpyrano*[3,2-c][1]*benzopyran-4,5-dione* (0·4 g) formed yellow needles, m.p. 208° (from ethanol) (Found: C, 64·4; H, 4·6%; M^+, 260. $C_{14}H_{12}O_5$ requires C, 64·6; H, 4·6%; *M*, 260). Dehydrogenation of this γ-pyrone (200 mg) by the bromination technique gave *9-methoxy-2-methylpyrano*[3,2-c][1]*benzopyran-4,5-dione* (50 mg) in yellow prisms, m.p. 275° (from chloroform) (Found: C, 65·2; H, 4·1%; M^+, 258. $C_{14}H_{10}O_5$ requires C, 65·1; H, 3·9%; *M*, 258). The same coumarin (20 mg) was obtained from the interaction of tetrolyl chloride (150 mg) and 4-hydroxy-6-methoxycoumarin (270 mg).

(iv) *From 4-hydroxy-5,7-dimethoxycoumarin.* Interaction of crotonyl chloride (0·45 g) and 4-hydroxy-5,7-dimethoxycoumarin gave *2,3-dihydro-8,10-dimethoxy-2-methylpyrano*[3,2-c][1]*benzopyran-4,5-dione* (280 mg) in yellow needles, m.p. 225° (from ethanol) (Found: C, 61·5; H, 4·8%; *M*, 290. $C_{15}H_{14}O_6$ requires C, 62·0; H, 4·8%; *M*, 290). Prepared from this coumarin (150 mg) by the dehydrobromination technique *8,10-dimethoxy-2-methylpyrano*[3,2-c][1]*benzopyran-4,5-dione* (20 mg) formed yellow prisms, m.p. 255° (from chloroform) (Found: C, 62·3; H, 4·1%; M^+, 288. $C_{15}H_{12}O_6$ requires C, 62·5; H, 4·1%; *M*, 288). The same product was obtained by the tetrolyl chloride route.

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