Derivatives of Pyrano[3,2-*c*][1]benzopyran; Synthesis of Di-*O*-methylcitromycin

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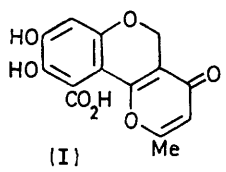
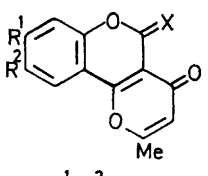
Summary Exemplified by a synthesis of di-*O*-methylcitromycin, a method is described for the synthesis of derivatives of pyrano[3,2-*c*][1]benzopyran from the appropriate derivatives of chroman-4-one and 3-acetylchroman-4-one.

DECARBOXYLATION followed by methylation converts the fungal metabolite citromycetin (I) into di-*O*-methylcitromycin[1] (II), oxidation of which gives di-*O*-methylcitromycinone[2] (III). Although this oxopyranopyrone was synthesised some time ago by application[3] of the Praill–Whitear acylation[4] to the appropriate coumarin derivative and has recently been prepared by other methods,[5] no synthesis of the pyranopyrone nucleus characteristic of the fungal product itself has been described before.

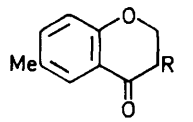
In model experiments 6-methylchroman-4-one (VI) could not be satisfactorily converted into its 3-acetyl derivative (VII) by alkaline reagents because these induced ring opening and allowed further unwanted reactions (*e.g.* refs. 6 and 7), but Ac_2O–BF_3[8] gave the complex (IX), m.p. 198°, in 89% yield. Removal of the boron residue by NaOAc–AcOH had to be carefully controlled to avoid ring opening but supplied the required compound (VII) in 91% yield as an enol (X?), m.p. 99—100°. Acetylation gave both possible acetates. One had m.p. 73° and was assigned structure (XI) for several reasons, *e.g.*, the low field (τ 2·26) at which the 5-H resonance occurred, this being indicative of an *ortho* carbonyl group. In the isomer (XII), m.p. 60°, this resonance occurs near τ 2·9.



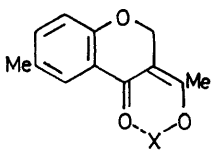
(I)



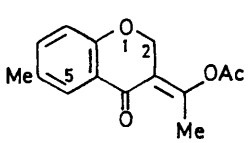
(II) $R^1=R^2=OMe$; X=H_2
(III) $R^1=R^2=OMe$; X=O
(IV) $R^1=H$; $R^2=Me$; X=H_2
(V) $R^1=H$; $R^2=Me$; X=O



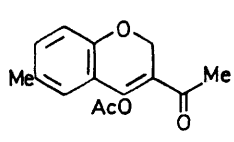
(VI) R=H
(VII) R=Ac
(VIII) R=CO·CH_2Ac



(IX) X=BF_2
(X) X=H



(XI)



(XII)

Next, the acetate (XII) was treated with bases under various conditions intended to induce an acyl migration similar to that in the Baker–Venkataraman rearrangement,[9] but evidence for the formation of the triketone (VIII) was found only with Ph_3CLi. Moreover, the isomeric acetate (XI), which cannot give (VIII) by any simple rearrangement, gave similar results. Evidently acetyl groups are transferred by intermolecular processes, and since these must denude half the material of its protection against base-catalysed ring opening, the poor yields (*ca.* 24%) are not surprising. Cyclisation of the (crude) triketone (VIII) in AcOH–HCl was nearly quantitative and gave the pyranobenzopyranone (IV), m.p. 212—213°, ν_{max} 1664 cm^{-1} 4-pyrone), τ 7·66 (ArMe), 8·84 (OCH_2), and 7·69 (3H) and 3·86 (1H) (broad singlets; pyrone MeC:C*H*), further identified by chromic oxidation to the oxopyranopyrone[10] (V).

Similarly, 6,7-dimethoxychroman-4-one[7] with AcO–BF_3 gave a complex, m.p. 232°, converted by NaOAc in EtOH into 3-acetyl-6,7-dimethoxychroman-4-one, m.p. 116—118°, acetylation of which gave only one acetate, m.p. 124—125°, allocated a structure similar to (XI) because it displayed long-range coupling between the vinylic methyl and ring methylene groups. Treatment with Ph_3CLi gave a crude triketone at once cyclised by HCl–AcOH to di-*O*-methylcitromycin (II), m.p. and mixed m.p. 224—227°, spectroscopically identical with an authentic specimen.

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