

TOTAL SYNTHESIS OF (\pm)-O-METHYLSTERIGMATOCYSTIN

Michael J. Rance and John C. Roberts

Department of Chemistry, University of Nottingham

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Sterigmatocystin (I, R = H), a carcinogenic metabolite of Aspergillus versicolor (Vuill.) Tiraboschi, proved to be the first-known natural product to contain the dihydrofurobenzofuran ring-system.¹ It was later found² that the powerfully carcinogenic aflatoxins (ex A. flavus) also contained this (or the closely related tetrahydro-) system and two of these (aflatoxin-B1 and -B2) have been synthesised.³ In a previous paper,⁴ we outlined a synthesis of (\pm)-dihydro-O-methylsterigmatocystin (Ia) and we now report the more difficult, and substantially different, synthesis of (\pm)-O-methylsterigmatocystin (I, R = Me). It is interesting to note that this latter compound has itself been isolated, in the (-)-form, as a co-metabolite of the aflatoxins in A. flavus.⁵

Treatment of the phenolic lactone (II)^{3(a)} with hydrogen chloride in dry methanol yielded the ring-opened compound (III) as a mixture of cis- and trans-isomers. Reaction of (III) with the bromo-ester (IV), in an Ullmann-type ether synthesis under mild solvent-assisted conditions,⁶ gave the diphenyl ethers (V). It was hoped that acid hydrolysis of the ether-esters (V) would provide the lactonic acid (VI, R = OH) but the aromatic ester grouping proved stable under these conditions and the product was shown to be (VI, R = OMe). However, rigorous base hydrolysis of (V) followed by acid treatment yielded the required lactonic acid (VI, R = OH). Heating a benzene solution of the corresponding acid chloride (VI, R = Cl) under reflux for 24hr.

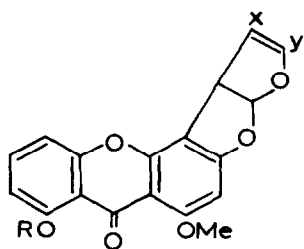
achieved the desired ring closure to yield the xanthone-lactone (VII, Z = O). Reduction of this latter compound with di-isobutylborane^{3(a),7} gave a low yield (10 - 20 per cent) of the hemiacetal (VII, Z = H, OH) which was isolated by preparative thin-layer chromatography. The corresponding acetate (VII, Z = H, OAc), on repeated sublimation in vacuo at 250^o, lost the elements of acetic acid to yield (±)-O-methylsterigmatocystin (I, R = Me) as colourless prisms (from ethanol), m.p. 274^o, unaltered by admixture with an authentic specimen prepared as described below.

Trifluoro-acetic acid catalysed addition of the elements of water to (-)-O-methylsterigmatocystin (prepared by methylation of natural sterigmatocystin) gave the optically active hemiacetal (VII, Z = H, OH) which dissolved in aqueous alkali to yield the ring-opened salt (VIII) (not isolated). The optical activity of the solution fell to zero within a few minutes. Acidification of the reaction mixture gave the (±)-hemiacetal (VII, Z = H, OH). Repeated sublimation of the corresponding acetate (VII, Z = H, OAc) yielded (±)-O-methylsterigmatocystin, m.p. 272-274^o, which was spectroscopically (ultra-violet and solution infrared) and chromatographically (t.l.c. on silica) identical with (-)-O-methylsterigmatocystin (m.p. 265 - 267^o) and with the synthetic product prepared as above.

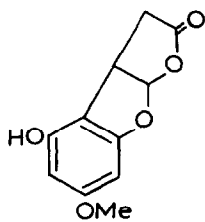
Satisfactory analyses and/or spectra have been obtained for the above mentioned new compounds.

Acknowledgement

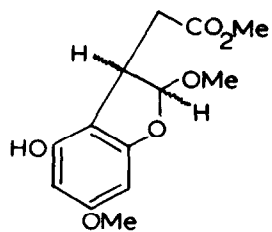
We thank the Science Research Council for the award of a maintenance grant (to M.J.R.).



(I)

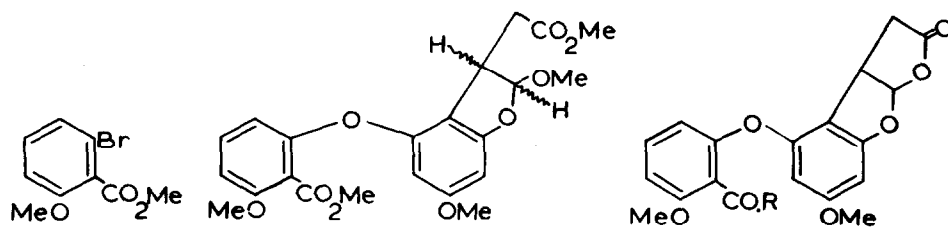


(II)



(III)

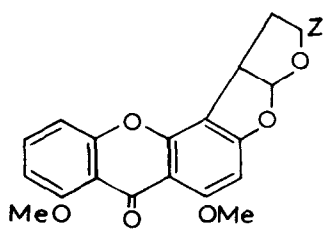
([a; R = Me; no $\Delta^{x,y}$)



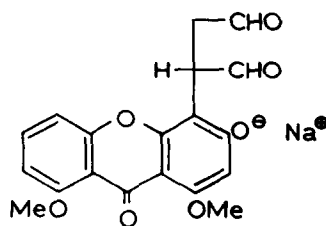
(IV)

(V)

(VI)



(VII)



(VIII)

R E F E R E N C E S

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