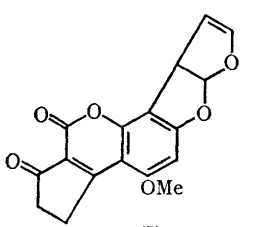
Synthesis of (±)-Tetrahydrodeoxoaflatoxin-B1, a Racemic Form of the Lævorotatory Hydrogenation Product of Aflatoxin-B1

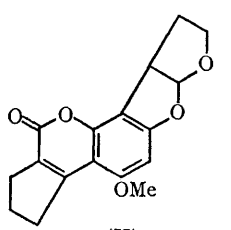
By J. A. KNIGHT, JOHN C. ROBERTS, PATRICK ROFFEY, and A. H. SHEPPARD
(*Department of Chemistry, The University, Nottingham*)

AFLATOXIN-B1 is the most important member of a group of toxins[1] (produced by *Aspergillus flavus*) which are responsible for Turkey "X-Disease". It is itself a powerful carcinogen.[2] An elegant analytical and spectroscopic investigation has established[3] the structure (I) for aflatoxin-B1 and structure (II) for its hydrogenation product, (−)-tetrahydrodeoxoaflatoxin-B1. No member of the aflatoxin group, nor the last-mentioned substance (which retains intact the carbon skeleton of aflatoxin-B1), has hitherto been synthesised. We now report a synthesis of the racemic form of the hydrogenation product.

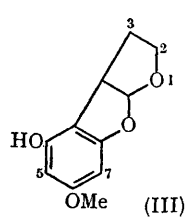
The key intermediate in our synthesis was (±)-tetrahydro-4-hydroxy-6-methoxyfuro[2,3-*b*]-benzofuran (III), a (−)-form of which we had obtained in small amount as a degradation product[4] of another mould metabolite, sterigmatocystin (*ex A. versicolor*). (A detailed account of the synthesis of this key intermediate is to be published shortly.[5]) Pechmann condensation of this intermediate (III) with ethyl cyclopentanone-2-carboxylate (IV) gave a mixture from which, by preparative thin-layer chromatography, there was separated (in 3% yield) a product which crystallised in small colourless needles, m.p. 208—209°. with the required molecular formula, $C_{17}H_{16}O_5$ (mass spec.), for a compound of structure (II). The proton magnetic resonance spectrum (in deuteriochloroform) of the synthetic product showed (i) a doublet (intensity 1) at τ 3·50 (J = 6 c./sec.) (–O–C*H*–O–); (ii) a singlet (intensity 1) at τ 3·63 (Ar–*H*); (iii) a singlet (intensity 3) at τ 6·10 (O·CH_3); and (iv) complex signals at



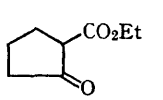
(I)



(II)



(III)



(IV)

τ 5·65—8·20 (corresponding to *ca.* 11 aliphatic protons). Its ultraviolet (EtOH) and infrared ($CHCl_3$) spectra were virtually identical with the corresponding spectra of a specimen (m.p. 247—248°) of (−)-tetrahydrodeoxoaflatoxin-B1 (kindly

provided by Dr. A. van Dorp) which had been prepared from the natural toxin. Further, the synthetic product and the "natural product" had the same blue fluorescence in ultraviolet light and had identical R_f-values (t.l.c., silica plates) in four different solvent systems.

We conclude that our synthetic product is the *cis*-form[5] of (±)-tetrahydrodeoxoaflatoxin-B1. This result confirms the structure of tetrahydrodeoxoaflatoxin-B1 and supports the allocation of structure (I) to aflatoxin-B1 itself.

(*Received, July* 22*nd,* 1966; *Com.* 532.)

[1] K. Sargeant, R. B. A. Carnaghan, and R. Allcroft, *Chem. and Ind.*, 1963, 53; K. J. van der Merwe, L. Fourie, and de B. Scott, *ibid.*, p. 1660.
[2] F. Dickens and H. E. H. Jones, *Brit. J. Cancer*, 1965, **19**, 392.
[3] T. Asao, G. Büchi, M. M. Abdel-Kader, S. B. Chang, E. L. Wick, and G. N. Wogan, *J. Amer. Chem. Soc.*, 1965, **87**, 882.
[4] J. E. Davies, D. Kirkaldy, and J. C. Roberts, *J. Chem. Soc.*, 1960, 2169; E. Bullock, J. C. Roberts, and J. G. Underwood, *ibid.*, 1962, 4179.
[5] J. A. Knight, J. C. Roberts, and (in part) P. Roffey, *J. Chem. Soc.* (*C*), 1966, in the press.