

## Total Synthesis of ( $\pm$ )-Flavipucine

By N. N. GIROTRA, (the late) Z. S. ZELAWSKI, and N. L. WENDLER\*  
(Merck Sharp & Dohme Research Laboratories, Rahway, N.J. 07065)

**Summary** The total synthesis of ( $\pm$ )-flavipucine and its diastereoisomer ( $\pm$ )-isoflavipucine is reported.

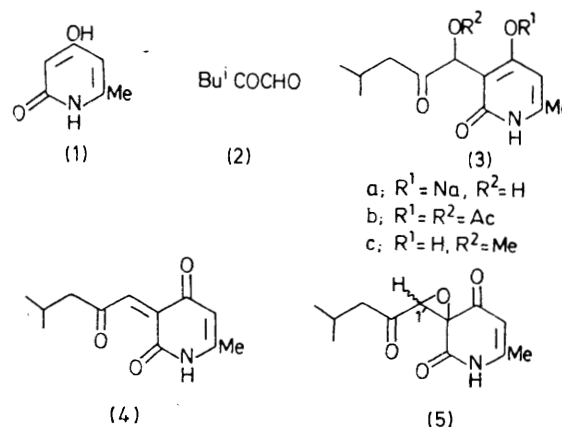
THE novel antibiotic flavipucine was isolated from a strain of *Aspergillus flavipes* by Casinovi *et al.*<sup>1</sup> and found to be active against both gram-positive and gram-negative organisms. These authors proposed a structure for this substance which was subsequently revised by Findlay and Radics<sup>2</sup> to the spirobicyclic epoxide (5). We now report the total synthesis of this antibiotic.

Condensation of the pyridone (1)<sup>3</sup> with the keto-aldehyde (2)<sup>4</sup> in methanol containing 1 equiv. of sodium methoxide at 25 °C yielded quantitatively the sodium salt (3a),<sup>5</sup> i.r. (Nujol) 5.84 and 6.08—6.29  $\mu\text{m}$ ; n.m.r. ( $\text{D}_2\text{O}$ )  $\delta$  5.82 (broad s, 5-H), 5.35 (s, 1'-H), 2.15 (s, 6-Me), and 0.85 and 0.82 (each d,  $J$  6 Hz,  $\text{CHMe}_2$ ). Acetylation of (3a) in acetic anhydride at 25 °C provided the diacetate (3b) likewise in excellent yield,†‡ m.p. 129—130 °C;  $M^+$  323; i.r. ( $\text{CHCl}_3$ ) 5.63, 5.73, 5.79, and 6.08  $\mu\text{m}$ ;  $\lambda_{\text{max}}$  (MeOH) 309 ( $\epsilon$ , 8800) and 230 nm (5500); n.m.r. ( $\text{CDCl}_3$ )  $\delta$  6.43 (s, 1'-H), 6.05 (broad s, 5-H), 2.37 (s, 6-Me), 2.28 and 2.12 (each s, 2OAc), and 0.93 and 0.90 (each d,  $J$  6 Hz,  $\text{CHMe}_2$ ).

† Satisfactory analytical data were obtained.

‡ A minor amount of lactim triacetate is also formed depending on the duration of acetylation. The latter in turn can be selectively converted into the diacetate (3b) by methanolysis.

Saponification of the diacetate (3b) in methanolic sodium hydroxide at ambient temperatures proceeded rapidly with incorporation of a methoxy-function to produce (3c) in high yield as a crystalline solid of indefinite m.p.;†  $M^+$  253;



i.r. ( $\text{CHCl}_3$ ) 5.83, 6.09, and 6.18  $\mu\text{m}$ ;  $\lambda_{\text{max}}$  (MeOH) 289 nm ( $\epsilon$ , 6900); n.m.r. ( $\text{CDCl}_3$ )  $\delta$  3.45 (s, OMe). This replacement reaction indicated the occurrence of an hydrolysis-elimination sequence; the intermediate formation of the enedione (**4**) is most likely, although this reactive species has not yet been isolated.<sup>§</sup> The diacetate (**3b**) was accordingly treated with alkaline  $\text{H}_2\text{O}_2$  in  $\text{Bu}^t\text{OH}$  or preferably with  $\text{KO}^t\text{Bu}$ – $\text{Bu}^t\text{OH}$  in  $t$ -butyl hydroperoxide as solvent at 0–25 °C, whereby incorporation of the epoxide function indeed occurred to yield ( $\pm$ )-flavipucine (**5**) together with its diastereoisomer in 55% yield.

The two isomers were separated by fractional crystallization from benzene. The isomer which crystallized

initially as plates, m.p. 154–155 °C,<sup>†</sup> was identical (t.l.c., and u.v., i.r., n.m.r., and mass spectra) with natural (–)-flavipucine.<sup>1</sup> The stereoisomer, ( $\pm$ )-isoflavipucine, was isolated as thin rectangular prisms, m.p. 136–138 °C;  $M^+$  237; i.r. ( $\text{CHCl}_3$ ) 2.92, 3.06, 3.14, 5.82, 6.00, and 6.12  $\mu\text{m}$ ;  $\lambda_{\text{max}}$  (MeOH) 326 nm ( $\epsilon$ , 6400); n.m.r. ( $\text{CDCl}_3$ )  $\delta$  5.65 (broad s, 5-H), 3.92 (s, 1'-H), 2.20 (s, 6-Me), and 0.98 (d,  $J$  6.5 Hz  $\text{CHMe}_2$ ).

The authors are indebted to Dr. Casinovi for a sample of natural (–)-flavipucine for comparison purposes.

(Received, 14th May 1976; Com. 550.)

<sup>§</sup> These attempts invariably resulted in the incorporation of groups from solvents or reagent to give side-chain-substituted species. These and other findings will be reported elsewhere.

<sup>1</sup> C. G. Casinovi, G. Grandolini, R. Mercantini, N. Oddo, R. Olivieri, and A. Tonolo, *Tetrahedron Letters*, 1968, 3175.

<sup>2</sup> J. A. Findlay and L. Radics, *J.C.S. Perkin I*, 1972, 2071.

<sup>3</sup> Prepared in excellent yield by the method of S. Seto, H. Sasaki, and K. Ogura, *Bull. Chem. Soc. Japan*, 1966, **39**, 281.

<sup>4</sup> H. D. Dakin and H. W. Dudley, *J. Biol. Chem.*, 1914, **18**, 29. This aldehyde was presently prepared by condensation of ethyl isovalerate with dimethyl sodium (method of E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, 1965, **87**, 1345) to give  $\text{MeSOCH}_2\text{C}(\text{O})\text{Bu}^t$ ; the latter was converted by the procedure of H.-D. Becker, G. J. Mikal, and G. A. Russell, (*J. Amer. Chem. Soc.*, 1963, **85**, 3410; *Org. Synth.*, Coll. vol. V, 937) into the keto-aldehyde (**2**) in 70–75% overall yield.

<sup>5</sup> J. A. Findlay and F. Y. Shum (*Synth. Comm.*, 1973, 355) reported the uncatalysed condensation of the pyridone (**1**) with  $\alpha$ -keto aldehydes. No particulars were mentioned regarding the pertinent compound (**3a**;  $\text{R}^1 = \text{H}$ ).