A Synthesis of the Antibiotic Pyoluteorin[1,2]

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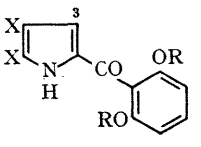
Summary Pyoluteorin, its 3,5-dichloro-isomer, and its bromo-analogue have been synthesised.

WE obtained didechloro-*OO'*-dimethylpyoluteorin (I; R = Me, X = H)[2,3] in low yield when 2,6-dimethoxybenzoyl chloride and the sodium salt of pyrrole-2-carboxylic acid were heated together to 150° and the products separated by chromatography.

Because it was possible to effect smooth stepwise demethylation with Lewis acids to give didechloropyoluteorin (I; R = X = H)[4] *via* the monomethyl ether[5] we repeated the reaction using sodium 4,5-dichloropyrrole-2-carboxylate. This gave, in about 10% yield, *OO'*-dimethylpyoluteorin (I; R = Me, X = Cl). Demethylation gave pyoluteorin (I; R = H, X = Cl) with m.p. 177—186° undepressed by an authentic sample kindly provided by Dr. I. Nakanishi of the Takeda Pharmaceutical Industries Ltd., Osaka. The i.r., u.v., and mass spectra of the synthetic and natural products were identical.



(I)

By the same reaction we have also made the 3,5-dichloro-isomer of pyoluteorin ("isopyoluteorin") m.p. 198–203° *via* its dimethyl ether, m.p. 204—205°.

Similarly, we prepared the bromo-analogue of pyoluteorin (I; R = H, X = Br), m.p. 163—164°. The n.m.r. and other spectra of the synthetic pyoluteorins are in complete agreement with their structures.

Pyoluteorin has *in vitro* activity against the Dutch Elm Disease fungus *Ceratocystis ulmi* (Buism) C. Moreau, which is as good as or better than that of either cryptosporiopsin or nystatin which were used as controls.[6]

Monodechloropyoluteorin[2,5] and monodesoxypyoluteorin[7] as well as newer methods of synthesising pyoluteorins will be reported later.

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