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A SYNTHETIC ROUTE TO PYOLUTEORIN

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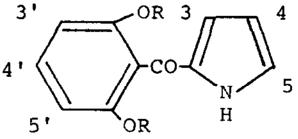
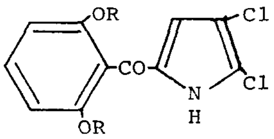
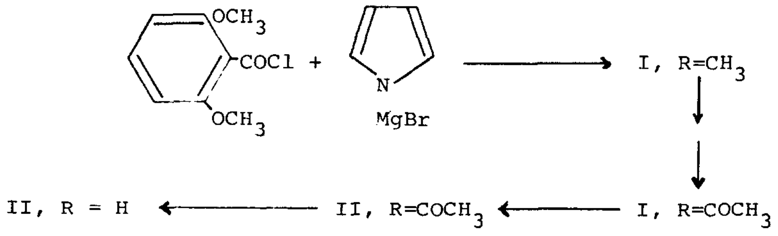
Pyoluteorin, the antibacterial agent produced by certain strains of the bacterium Pseudomonas aeruginosa,[1] has been shown [2,3,4] to have structure (II,R=H). The recent communication of Bailey and Rees [5] describing a synthesis of pyoluteorin prompts us to describe our work on this topic. We have synthesised OO-diacetylpyoluteorin (II, $R=COCH_3$) by the reaction sequence outlined below. Since it is known[2] that this derivative can be hydrolysed to pyoluteorin (72% yield), these reactions provide a synthetic route to the natural product. Prior to the above successful synthetic routes, attempts to synthesise pyoluteorin have terminated with derivatives of pyoluteorin which could not be converted into the natural product. [4,6]



(I)



(II)



Reaction of 2,6-dimethoxybenzoyl chloride with pyrrylmagnesium bromide as described previously [4] gave didechloro-OO-dimethylpyoluteorin (I, R=CH_3), m.p. 194-6° (lit., [4] m.p. 193-196°) in 58% yield.[7] This compound was treated with anhydrous aluminium trichloride in refluxing chlorobenzene and the crude phenolic product was acetylated with acetic anhydride in benzene. Preparative t.l.c. of the crude acetylation product gave didechloro-OO-diacetylpyoluteorin (I, R=$COCH_3$), m.p. 112-114° (lit.,[2,3] m.p. 110°) in 53% overall yield [7] from compound (I,R=CH_3). The NMR spectrum of the diacetate (in $CDCl_3$) shows a singlet at 1.99δ due to the acetyl groups, multiplets at 6.22, 6.60 and 7.08δ due [8] respectively to the pyrrole hydrogens H-4, H-3 and H-5, and a 7-line pattern [9] between 6.95 and 7.62δ due to the benzenoid hydrogens H-3', H-4', and H-5'.

The diacetate (I, R=$COCH_3$) in acetic acid was treated with 2.2 moles of chlorine in acetic acid and the mixture left at 20° for 15 hrs. The solvent was removed under reduced pressure and the crude product purified by preparative t.l.c. The major product was OO-diacetylpyoluteorin (II, R=$COCH_3$). It had m.p. 213-217° (from hexane/acetone) and was obtained in 60% yield.[7] The NMR spectrum of this product (in $CDCl_3$) shows a singlet at 2.10δ due to the acetyl groups, a doublet (singlet after addition of D_2O) at 6.58δ due to the pyrrole hydrogen H-3, and a 7-line pattern [9] between 6.95δ and 7.65δ due to the benzenoid hydrogens.

The synthetic diacetate (II, R=$COCH_3$) was compared directly with an authentic sample of OO-diacetylpyoluteorin, m.p. 215-219° (from hexane/acetone). The mixed m.p. was not depressed and both products had the same Rf value on thin layer chromatography and identical UV (in both neutral and basic solutions) and NMR spectra.

In the above route, chlorine in acetic acid was used for the chlorination step because it is known that dichlorination of methyl pyrrole-2-carboxylate with this reagent affords mainly the 4,5-dichloro isomer.[10] To increase the probability of chlorinating the pyrrole ring selectively, the diacetate (I, R=$COCH_3$) was used as the substrate in preference to the dimethyl ether (I, R=CH_3), since the acetoxyl group activates the benzenoid ring less than a methoxyl group. Being able to introduce the chloro substituents after the C-skeleton is formed simplifies the problem of synthesising the C-skeleton in good yield with a minimum of protecting groups.

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4. A.J. Birch, P. Hodge, R.W. Rickards, R. Takeda & T.R. Watson, J.Chem.Soc., 1964, 2641
5. K. Bailey & A.H. Rees, Chem.Comm., 1969, 1284
6. J.A. Elix & M.V. Sargent, J.Chem.Soc(C), 1967, 1718
7. No systematic attempt was made to maximise the yields.
8. The pyrrole hydrogens were assigned in a similar way to those in dechloro-OON-trimethylpyoluteorin.[4]
9. In the NMR spectra of these and some other pyoluteorin derivatives[4,6] the 6- or 7-line pattern observed for the three benzenoid hydrogens is correctly interpreted as that arising from an AB_2 system in which the difference in chemical shift between the aromatic protons is only ca. 2.5 times the magnitude of the coupling constant. See, for example, L.M. Jackman & S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, London, 1969, p.130.
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