Tetrahedron Letters No.56, pp. 4879-4882, 1970. Pergamon Press. Printed in Great Britain.

NEWER SYNTHESES OF THE PYOLUTEORIN ANTIBIOTICS

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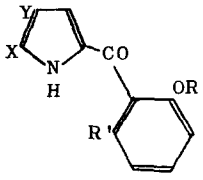
(Received in USA 21 October 1970; received in UK for publication 2 November 1970)

Three syntheses of the antibiotic pyoluteorin I, have recently been reported[1,2,3]. To these we now add the novel route via the first reported Friedel Crafts reaction on 2,3-dichloropyrrole (obtained by decarboxylation of 2,3-dichloropyrrole carboxylic acids). Using 2,6-dimethoxybenzoyl chloride and Lewis acids such as stannic chloride, we obtained dimethyl pyoluteorin. Demethylation[1] then gave I in better than 50% yield. This method was also used to synthesize the active monodeoxypyoluteorin II[1] via its ether.

The above synthesis of substituted 2-benzoylpyrroles is general. For example, pyrrole and anisoyl chloride gave III. Halogenation of III followed by demethylation[1] afforded II in good yield. The bromine IV and iodine analogues V were likewise made. Nitration similarly gave the nitro analogue VI ($J_{3,4}$ = 4 Hz)[4].

Controlled chlorination of III took place at position 4 and led to VII ($J_{3,5}$ = 1.6 Hz) via its ether. Similarly, chlorination of VIII (made from pyrrole and dimethoxybenzoyl chloride) gave the 4-monochloro derivative which then chlorinated in position 5 (giving dimethylpyoluteorin) or in position 3'. Further chlorination of these compounds then led to 3'-chloropyoluteorin via its dimethyl ether.

In a variation of our original synthesis[1] via the reaction of sodium



I, X = Y = Cl, R = H, R' = OH

II, X = Y = Cl, R = R' = H m.p. 174-176°

III, X = Y = R' = H, R = Me m.p. 130-132°

IV, X = Y = Br, R = R' = H m.p. 152°

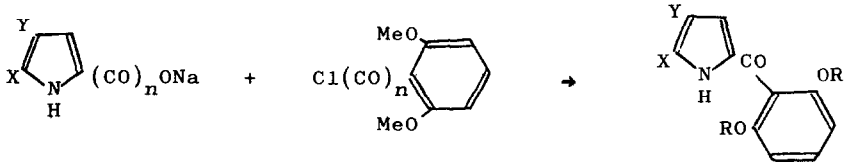
V, X = Y = I, R = R' = H m.p. 190-196°

VI, X = NO_2, Y = R = R' = H m.p. 146-147°

VII, X = R = R' = H, Y = Cl m.p. 160-162°

VIII, X = Y = H, R = Me, R' = MeO

IX, X = Y = 3' = Cl, R = H, R' = MeO m.p. 200-205°



X XI XII

pyrrole-2-carboxylates X (n = 1) with 2,6-dimethoxybenzoyl chloride XI (n = 1), we have used sodium pyrrole-2-glyoxylates X (n = 2) and obtained pyoluteorins XII.

We have also shown that 2,6-dimethoxyphenylglyoxylyl chloride XI (n = 2) can replace XI (n = 1). We have thus synthesized dimethyl pyoluteorin and 5-dechloro-O,O'-dimethylpyoluteorin XII (Y = Cl, X = H, R = Me) which underwent stepwise demethylation to 5-dechloropyoluteorin via its monomethyl ether.

We believe our dechloropyoluteorin m.p. 197° to be identical with the one m.p. 196-197° made by Takeda[5] by partial hydrogenation of pyoluteorin as hydrogenation of our dimethylpyoluteorin XII (X = Y = Cl, R = Me), obtained from X (X = Y = Cl, n = 2) yielded the same monodechloropyoluteorin as we synthesized from X (X = H, Y = Cl, n = 2) above.

All new compounds whose melting points are quoted above gave satisfactory elemental analyses, n.m.r., mass and other spectra.

We continue to prepare novel compounds for investigation of their structure/activity relationship. Details of this work will be published elsewhere.

Acknowledgements

This work was supported by the National Research Council of Canada and this University, both of which we thank.

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