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TOTAL SYNTHESIS OF PYRROLNITRIN, A NEW ANTIBIOTIC.

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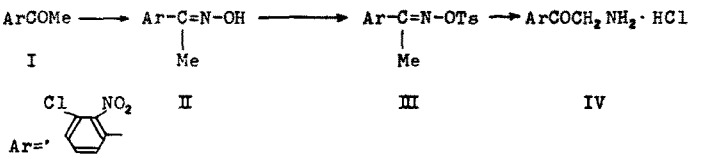
Pyrrolnitrin is an antibiotic isolated from the bacterial cells of Pseudomonas by K. Arima et al. [1] and established the structure XVII, 3-(2'-nitro-3'-chlorophenyl)-4-chloropyrrole by the same authors. [2] We wish to report the total synthesis of the antibiotic, pyrrolnitrin (XVII).

2'-Nitro-3'-chloroacetophenone (I), m.p. 96°, was changed to the oxime (II), m.p. 165°, then tosylated to the compound (III), m.p. 148°, which was converted by Neber rearrangement to the amino ketone·HCl (IV), m.p. 213° (decomp.).

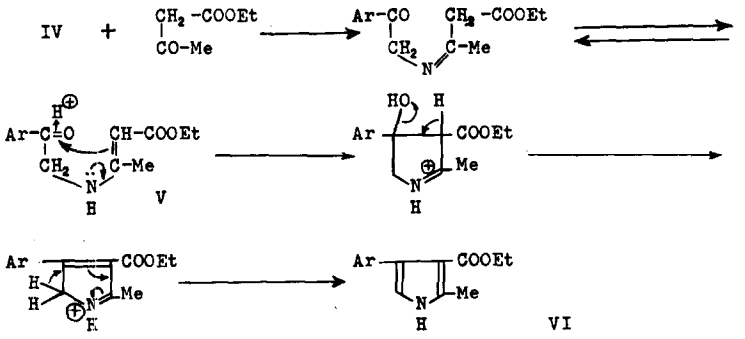
SCHEME 1



The ringclosure of the aminoketone·HCl (IV) with ethyl acetoacetate in acidic condition afforded ethyl 2-methyl-4-(2'-nitro-3'-chlorophenyl)-pyrrole-3-carboxylate (VI), m.p. 187-188°

An intermediate, ethyl 3-(2′-nitro-3′-chlorobenzoylmethylamino)-crotonate (V), m.p. 156° (decomp.), was isolated in milder reaction condition, so we suppose a mechanism of this pyrrole ringclosure reaction as follows (Scheme 2).

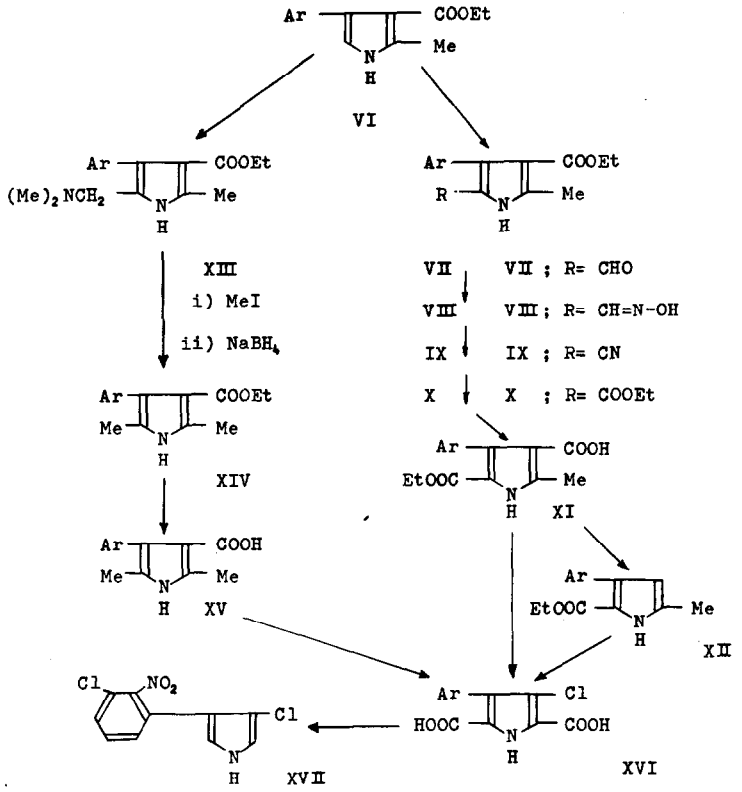
SCHEME 2



In order to protect 5-position of the pyrrole nucleous of (VI) against subsequent chlorination, introduction of an ester group or a methyl group was carried out as below (Scheme 3).

In the case of introduction of the ester group, at first a formyl group was introduced by Vilsmeier reaction to give 5-formyl compound (VII), m.p. 188°, then the product was converted using NH_2OH to 5-aldoxime pyrrole ester (VIII), m.p. 222°. Dehydration of the 5-aldoxime pyrrole ester (VIII) in boiling AC_2O afforded the corresponding nitrile (IX), m.p. 143°, which was converted by alcoholysis to the 3,5-diester (X), m.p. 159°. This diester (X) was partialy hydrolized by treatment with conc. H_2SO_4 to the half-ester (XI), which was decarboxylated accordirg to usual manner to yield ethyl 2-methyl-4-(2′-nitro-3′-chlorophenyl)-pyrrole-5-carboxylate (XII), m.p. 223°.

SCHEME 3



On the other hand, the starting pyrrole (VI) smoothly gave by Mannich reaction 5-dimethylaminomethyl derivative (XIII) (HCl salt, m.p. 225°), then it was converted to methiodide, m.p. 231°, which afforded on $NaBH_4$ reduction ethyl 2,5-dimethyl -4-(2′-nitro-3′-chlorophenyl)-pyrrole-3-carboxylate (XIV), m.p. 192°, in good yield, and hydrolysis of this ethyl ester with conc. H_2SO_4 gave corresponding carboxylic acid (XV).

Then three kinds of intermediates, (XI), (XII) and (XV), being protected at 5-positions as above described, were submitted to chlorination with sulfurylchloride and to subsequent hydrolysis to yield the same product, 3-chloro-4-(2'-nitro-3'-chlorophenyl)-pyrrole-2,5-dicarboxylic acid (XVI), m.p.$>300^{\circ}$ (decomp.).

Decarboxylation of this dicarboxylic acid (XVI) gave almost quantitatively 3-chloro-4-(2'-nitro-3'-chlorophenyl)-pyrrole (XVII), m.p. 125° (from benzene).

No depression was observed in admixture of natural pyrrolnitrin and the synthetic pyrrole (XVII), and spectra of I.R. and U.V. were shown to be identical. Thus it was firmly proved that pyrrolnitrin must be represented by the formula (XVII) established by K. Arima et al.

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