

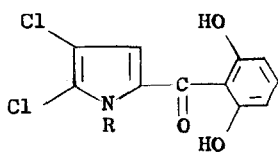
## THE SYNTHESIS OF PYOLUTEORIN

Denis M. Bailey and Robert E. Johnson

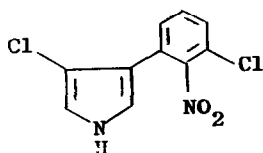
Department of Chemistry, Sterling-Winthrop Research Institute, Rensselaer, N.Y.

(Received in USA 15 June 1970; received in UK for publication 30 July 1970)

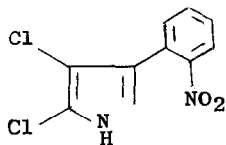
Pyoluteorin (I, R = H), a pigment produced by a strain of Pseudomonas aeruginosa (1), is a member of a group of relatively rare, naturally occurring halogeno-pyrroles which includes pyrrolnitrin (II), (2) isopyrrolnitrin (III), (3) and the bromopyrrol (IV), (4,5).



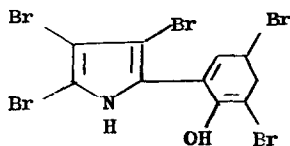
I



II



III

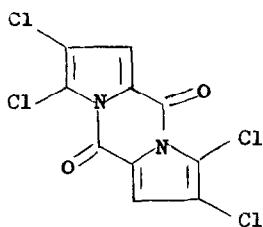


IV

The interesting antibiotic properties of pyoluteorin have been described (6) and the structure (I) has been proposed (7,8) and confirmed by synthesis (9). We now wish to report our own synthesis of this interesting compound.

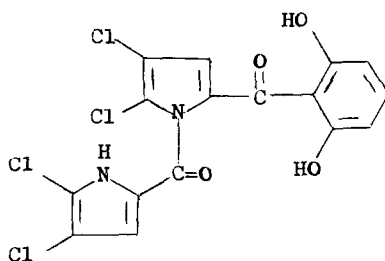
Previous attempts at the synthesis of (I) proceeded to the extent of obtaining (I) R = benzyl (10) but these authors could not remove the protecting group. As a prime target, therefore, we sought a labile N-protecting group for pyrrole which would be readily formed, and readily removed but stable to the organo-metallic reagents which we proposed for the

aroyl moiety. A structure which uniquely uses the same function as reactant and protecting group is (V).



V

Thus, treatment of 4,5-dichloropyrrol-2-carbonyl chloride (10a), obtained from pyrrole (10b), triethylamine in benzene gave an excellent yield of the pyrocoll (V), m.p. 327-331° dec.,  $IR_{\text{mull}}$ , 1718  $\text{cm}^{-1}$  (C = O, amide). Calcd. for  $\text{C}_{10}\text{H}_2\text{Cl}_4\text{N}_2\text{O}_2$ : C, 37.07; H, 0.62; N, 8.65. Found: C, 37.38; H, 0.98; N, 8.78. Addition of (V) to an excess of 1-lithio-2,6-di(tetrahydropyranyloxy) benzene (11) in ether resulted in an exothermic reaction and, after mild acid hydrolysis, the isolation of the acylated pyoluteorin (VI), m.p. 214-215° dec.,  $IR_{\text{mull}}$  1622  $\text{cm}^{-1}$  (C = O, ketone), 1705  $\text{cm}^{-1}$  (C = O, amide). Calcd. for  $\text{C}_{16}\text{H}_8\text{Cl}_4\text{N}_2\text{O}_4$ : C, 44.27; H, 1.85; N, 6.46. Found: C, 44.50; H, 1.90; N, 5.96.



VI

On brief exposure to hot 10% aqueous NaOH, (VI) was smoothly converted to pyoluteorin, (I, R = H), 9% over-all yield from pyrrole, m.p. 171-172° dec., reported (6) 174-175° dec. Calcd. for  $\text{C}_{11}\text{H}_7\text{Cl}_2\text{NO}_3$ : C, 48.55; H, 2.59; Cl, 26.06; N, 5.15. Found: C, 48.84; H, 2.57; Cl, 26.37; N, 5.19. Infra-red (KBr), NMR, and mass spectral comparisons as well as mixed melting point

determinations with authentic materials obtained from Takeda Chemical Industries, Ltd., Osaka, Japan<sup>1</sup> and by fermentation<sup>2</sup> according to the procedure of O'Connor et. al. (12) confirmed the identity of our product with naturally occurring material.

Acknowledgements. 1. We are grateful to Drs. Nawa and Takeda for providing us with this sample. 2. We express our thanks to Mr. Rosi of the fermentation group for cooperating in this project.

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