Synthesis of the 5,11-Dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine Nucleus of Anthramycin and Related Natural Products

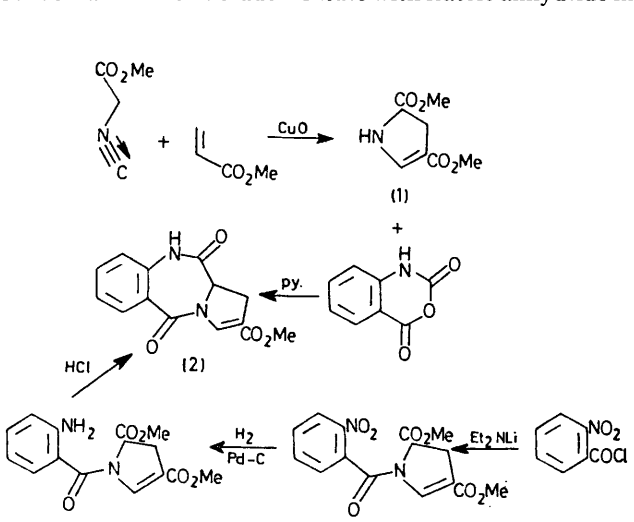
By ROBERT V. STEVENS,* ROBERT M. CORY, and SANDRA ROSSEN
(*Department of Chemistry, Rice University, Houston, Texas* 77001)

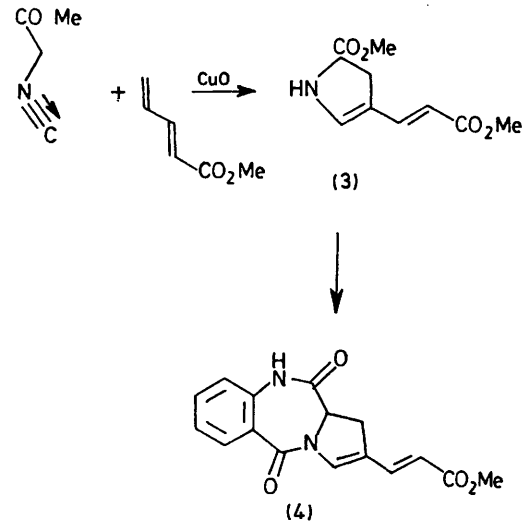
Summary A simple two step synthesis of the anthramycin skeleton is described.

SEVERAL antitumour antibiotics, such as anthramycin[1] and tomaymycin,[2] have been isolated recently which possess the relatively rare 5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine nucleus (**2**; H replaces CO_2Me). In addition to the total synthesis of anthramycin itself,[3] several recent communications[4] have dealt with methods for elaborating the basic nucleus found in these substances. We now report a simple two-step synthesis.

The copper oxide-promoted condensation of a benzene solution of methyl isocyanoacetate and methyl acrylate yielded the unstable pyrroline (**1**) and its Δ^1-tautomer.[5] Condensation of this crude mixture with isatoic anhydride in pyridine yielded the crystalline product (**2**), m.p. 257—258°C (*ca.* 35%). The structure of this product was confirmed by elemental analysis and by acylating the lithium salt of the pyrroline (**1**) with *o*-nitrobenzoyl chloride followed by selective reduction of the nitro-group over a Pd–C catalyst and subsequent acid-catalysed (1N HCl) ring closure.†

The success of the above experiments prompted us to investigate the possibility of incorporating the acrylamide side chain found in anthramycin by a similar sequence. The copper oxide-promoted 1,6-addition of methyl isocyanoacetate and methyl pentadienoate provided a mixture of extremely unstable products containing the desired pyrroline (**3**) which was identified by n.m.r. spectroscopy. Direct treatment of a pyridine solution of this crude mixture with isatoic anhydride and subsequent chromatography of the crude mixture gave crystals of the adduct (**4**),† m.p. 262—264 °C, in low yield.





We thank The Robert A. Welch Foundation and the National Science Foundation for financial support.

(*Received, 28th May* 1975; *Com.* 582.)

† The structures of all new compounds reported herein were confirmed by i.r., ^1H n.m.r., and mass spectral analysis.

[1] W. Leimgruber, V. Stefanovic, F. Schenker, A. Karr, and J. Berger, *J. Amer. Chem. Soc.*, 1965, **87**, 5791; W. Leimgruber, A. D. Batcho and F. Schenker, *ibid.*, p. 5793.
[2] K. Arima, M. Kohsaka, G. Tamura, H. Imanaka, and H. Sakai, *J. Antibiot.*, 1972, **24**, 437; K. Kariyone, H. Yazawa, and M. Kohsaka, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 2289.
[3] W. Leimgruber, A. D. Batcho, and R. C. Czajkowski, *J. Amer. Chem. Soc.*, 1968, **90**, 5641.
[4] M. Artico, G. De Martino, R. Giuliano, S. Massa, and G. C. Porretta, *Chem. Comm.*, 1969, 671; G. De Martino, R. Giuliano, S. Massa, and G. C. Porretta, *Il Farmaco. Ed. Sc.*, 1972, **27**, 971; G. De Martino, M. Scalzo, S. Massa, R. Giuliano, and M. Artico, *ibid.*, p. 980; and references cited therein.
[5] T. Saegusa, Y. Ito, H. Kinoshita, and S. Tomita, *J. Org. Chem.*, 1971, **36**, 3316.