Plant Antitumour Agents: Alkaloids: Synthesis of a Pentacyclic Camptothecin Precursor[1]

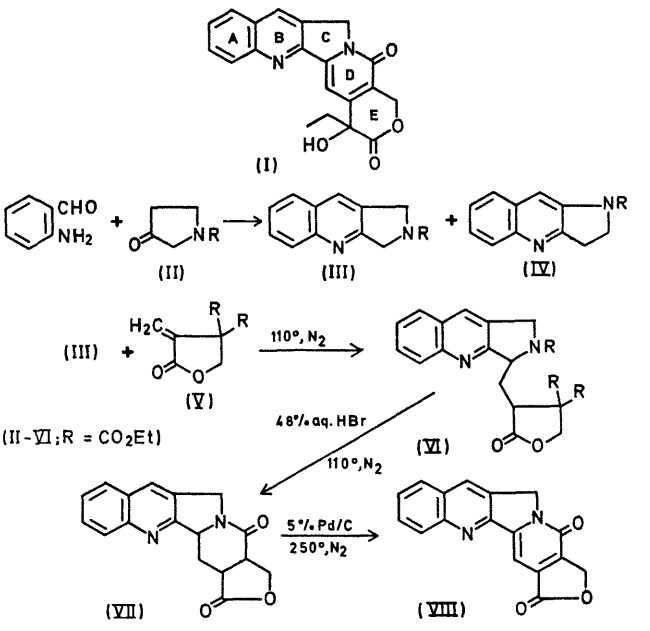
By M. C. WANI,* J. A. KEPLER, J. B. THOMPSON, MONROE E. WALL, and S. G. LEVINE

(*Chemistry and Life Sciences Laboratory, Research Triangle Institute, Research Triangle Park, North Carolina* 27709)

Summary A pentacyclic product (VIII) suitable for conversion into camptothecin (I)[2] has been synthesized.

THE isolation and structure of camptothecin (I), an alkaloid with a novel ring system exhibiting potent antileukaemic and antitumour activities, has been reported from our laboratory.[2] We now describe the preparation of an advanced intermediate for the synthesis of (I).

An acid-catalysed Friedlander condensation of anthranilaldehyde[3] with *N*-ethoxycarbonyl-3-pyrrolidone (II)[4] gave a mixture of 1,3-dihydro-2-ethoxycarbonyl-2*H*-pyrrolo-[3,4-*b*]quinoline (III) and 2,3-dihydro-1-ethoxycarbonyl-1*H*-pyrrolo[3,2-*b*]quinoline (IV).† The Michael condensation of (III) with α-methylene-ββ-diethoxycarbonyl-γ-butyrolactone (V)[5] at 120° without added catalyst gave (VI) as a viscous oil. Although (VI) appeared to be a mixture of two diastereomers, no attempt was made to separate them. Treatment of (VI) with aqueous hydrobromic acid at 110°, followed by neutralization (pH 7·5) with saturated sodium bicarbonate effected hydrolysis, decarboxylation, and cyclization in one experimental step. The mixture of isomeric products [(VII), separable by preparative t.l.c.] was converted into (VIII) by heating at 250° with 5% palladium on carbon. The i.r. and u.v. spectra of (VIII) and (I) had the expected similarities.



(*Received, February* 16*th*, 1970; *Com.* 218.)

† Analytical and spectral data for all new compounds were in agreement with their formulation.

[1] For previous paper in this series see: J. A. Kepler, M. C. Wani, J. N. McNaull, M. E. Wall, and S. G. Levine, *J. Org. Chem.*, 1969, **34**, 3853.
[2] M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, 1966, **88**, 3888.
[3] L. L. Smith and I. Opie, *Org. Synth.*, 1948, **28**, 11.
[4] von M. Viscontini and H. Buhler, *Helv. Chim. Acta*, 1967, **50**, 1289.
[5] V. B. Piskov, *Zhur. obshchei Khim.*, 1960, **30**, 1390; *J. Gen. Chem.* (*U.S.S.R.*), 1960, **30**, 1421.