

A Convenient Route to the Camptothecin Chromophore

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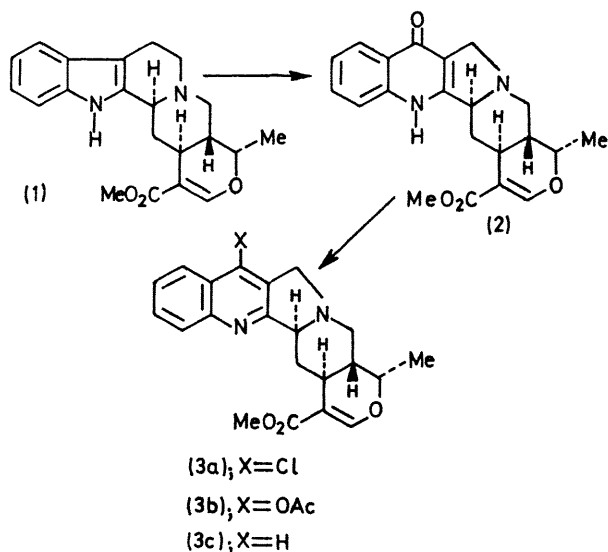
Summary Indoles were converted by a high yield autoxidation process into quinolones, chlorination of which with thionyl chloride, was accompanied, in the case of unsaturated lactams, by dehydrogenation into the camptothecin-chromophore.

THE observation that indoles on treatment with potassium t-butoxide in dimethylformamide are readily autoxidized to quinolones, which can be converted into quinolines¹ (as

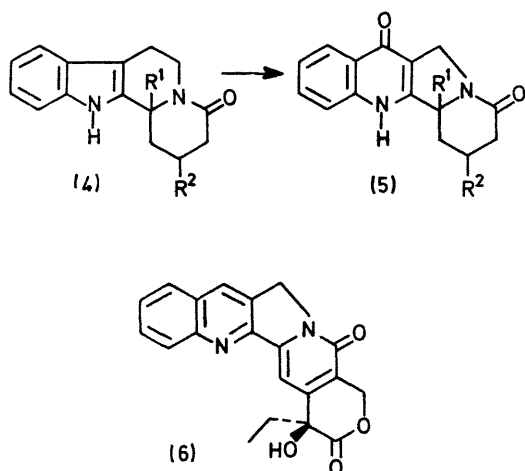
shown for ajmalicine in Scheme 1) has prompted further work on the preparation of the chromophore of camptothecin 6,² a powerful tumor-inhibiting compound that is biogenetically linked to the indole alkaloid group.³

The model lactams (4a)—(4c) were easily converted into the corresponding quinolones (5a)—(5c) and lactam (9) was synthesized *via* (7)⁵ and (8).† Autoxidation of compound (9) gave (10) which on treatment with thionyl chloride in dimethylformamide at room temperature yielded, by

chlorination and dehydrogenation, compound **(11)** (75%): λ_{\max} 256 and 364 nm (lit. value for camptothecin 254 and 365 nm).



SCHEME 1

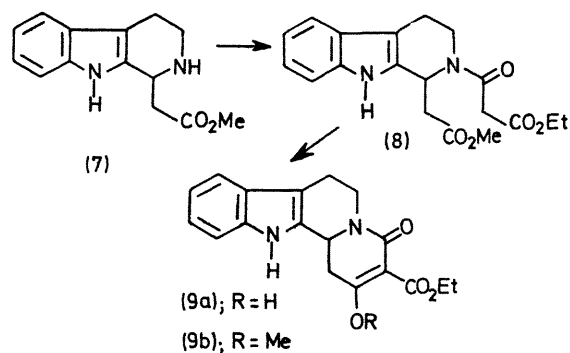


SCHEME 2

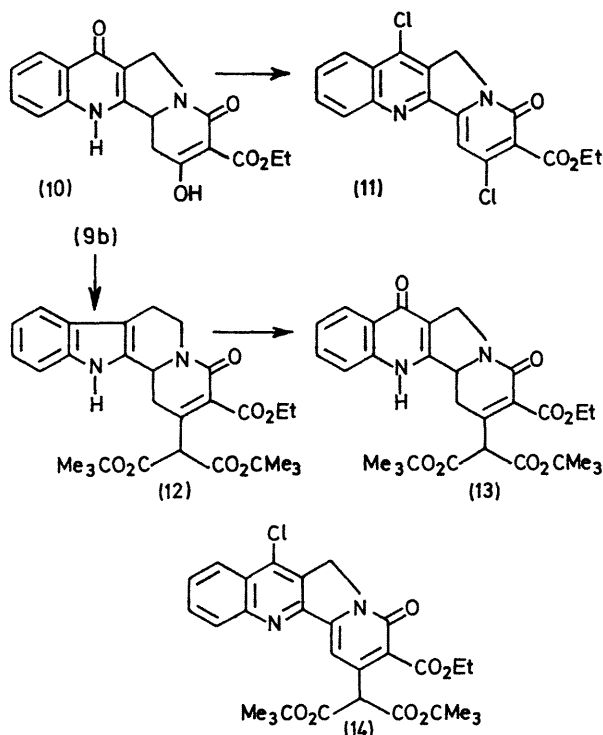
(4a) and (5a); $R^1 = H, R^2 = H$
(4b) and (5b); $R^1 = Me, R^2 = H$
(4c) and (5c); $R^1 = Me, R^2 = CH_2CO_2Me$

In order to use both these reactions for a camptothecin synthesis the enol-ether **(9b)** obtained by treatment of **(9a)** with diazomethane was treated with di-*t*-butyl malonate and

sodium hydride in dioxan to yield **(12)**. This compound was easily autoxidized to **(13)** and finally gave pyridone **(14)** (λ_{\max} 255 and 372 nm) in the chlorination-dehydrogenation sequence described above.



Further work on a biogenetic route to camptothecin is in progress.



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† All compounds were characterised by i.r., u.v., n.m.r., and mass spectra and gave satisfactory C, H, and N analyses.

¹ E. Winterfeldt, *Annalen*, in the press.

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; A. T. McPhail and G. A. Sim, *J. Chem. Soc. (B)*, 1968, 923.

³ E. Wenkert, K. G. Dave, R. G. Lewis, and P. W. Sprague, *J. Amer. Chem. Soc.*, 1967, **89**, 6741.

⁴ E. Winterfeldt, *Chem. Ber.*, 1964, **97**, 2463.

⁵ G. B. Kline, *J. Amer. Chem. Soc.*, 1959, **81**, 2251.