Biomimetic Chemistry of Camptothecin: Involvement of Isovincoside Lactam (Strictosamide)

By C. RICHARD HUTCHINSON*† and GARY J. O'LOUGHLIN
(*School of Pharmacy, University of Connecticut, Storrs, CT* 06268)

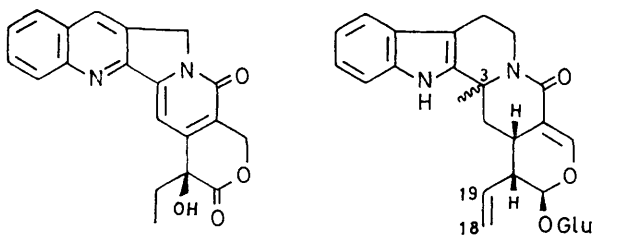
and RICHARD T. BROWN and STUART B. FRASER
(*Department of Chemistry, The University, Manchester* M13 9PL)

Summary The indole $\alpha\beta$-bond of isovincoside lactam (strictosamide) (**2a**) is cleaved much more rapidly by either $NaIO_4$ or oxygen–$KBuO^t$ than the corresponding bond of vincoside lactam (**2b**), which may be significant in the biosynthetic preference of (**2a**) over (**2b**) in the biosynthesis of camptothecin (**1**).

THE biosynthesis of camptothecin (**1**) has been shown to proceed *via* isovincoside lactam (strictosamide) (**2a**)[1], in contrast to the involvement of vincoside (**3b**) as the penultimate precursor of the indole alkaloids of other higher plants, notably those of *Catharanthus roseus* G. Don.[2] Since this observation is the first indication that there are two closely related pathways for indole alkaloid biosynthesis among higher plants, we report results from *in vitro* experiments on the cleavage of the indole $\alpha\beta$-bond of (**2a**) and vincoside lactam (**2b**) that may have significant bearing on *in vivo* bio-organic chemistry. Analogous results of *in vitro* experiments have recently led to an attractive rationalization of why the biosynthesis of Corynanthé-type indole alkaloids proceeds *via* (**3b**) and not (**3a**).[3]

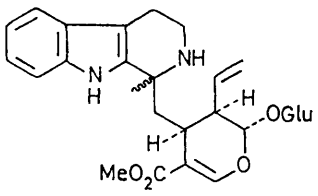
In parallel *in vitro* experiments the 18,19-dihydrotetraacetates of (**2a**) and (**2b**) were allowed to react with excess of $NaIO_4$ in aqueous MeOH to give (**4a**) and (**4b**) respectively which were then separately cyclized by treatment with Et_3N in EtOH to give the quinolones (**5a**), m.p. 209—210°, and (**5b**), m.p. 206—208°; λ_{max} 213, 245, 314, and 326 nm; $\bar{\nu}_{max}$ 1765, 1640, 1610, and 1595 cm^{-1}; *m/e* 682 (M^+). Acetylation afforded the corresponding quinolol pentaacetates, (**6a**), m.p. 171—173°; λ_{max} 207, 232, 291, 304, and 318 nm; $\bar{\nu}_{max}$ 1760, 1670, and 1630 cm^{-1}; *m/e* 724 (M^+) and 681 ($M - CH_3(O)^+$, and (**6b**), m.p. 156–157°.‡ The cleavage of (**2a**) proceeded quite rapidly at room temperature, whereas (**2b**) reacted much more slowly and incompletely. Similarly, (**2a**) and (**2b**) were cleaved by oxygen–$KBuO^t$ in dimethylformamide giving (**5a**) and (**5b**) directly according to Winterfeldt;[4] (**2a**) again reacted much faster than (**2b**) and gave its quinolone in better yield, although in lower overall yield than with the $NaIO_4$ cleavage method.

Although from the available evidence on the mechanism by which metaperiodate,[5] oxygen–$KBuO^t$,[6] singlet oxygen,[7,8] and tryptophan oxygenase[9] oxidatively cleave the indole $\alpha\beta$-bond, the involvement of a β-hydroperoxy-indolenine and/or a dioxetan[6] intermediate in the *in vitro* and *in vivo* cleavage of (**2**) seems probable, its involvement in the present case is being investigated.

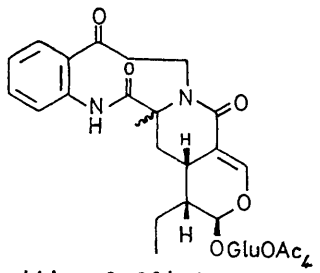


(**1**)

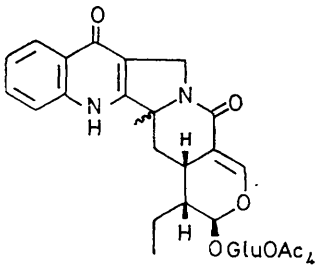
(**2**) a; C-3*S* (α)
b; C-3*R* (β)



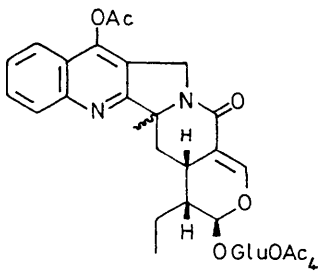
(**3**) a; C-3*S* (α)
b; C-3*R* (β)



(**4**) a; C-3*S* (α)
b; C-3*R* (β)



(**5**) a; C-3*S* (α)
b; C-3*R* (β)



(**6**) a; C-3*S* (α)
b; C-3*R* (β)

We are indebted to the National Institutes of Health for financial support in part.

(*Received, 29th July* 1974; *Com.* 942.)

† *Present address:* School of Pharmacy, University of Wisconsin, Madison, WI 53706.

‡ Satisfactory spectroscopic and analytical data have been obtained for (**5**) and (**6**).

[1] C. R. Hutchinson, A. H. Heckendorf, P. E. Daddona, E. Hagaman, and E. Wenkert, *J. Amer. Chem. Soc.*, 1974, **96**, 5609.
[2] A. R. Battersby, A. R. Burnett, and P. G. Parsons, *J. Chem. Soc.* (*C*), 1969, 1193.
[3] R. T. Brown and C. L. Chapple, *J.C.S. Chem. Comm.*, 1973, 886.
[4] E. Winterfeldt, *Annalen*, 1971, **745**, 23.
[5] L. J. Dolby and R. M. Rodia, *J. Org. Chem.*, 1970, **35**, 1493; A. J. Fatiadi, *Synthesis*, 1974, 229.
[6] F. McCapra, *Pure Appl. Chem.*, 1970, **24**, 611, and references therein; see also ref. 4.
[7] M. Nakagawa, T. Kaneko, K. Yoshikawa, and T. Hino, *J. Amer. Chem. Soc.*, 1974, **96**, 625.
[8] J. I. Teng and L. L. Smith, *J. Amer. Chem. Soc.*, 1973, **95**, 4060, have presented evidence that singlet oxygen is not a likely intermediate in several biological reactions involving molecular oxygen.
[9] O. Hayaishi, S. Rothberg, A. H. Mehler, and Y. Saito, *J. Biol. Chem.*, 1957, **229**, 889; T. Tanaka and W. E. Knox, *ibid.*, 1959, **234**, 1162.