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SYNTHESIS AND BIOLOGICAL ACTIVITY IN THE CAMPTOTHECIN SERIES

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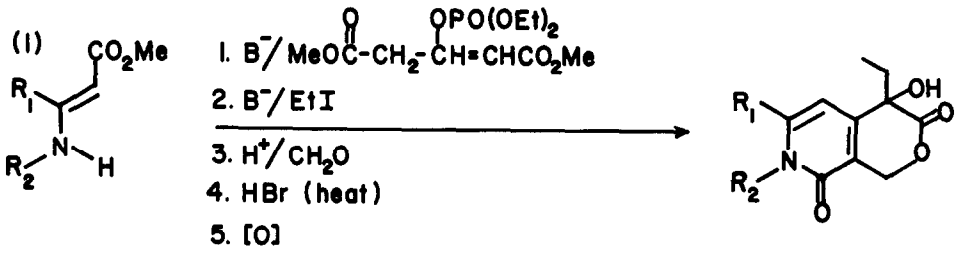
Early reports ascribing promising antitumor properties to the novel pentacyclic alkaloid, camptothecin (I) prompted activity directed toward its total synthesis [1a-g] More recently, discouraging clinical findings,[2] coupled with unusual properties at the cellular level, ascribed to the natural product,[3a-e] provide an impetus for synthesizing and evaluating analog structures which might serve to identify those features of the molecule relevant to biological function In this connection, considerable attention has been directed toward the structurally novel D-E system [4a-c] However, little in the way of concrete evidence has been presented in support of the contention that this region of the molecule is the central repository of the activity of camptothecin

Crucial to our preparative approach, is a departure from the route employed in the total synthesis [1b,5] This modification, which allows for positional control in the elaboration of the E ring, is achieved by executing a formaldehyde incorporation on a 4-carboxymethylpyridone derivative in which the 5-position is substituted by an ester function After lactomethylation, the blocking group is removed by the action of HBr A spectrum of analogs, containing the D-E segment, may be readily prepared according to formulation (1) Below the synthesis and biological evaluation of a simple analog system is reported

Treatment of 1 eq of enamine III (derived from the reaction of methyl acetoacetate and butylamine) with 1 eq of enolphosphate, IV,[6] in the presence of 1 eq of triethylamine in dimethoxyethane (D M E) gives pyridone V[7] in 54% yield Compound V is



ethylated (potassium-tert-butoxide-ethyl iodide-D M E) to afford (84%) pyridone VI [7] The latter is transformed (1 eq of VI, 6 eq paraformaldehyde-dioxane-10% 1·1 H_2SO_4-H_2O; 94°, 24 hr sealed tube) into intermediate lactone ester VII, mp 70-71°, which gives 48% HBr, reflux 17 hr) desoxyanalog VIII[7] (37% from VI), mp, 90-93°. Hydroxylation (1.2 eq potassium-tert-butoxide-tert-butanol-2 eq of 30% aqueous H_2O_2) gives analog II[7], mp 120-121°.

Compounds II and VII show no discernible activity against L-1210 carcinoma at dosages where optically active camptothecin showed marked capabilities in increasing mean survival times It should, however, be noted that L-1210 results for dl-camptothecin, as opposed to the natural product, are not available. Compounds II and VIII are also essentially inactive as nucleic acid inhibitors in, *in vitro* tests using HeLa cells[3b] at concentrations where dl-desoxycamptothecin and dl-camptothecin were active [5] Structural character, beyond the chemically novel D-E region, may be required for biological activity

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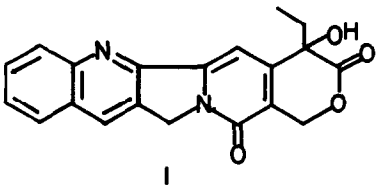
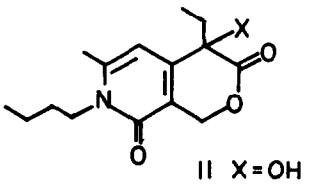
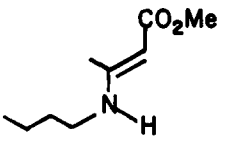


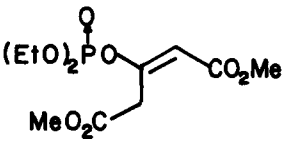
I



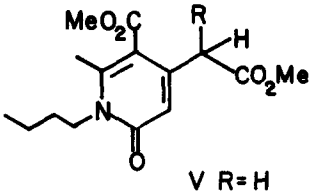
II X=OH
VIII X=H



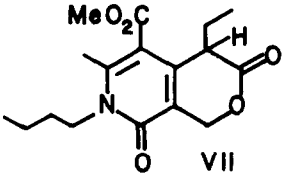
III



IV



V R=H
VI R=Et



VII

References

1. For successful total synthesis see. (a) G Stork and A Schultz, J Amer Chem. Soc , 93, 4074 (1971), (b) R Volkmann, S Danishefsky, J Eggler and D. M Solomon, ibid, 93, 5576 (1971), (c) M C. Wani, H F Campbell, G A. Brine, J A Keppler, M. E Wall and S G Levine, ibid, 94, 3630 (1972), (d) C. Tang and H Rapoport, ibid, 94, 8615 (1972), (e) M. Boch, T. Korth, J M Nelke, D Pike, H Radunz and E Winterfeldt, Chem, Ber., 105, 2126 (1972), (f) T Sugasawa, T. Toyoda and K Sasakura, Tetrahedron Letters. 5109 (1972), A S Kende, T J Bentley, R W. Draper, J K. Jenkins, M Joyeux and I Kubo, Tetrahedron Letters, 1307, (1973), (h) A I Meyers, R. L. Nolen, E W. Collington, T. A Narwid and R C Strickland, J Org Chem In Press

2a C. G Moertel, A. J Schutt, R. J Reitmeir and R. G Hahn, Chermother Rep , 56, 95 (1972), (b) J A. Gottlieb and J K Luce, ibid , 56, 103 (1972)

3a M. S Horwitz and S B Horwitz, Biochem Biophys Research Commun 45, 723 (1971), (b) S B. Horwitz, C K Chang and A P Grollman, Mol Pharmacol, 7, 632 (1971), (c) R S Wu, A Kumar and J R. Warner, Proc Nat Acad Sci , (U S) 68, 3009 (1971), (d) H T Abelson and S Penman, Nature, New Biol. 237, 144 (1972, (e) D. Kessel, B. H Bosmann, K Lohr Biochem Biophys Acta , 269 210 (1972)

4a R L Flurry and J C Howland, Abstracts, 162nd Meeting of the American Chemical Society, Washington, D C , Sept 1971, MEDI 30, (b) M E Wall, H F Campbell, M C Wani and S G Levine, J Amer Chem Soc , 94, 3631 (1972), (c) J J Plattner, R D Glass and H Rapoport, ibid, 94, 8613 (1972)

5 S Danishefsky and R Volkmann, Tetrahedron Letters, Preceeding Communication

6 J Cymmerman - Craig and M J Moyle, J Chem. Soc , 5356 (1963)

7 C, H and N, combustion analyses within 0 3% of theory were obtained for this compound