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# A TOTAL SYNTHESIS OF dl-CAMPTOTHECIN

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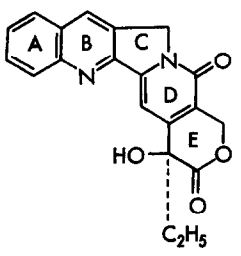
Since the finding of camptothecin I,[1] an alkaloid with a novel ring system exhibiting potent anti-leukemic and antitumor activity, work on many challenging synthetic problems[2a-k] including the successful total syntheses[3a-d] have been published.

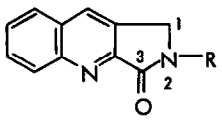
We now describe a total synthesis of dl-camptothecin involving a unique formation of the 4-hydroxy-2-pyridone and the adjacent lactone rings.

Heating of 3-oxo-dihydro-2H-pyrrolo[3,4b]quinoline II[4] in diethyl acetonedicarboxylate at 160-165° gave the imido ester III[5] in 95% yield. The 3-oxo group of the imido ester III being sufficiently activated by the adjacent electron-withdrawing quinoline nucleus, it underwent smooth intramolecular cyclization to afford the hydroxy-pyridone ester IV in 87% yield on being treated with refluxing acetonitrile containing piperidine: (m/e 322; ir 1730 and 1630 $cm^{-1}$; uv 250 mμ (ε 57,500), 355 (18,500) and 362 (19,000)). Hydrolysis of IV concomitant with decarboxylation was effected by heating with conc. hydrochloric acid in a glass tube at 150°, giving the 4-hydroxy-2-pyridone V, which was methylated with dimethylsulfate and potassium carbonate in refluxing acetone to furnish the 4-methoxy-2-pyridone VI in 85% yield from IV. Reaction of VI with phosphorusoxychloride in dimethylformamide (DMF) (Vilsmeier reaction) gave the methoxy-aldehyde VII in 72% yield, the structure of VII containing the A, B, C, and D rings of I and the appropriate substituents to annelate the E ring.

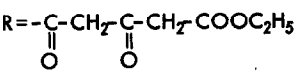
On the other hand we prepared the D and E rings of I starting from 4-methoxy-1-methyl-2-(1H)-pyridone[6] VIII as follows. Vilsmeier reaction of VIII gave the pyridone-aldehyde IX in 73% yield, whose NMR-spectrum showed that the aldehyde group was introduced at the expected position (nmr (δ): 6.09 (1H, d, J = 7.5 Hz), 7.63 (1H, d, J = 7.5 Hz), and 10.39 (1H, s)). Treatment of IX with di-tert-butyl malonate and sodium hydride in refluxing dimethoxyethane gave the pyridone-malonester X (ir 1730 $cm^{-1}$, nmr no

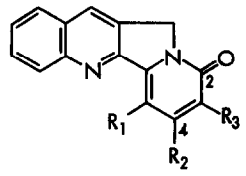


I



II, R = H

III, R = 

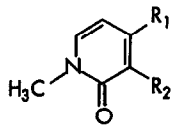


IV, $R_1$ = $COOC_2H_5$, $R_2$ = OH, $R_3$ = H

V, $R_1$ = $R_3$ = H, $R_2$ = OH

VI, $R_1$ = $R_3$ = H, $R_2$ = $OCH_3$

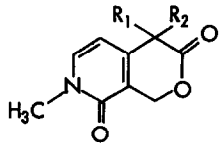
VII, $R_1$ = H, $R_2$ = $OCH_3$, $R_3$ = CHO



VIII, $R_1$ = $OCH_3$, $R_2$ = H

IX, $R_1$ = $OCH_3$, $R_2$ = CHO

X, $R_1$ = $CH(COOtBu)_2$, $R_2$ = CHO

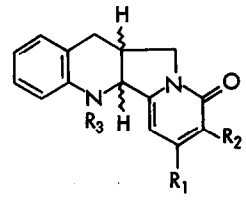


XI, $R_1$ = $R_2$ = H

XII, $R_1$ = $C_2H_5$, $R_2$ = H

XIII, $R_1$ = $R_2$ = $C_2H_5$

XIV, $R_1$ = $C_2H_5$, $R_2$ = OH



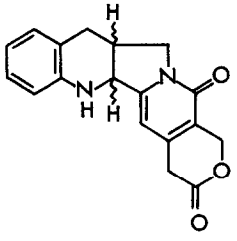
XV, $R_1$ = $OCH_3$, $R_2$ = $R_3$ = H

XVI, $R_1$ = $OCH_3$, $R_2$ = H, $R_3$ = CHO

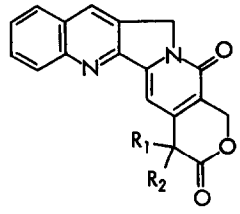
XVII, $R_1$ = $OCH_3$, $R_2$ = -CHO, $R_3$ = -CHO

XVIII, $R_1$ = $CH(COOtBu)_2$, $R_2$ = CHO, $R_3$ = CHO

XIX, $R_1$ = $CH(COOtBu)_2$, $R_2$ = $CH_2OH$, $R_3$ = CHO



XX



XXI, $R_1$ = $R_2$ = H

XXII, $R_1$ = $C_2H_5$, $R_2$ = H

$OCH_3$-signal). Sodium borohydride reduction of X and subsequent refluxing in trifluoroacetic acid smoothly afforded the lactone XI in 52% yield from X. The ethylation of XI with sodium hydride and ethyl bromide in DMF gave the monoethyl lactone XII in 43% yield, besides the diethyl lactone XIII and the starting material XI, both in 17% yield. Bubbling of oxygen through a solution of XII in ethanol in the presence of copper acetate and triethyl amine[7] furnished compound XIV in 46% yield (mp 180-181°, m/e 223), the structure of XIV containing the D and E ring moiety of camptothecin I.

This E ring annelation method was now applied to the methoxy-aldehyde VII but the reaction unfortunately failed because of the lability of VII under basic conditions. VI was therefore reduced with Adams-catalyst in methanol-dioxane containing hydrochloric acid to give the amorphous N-tetrahydroquinoline-pyridone XV, in order to obtain a better analogy to the model compound VIII. Formylation of XV in hot formic acid gave the corresponding N-formate XVI (ir 1630 $cm^{-1}$, uv 236 mμ (ε 11,400), 282 (6,880)), which was subjected to Vilsmeier-reaction to give the N-formyl-methoxy-aldehyde XVII in 63% yield from XVI. The thus obtained XVII gave the expected pyridone-malonate XVIII (ir 1750-1770 $cm^{-1}$, nmr no $OCH_3$-signal) in 60% crude yield, on being treated with di-tert-butyl malonate and sodium hydride in refluxing dioxane. The crude XVIII was reduced with sodium borohydride to give XIX, which was directly treated with conc. hydrochloric acid at room temperature to afford XX by simultaneous lactone formation and deformylation. Dehydrogenation of XX with dichlorodicyanoquinone in refluxing dioxane gave the lactone XXI (mp (dp) >275°, m/e 304, ir 1750 and 1640 $cm^{-1}$, uv 254 mμ (ε 31,400), 288 (6,030) and 360-370 (20,500-20,100)) in 32% yield from XVIII. Ethylation of XXI with sodium hydride and ethyl iodide in DMF gave dl-desoxycamptothecin XXII (mp (dp) 258-264°).[3b] XXII was converted by passing oxygen in the presence of triethyl amine and copper acetate in DMF-methanol to afford dl-camptothecin (mp (dp) 276-278°) after thin-layer chromatographic purification (silica-gel, chloroform containing 5% methanol) in 8% yield from XXI. The tlc properties, low-resolution mass spectra and ir spectra in chloroform[8] of synthetic dl-camptothecin were identical with those of the natural product.[9]

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8. The ir spectra were taken in 1 mm-cell.


9. The authors are very grateful to Dr. Monroe E. Wall of the Research Triangle, N. C. for kindly providing us with a sample of authentic natural comptothecin.