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A TOTAL SYNTHESIS OF (±)-CAMPTOTHECIN

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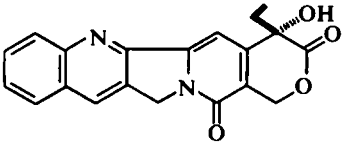
Abstract—The pentacyclic alkaloid (±)-camptothecin (**1**) has been synthesized from the dihydropyridone derivative **13**, through the intermediacy of the pyrone **15** and the ketolactone **19**.

In 1966, Wall *et al.* reported the isolation of the new and unusual alkaloid (+)-camptothecin (**1**) from *Camptotheca acuminata* Decaisne (Nyssaceae), a deciduous tree which grows almost exclusively in the interior of mainland China.[1] The structure was elucidated by a combination of spectral methods and X-ray analysis of the iodoacetate salt.[1,2] The fact that camptothecin was thought to have antineoplastic activity,[3] coupled with the difficulty in obtaining free supplies of the alkaloid, was enough to stimulate efforts at total synthesis in a number of laboratories.[4-8]



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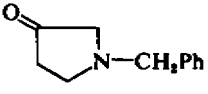
From the outset, it was clear that it was preferable to construct the quinoline moiety in the terminal stages of the synthesis, since camptothecin (**1**) as well as the synthetic analogs **2**, **3**, and **4** exhibit only minimal solubility in the usual organic solvents.[9,10] Furthermore, in some earlier work, it had been determined that Friedländer condensation of anthranilaldehyde with the amino ketone **5** yields mainly the quinoline derivative **6**.[9]

A total synthesis of camptothecin, therefore, revolved around the preparation of the key tricyclic lactone **18**. Once available, this intermediate could be C-alkylated and oxidized to the precursor **20** which could be hydrolyzed to the ketone **21** prior to Friedländer condensation with anthranilaldehyde to afford camptothecin. Alternatively, the intermediate **19** could be condensed with anthranilaldehyde, and then C-alkylated and oxidized to afford the racemic alkaloid.



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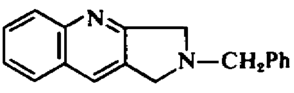

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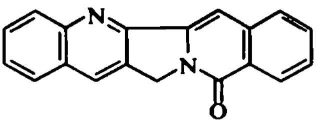
Prolonged treatment of the ethylene ketal of the known urethan **7**[11,12] with 1 M ethanolic potassium hydroxide at room temperature provided the carboxylic acid **8** in 91% yield. The acid chloride of **8** was converted to the dione **9** in 79% yield by reaction with the sodium salt of diethyl malonate and acid hydrolysis of the resulting diester. The diethylene ketal of **9** was then refluxed for two days in dilute ethanolic potassium hydroxide in a nitrogen atmosphere, because of the extreme sensitivity of the hydrolysis to traces of oxygen. The resulting amine **10** was formed in 89% yield. The hydrochloride salt of **10** could be efficiently acylated in 91% yield using carbethoxyacetyl chloride in basic solution to afford the diketal ester **11**. The critical selective hydrolysis of **11** to the mono-



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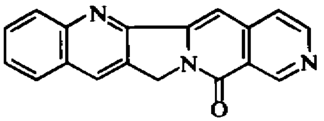

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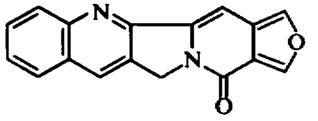

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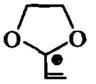
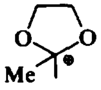
ketone **12** was achieved in 75% yield using 50% aqueous acetic acid at 60° for 18 hr. Under these conditions, only the side chain ketal was hydrolyzed as indicated by IR CO bands in the product at 1735 (ester C=O), 1720 (acyclic ketone C=O), and 1650 cm^{-1} (amide C=O); while a ring ketone band at 1760 cm^{-1} was absent. Mass spectral data also supported this conclusion; a ring ketal peak at *m/e* 99 was present, but the peak for the side chain ketal fragment at *m/e* 87 was lacking.

Treatment of the monoketone **12** with sodium ethoxide at 0° furnished the dihydropyridone **13** in 83% yield, in what amounts to a new synthesis of dihydropyridones. Subsequent treatment of **13** with excess DDQ produced a red-brown oil which was passed through a short alumina column to provide the pyridone **14** in 40% yield.



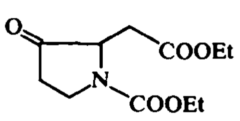
m/e 99
(base)



m/e 87

Attention was now turned to the construction of the δ-lactone ring of the key tricyclic intermediate **18**. Base catalyzed condensation of the pyridone **14** with diethyl oxalate followed by treatment of the crude product with ethanolic hydrogen chloride led to the pale yellow vinyl lactone **15** in 65% yield, by the mechanism indicated in Scheme 1.

It was now necessary to convert the vinyl lactone **15** to the δ-lactone **18**. An important observation at this stage was that the vinyl lactone **15** readily dissolved in aqueous bicarbonate, indica-



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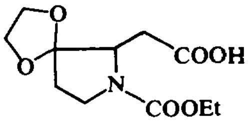

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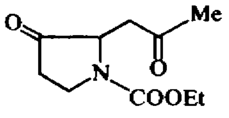

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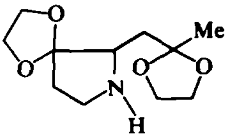

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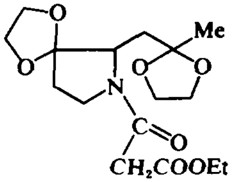

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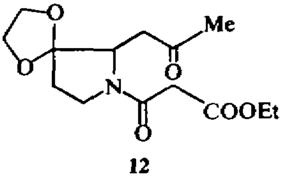

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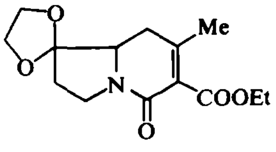

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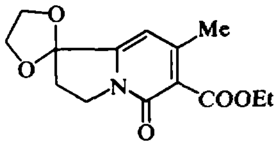

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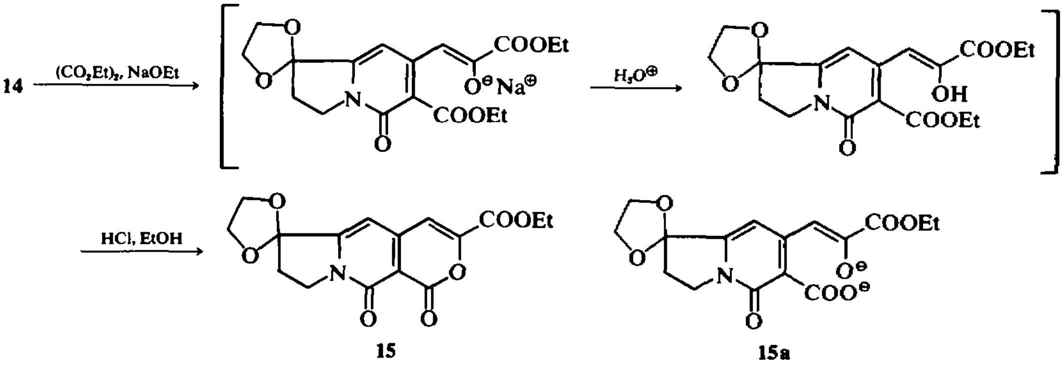
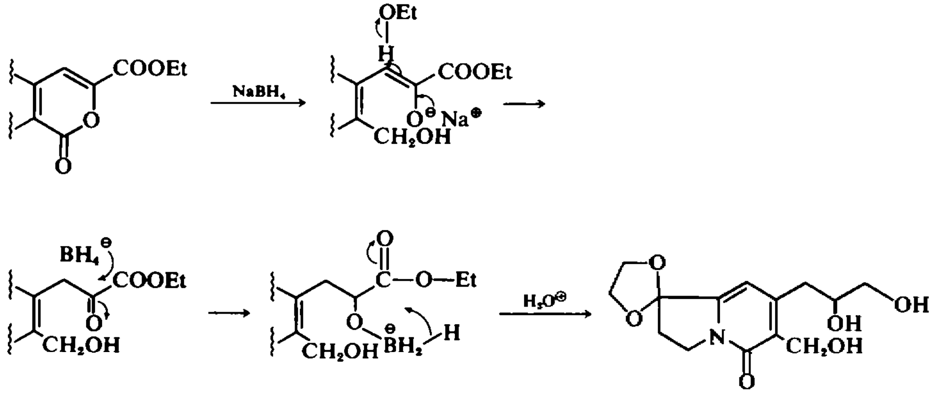


SCHEME 1

ting rapid hydrolysis to the enolate dianion **15a**. The marked susceptibility of the pyrone carbonyl to nucleophilic attack suggested that **15** should undergo facile reduction with a mild nucleophilic reducing agent; and indeed treatment of an ethanolic solution of the vinyl lactone with sodium borohydride resulted in the immediate appearance of a bright yellow color indicating opening of the lactone to an enolate ion by hydride attack at the pyrone carbonyl. The yellow color then slowly faded pointing to the disappearance of the enolate species and formation of the triol **16** which was not isolated (Scheme 2). Rather, cleavage of the water-soluble product with periodic acid gave rise to the crystalline hemiacetal **17** in 77% yield from the vinyl lactone **15**. Oxidation to the desired δ-lactone **18** was achieved using platinum and oxygen.

At this stage in the synthesis, a report appeared in the literature describing an independent preparation of the pentacyclic precursor **22** and its conversion to (±)-camptothecin.[6] It was, therefore, decided to convert the δ-lactone **18** to the precursor **22**. This conversion was readily achieved through hydrolysis of the ketal function of **18** using oxalic acid in hot aqueous ethanol, and condensation of the resulting keto lactone **19** with anthranilaldehyde; thus affording an alternate synthesis of (±)-camptothecin.

It is relevant to point out that the efficacy of camptothecin as an anti-cancer drug has been recently seriously questioned. Camptothecin was



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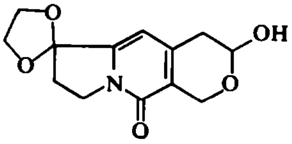
SCHEME 2



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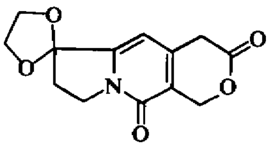

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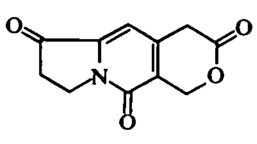

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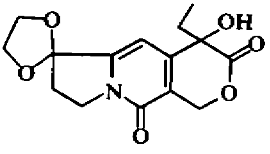

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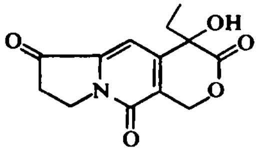

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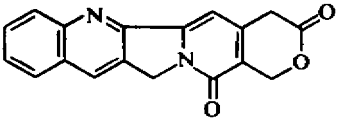

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used in the treatment of sixty-one patients at the Mayo Clinic in Rochester, Minnesota, suffering from advanced gastrointestinal adenocarcinoma. After two months, only two of the patients (3%) showed partial objective responses.[13]

EXPERIMENTAL

M.ps are uncorrected. NMR spectra are at 60 MHz with TMS as internal standard, and $CDCl_3$ as solvent. Mass spectra were recorded on an A.E.I. MS-902 spectrometer at 70 eV. TLC was on Merck Silica Gel plates F-254. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis.

1-Carbethoxy-2-carbethoxymethyl-3-oxopyrrolidine (**7**). This cyclic ketone was prepared from β-alanine and diethyl fumarate.[11,12]

Ethylene ketal of **7**. Prepared from **7** using ethylene glycol, dry benzene and a little *p*-toluenesulfonic acid in a Dean-Stark water separator. A clear viscous oil, 80% yield, b.p. 127–135° (0·2 mm). (Found: C, 54·06; H, 7·63. Calcd. for $C_{13}H_{21}NO_6$: C, 54·33; H, 7·38%).

1-Carbethoxy-2-carboxymethyl-3-oxopyrrolidine ethylene ketal (**8**). The ethylene ketal of **7** (32·9 g, 0·115 mol) was dissolved in 75 ml deoxygenated EtOH and added rapidly, under a stream of N_2 to a stirred soln of KOH (19·2 g) in 230 ml deoxygenated 67% aq EtOH. The orange-yellow soln was allowed to stand under a N_2 atm for 18 hr and then brought to pH 8 and concentrated *in vacuo*. The mixture was diluted with water, acidified at 0°, and saturated with NaCl. Extraction with EtOAc followed by drying and evaporation produced an orange-brown oil. The crude acid slowly crystallized to give 27 g (91%) of a tan solid, m.p. 64–75° which was used in the next step. Recrystallization from benzene-light petroleum gave white crystals, m.p. 78–80°. (Found: C, 50·97; H, 6·61. Calcd. for $C_{11}H_{17}NO_6$: C, 50·96; H, 6·61%).

Acid chloride of **8**. Oxalyl chloride (18·5 g, 0·145 mol) was added rapidly to a soln of the above acid (25·0 g, 0·0965 mol) in 150 ml dry benzene, and the mixture provided with a carborundum chip to promote the emission of gases. After 3 hr the solvent was evaporated *in vacuo* at room temp. A second portion of benzene was added, and again evaporated. The residue was a viscous brown colored oil which was used directly in the next step. $\nu_{max}^{CHCl_3}$ 1685 and 1795 cm^{-1}.

1-Carbethoxy-2-β-oxoproply-3-oxopyrrolidine (**9**). NaOEt prepared from 9·5 g of Na (0·412 mol) and 400 ml dry EtOH was added slowly to a soln of malonic ester (68 g, 0·425 mol) in 100 ml EtOH. The mixture was concentrated and several portions of dry ether added and evaporated. The white Na-salt was then dried and crushed to a fine powder.

The above Na-salt was suspended in 800 ml dry ether and the crude acid chloride (26·7 g, 0·0965 mol) in 150 ml dry ether was added dropwise with stirring over a 30 min period. After refluxing for 2 hr, ice and water were added and the resultant two phase system acidified with 10% HCl. The two layers were separated and the aqueous layer extracted with a second portion of ether. The combined ether extracts were evaporated to provide a mixture of diethyl malonate and the crude diethyl malonate adduct.

The above orange-brown liquid was refluxed for 12 hr in a mixture of 350 ml HOAc and 350 ml 3% HCl. The mixture was evaporated and water added and again evaporated. More water was then added and the aqueous soln basified with solid Na_2CO_3. Extraction of the aq soln with ether followed by drying and evaporation gave a dark red-brown liquid. Vacuum distillation afforded 16·2 g (79%) of a viscous light yellow liquid, b.p 95° (0·03 mm); $\nu_{max}^{CHCl_3}$ 1690, 1715 and 1760 cm^{-1}. (Found: C, 55·92; H, 7·46. Calcd. for $C_{10}H_{15}NO_4$: C, 56·32; H, 7·10%).

Diethylene ketal of **9**. A mixture of diketone **9** (16·2 g, 0·076 mol) and *p*-toluenesulfonic acid monohydrate (0·95 g, 0·005 mol) was dissolved in 500 ml dry benzene containing 22 ml ethylene glycol. The flask was fitted with a Dean–Stark water separator and the mixture stirred under reflux overnight. After cooling, the mixture was shaken with sat $NaHCO_3$aq and the benzene soln dried and evaporated to furnish a nearly colorless liquid. Vacuum distillation of the crude diketal produced 20·6 g (90%) of a clear, colorless liquid, b.p 122° (0·03 mm); $\nu_{max}^{CHCl_3}$ 1680 cm^{-1}. High resolution mass measurement: M^+ Calcd. for $C_{14}H_{23}NO_6$: *m/e* 301·1524. Found: *m/e* 301·1528.

2-β-Oxopropyl-3-oxopyrrolidine diethylene ketal hydrochloride (**10**. HCl). A soln of the diethylene ketal of the urethan **9** (20·6 g, 0·0685 mol) in 60 ml EtOH was added rapidly under a stream of deoxygenated N_2 to a soln of KOH (56 g) in 195 ml EtOH and 30 ml water. The resultant yellow soln was refluxed under a N_2 for 43 hr. The dark brown soln was concentrated *in vacuo*, diluted with water, and extracted with ether. The aqueous soln was saturated with NaCl and extracted with ether. Combination of the ether extracts, followed by drying and evaporation gave a dark brown liquid from which vacuum distillation provided 14·0 g (89%) of the light yellow amine, b.p 97–102° (0·05 mm). High resolution mass measurement: M^+ Calcd. for $C_{11}H_{19}NO_4$: *m/e* 229·1314. Found: *m/e* 229·1310.

The amine was dissolved in 250 ml dry ether and HCl gas bubbled in slowly at intervals until no more salt precipitated from soln. The crude hydrochloride salt was filtered and dried *in vacuo* to yield 15·6 g (83% based on urethan) of white crystals, m.p 139–141°, and was used directly in the next step. The analytical sample was prepared by recrystallization from EtOH-ether. (Found: C, 49·61; H, 7·48. Calcd. for $C_{11}H_{20}ClNO_4$: C, 49·71; H, 7·60%).

1-Ethoxycarbonylacetyl-2-β-oxopropyl-3-oxopyrrolidine diethylene ketal (**11**). A mixture of the above amine hydrochloride (12·9 g, 0·0487 mol) in 175 ml chloroform and K_2CO_3 (28·5 g, 0·21 mol) in 175 ml water was chilled in an ice bath. Carbethoxyacetyl chloride[14] (22·0 g, 0·146 mol) in 50 ml chloroform was added dropwise with stirring over a period of 20 min. The mixture was stirred an additional 30 min and the two layers separated. The chloroform soln was washed with cold 1% HCl and then with Na_2CO_3 soln. After drying, the chloroform soln was treated with Norit filtered and evaporated to furnish 15·2 g (91%) of a light green viscous oil which was essentially pure and was used in the next step without purification; $\nu_{max}^{CHCl_3}$ 1645 and 1735 cm^{-1}. High resolution mass measurement: M^+ Calcd. for $C_{16}H_{25}NO_7$: *m/e* 343·1630. Found: *m/e* 343·1633.

1-Ethoxycarbonylacetyl-2-β-oxopropyl-3-oxopyrrolidine monoethylene ketal (**12**). Diketal **11** (6·02 g, 0·0175 mol) was dissolved in 270 ml of 50% aqueous AcOH and heated at 60° for 18 hr. Evaporation of the solvent provided a light yellow liquid which was diluted with water and neutralized with solid Na_2CO_3. The mixture was extracted with chloroform, dried, and evaporated to give a yellow oil which crystallized upon trituration with ether. Recrystallization from benzene-light petroleum produced 4·0 g (75%) of the monoketone as white needles, m.p. 81–82°; $\nu_{max}^{CHCl_3}$ 1650, 1720 and 1735 cm^{-1}. Mass spectrum *m/e* 299 (9) (M$^+$), 254 (8), 212 (8), 184 (6), 140 (7), 115 (11), 100 (22), 99 (100), 56 (36) and 55 (26). (Found: C, 56·10; H, 7·05. Calcd. for $C_{14}H_{21}NO_6$: C, 56·17; H, 7·08%).

2′,3′,8′,9′-*Tetrahydro*-6′-*carbethoxy*-7′-*methyl*-5′-*oxo*-*spiro*-[1,3-*dioxolane*-2,1′(5′H)-*indolizine*] (**13**). A soln of ethanolic NaOEt, prepared from Na metal (0·73 g, 0·0317 mol) in 50 ml abs EtOH, was added dropwise under a stream of N_2 to an ice cold soln of **12** (7·91 g, 0·0264 mol) in 100 ml abs EtOH. Stirring was continued for an additional 15 min at 0° and the mixture then diluted with 400 ml water and neutralized with 10% HCl. The aqueous soln was extracted with chloroform and the extracts dried and evaporated to afford a light yellow oil which readily crystallized upon trituration with ether. Recrystallization from benzene-light petroleum furnished 6·2 g (83%) of white crystals, m.p. 89–90°; $\nu_{max}^{CHCl_3}$ 1625, 1660 and 1725; λ_{max}^{EtOH} 260 nm ($\log \epsilon$ 3·08); NMR δ 2·06 (3H, s, C=C—C$\underline{H}_3$). (Found: C, 59·62; H, 6·92. Calcd. for $C_{14}H_{19}NO_5$: C, 59·76; H, 6·82%).

2′,3′-*Dihydro*-6′-*carbethoxy*-7′-*methyl*-5′-*oxo*-*spiro*-[1,3-*dioxolane*-2,1′(5′H)-*indolizine*] (**14**). A soln of the unsaturated lactam ester **13** (3·1 g, 0·011 mol) and DDQ (4·0 g, 0·0173 mol) in 250 ml dry benzene was refluxed with stirring for 18 hr under a N_2. After cooling, the solid hydroquinone was filtered and washed thoroughly with benzene. Evaporation of the combined benzene soln furnished a red-brown oil which was passed rapidly through a short column of base washed Fisher Alumina using chloroform as an eluent. Evaporation of the chloroform gave rise to 1·27 g (41%) of a nearly colorless solid which was recrystallized from benzene–hexane to afford white crystals, m.p. 110–112°; $\nu_{max}^{CHCl_3}$ 1605, 1660 and 1725; λ_{max}^{EtOH} 232 (sh) and 310 nm ($\log \epsilon$ 3·47 and 3·73); NMR δ 2·28 (3H, s, C=C—C$\underline{H}_3$), δ 6·15 (1H, s, pyridone H). (Found: C, 60·35; H, 6·09. Calcd. for $C_{14}H_{17}NO_5$: C, 60·20; H, 6·15%).

3′-*Carbethoxy*-7′-8′-*dihydro*-1′,10′-*dioxo*-*spiro*[1,3-*dioxolane*-2,6′(10′H)-[1H]*pyrano*[3,4-f]*indolizine*] (**15**). A mixture of the above pyridone (0·48 g, 1·72 mmol) and 2 ml diethyl oxalate was dissolved in 45 ml dry benzene. A soln of ethanolic NaOEt, prepared from Na metal (0·19 g, 8·6 mmol) in 8·5 ml EtOH, was then added rapidly and the soln stirred under N_2 for 19 hr. The resultant orange-yellow suspension was shaken with water and the combined aqueous extracts washed with ether. Acidification with 10% aq HCl, followed by extraction with chloroform furnished an orange soln which was dried and evaporated. The crude oil was dissolved in EtOH and treated with 12 drops of ethanolic HCl. After stirring for 3 hr, the orange color had disappeared and a considerable amount of yellow solid had precipitated out of soln. Evaporation produced the crude vinyl lactone which was recrystallized from MeOH to afford 372 mg (65%) of pale yellow needles, m.p. 218–220°; $\nu_{max}^{CHCl_3}$ 1610, 1640, 1665, 1730 and 1760 cm^{-1}; λ_{max}^{EtOH} 240 (sh), 248, 262, 298 (sh), 313, 325 (sh) and 364 nm ($\log \epsilon$ 4·03, 4·08, 4·06, 3·85, 3·99, 3·96 and 3·88); NMR δ 6·32 (1H, s, pyridone $\underline{H}$), δ 7·18 (1H, s, pyrone $\underline{H}$). (Found: C, 56·91; H, 4·65. Calcd. for $C_{16}H_{15}NO_7 \cdot 1/2\, CH_3OH$: C, 56·73; H, 4·91%).

3′,4′,7′,8′-*Tetrahydro*-3′-*hydroxy*-10′-*oxo*-*spiro*[1,3-*dioxolane*-2,6′(10′H)-[1-H]*pyrano*[3,4-f]*indolizine* (**17**). Vinyl lactone **15** (447 mg, 1·32 mmol) was stirred with an equal weight of $NaBH_4$ in 65 ml EtOH for 18 hr. Aqueous AcOH was added dropwise and the mixture evaporated to dryness. The gummy solid was dissolved in 25 ml water, neutralized with dil H_2SO_4 and cooled to 0°. Periodic acid (920 mg, 3·96 mmol) was dissolved in the aqueous soln and enough dil H_2SO_4 added to adjust the pH to approximately 3. After standing in the refrigerator for 4 hr, the cold mixture was treated with solid $NaHSO_3$ until the dark brown color disappeared and the soln became yellow. The aqueous soln was extracted with chloroform and the extracts dried and evaporated to give 275 mg (77%) of the crude solid hemiacetal. Recrystallization from acetone produced the pure sample, m.p. 183–185°; $\nu_{max}^{CHCl_3}$ 1600, 1665, 3370 and 3590 cm^{-1}; λ_{max}^{EtOH} 238 and 298 nm ($\log \epsilon$ 3·59 and 3·76); NMR DMSO-d_6 δ 4·53 (2H, s, CH_2O), δ 5·20 (1H, d, J = 4·5 Hz, methinyl $\underline{H}$), δ 6·27 (1H, s, pyridone $\underline{H}$). (Found: C, 58·84; H, 6·11. Calcd. for $C_{13}H_{15}NO_5$: C, 58·85; H, 5·71%).

7′,8′-*Dihydro*-3′,10′-*dioxo*-*spiro*(1,3-*dioxolane*-2,6′-(10′H)-(1H,3H,4H)*pyrano*-(3,4-f)*indolizine*) (**18**). A suspension of 10 mg of PtO_2 in 5 ml freshly distilled EtOAc was stirred in an atmosphere of H_2 until reduction to Pt was complete.[15] The H_2 in the system was replaced with air by careful and repeated evacuation. O_2 was admitted and stirring continued until no further O_2 was absorbed. A soln of 11 mg of hemiacetal **17** in 5 ml freshly distilled EtOAc was then added, and the mixture was stirred for 64 hr at room temp. The mixture was filtered and the solvent evaporated *in vacuo* yielding 10 mg of a pale yellow oil which gradually solidified. The compound was crystallized from MeOH, m.p. 174–6°; $\nu_{max}^{CHCl_3}$ 1750 and 1670 cm^{-1}; λ_{max}^{EtOH} 235 and 305 nm. High resolution mass measurement: M$^+$ Calcd. for $C_{13}H_{13}NO_5$: *m/e* 263·0793. Found: *m/e* 263·0797.

Monoketone **19** *derived from ketal lactone* **18**. (**19**). A mixture consisting of 9 mg of lactone **18**, 10 mg oxalic acid, 4 ml EtOH and 8 ml water was heated at 90–5° for 16 hr. The mixture was concentrated and extracted with chloroform. After drying, the solvent was evaporated leaving 4 mg of an oil which gradually solidified. The compound showed a strong blue fluorescence under UV light, and was homogeneous by TLC. High resolution mass measurement: M$^+$ Calcd. for $C_{11}H_9NO_4$: *m/e* 219·1975. Found: *m/e* 219·2003.

20,20-*Deoxydeethylcamptothecin*[16] (**22**). A mixture of 1 mg ketolactone **19**, 0·8 mg anthranilaldehyde, 0·2 mg NaOH and 0·4 ml EtOH was allowed to stand for 16 hr at room temp. The separated pale yellow solid (1 mg) was identical with an authentic sample provided by Professor Winterfeldt,[6] m.p. 250° (dec). Both materials were essentially insoluble in the usual organic solvents.

TLC of either sample, using benzene-MeOH (3 : 1), gave a single spot, R_f 0·70, showing an intense blue fluorescence under long wave length UV light.

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REFERENCES

[1] M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail and G. A. Sim, *J. Am. Chem. Soc.* **88**, 3888 (1966). A new source of camptothecin is *Mappia*

foetida Miers, see T. R. Govindachari and N. Viswanathan, *Indian J. Chem.* **10**, 453 (1972)

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

[3] J. A. Gottlieb, A. M. Guarino, J. B. Call, V. T. Oliverio and J. B. Block, *Cancer Chemotherapy Rept.* Part I, **54**, 461 (1970)

[4] G. Stork and A. G. Schultz, *J. Am. Chem. Soc.* **93**, 4074 (1971)

[5] R. Volkmann, S. Danishefsky, J. Eggler and D. M. Solomon, *Ibid.* **93**, 5576 (1971)

[6] E. Winterfeldt, T. Korth, D. Pike and M. Boch, *Angew. Chem. Internat. Edit.* **11**, 289 (1972); and *Chem. Ber.* **105**, 2126 (1972)

[7] M. C. Wani, H. F. Campbell, G. A. Brine, J. A. Kepler and M. E. Wall, *J. Am. Chem. Soc.* **94**, 3631 (1972)

[8] Two additional syntheses of camptothecin have recently appeared: [a]C. Tang and H. Rapoport, *J. Am. Chem. Soc.* **94**, 8615 (1972); and [b]T. Sugasawa, T. Toyoda and K. Sasakura, *Tetrahedron Letters* 5109 (1972)

[9] M. Shamma and L. Novak, *Tetrahedron* **25**, 2275 (1969); and *Coll. Czech. Chem. Commun.* **35**, 3280 (1970)

[10] A. S. Kende, R. W. Draper, I. Kubo and M. Joyeux, *Abstracts, 160th National Meeting of the American Chemical Society*, ORGN 10. Chicago, Ill., Sept. (1970)

[11] L. L. Braun and J. H. Looker, *J. Am. Chem. Soc.* **80**, 359 (1958)

[12] J. W. Clark-Lewis and P. I. Mortimer, *J. Chem. Soc.*, 191 (1961)

[13] C. Moertel, A. J. Schutt, R. J. Reitemeier and R. G. Hahn, *Cancer Chemotherapy Rept.*, Part 1, **56**, 95 (1972)

[14] L. Goldfarb, S. Q. Taits and V. N. Bulgakova, *Izv. Akad. Nauk SSSR, Ser. Khim.* 7, 1299 (963)

[15] R. P. A. Sneeden and R. B. Turner, *J. Am. Chem. Soc.* 77, 190 (1955)

[16] For a numbering system for camptothecin see M. Shamma, *Experientia* **14**, 107 (1968)