Studies on the Syntheses of Heterocyclic Compounds. Part 878.[1] Synthesis of (±)-Camptothecin and (±)-10-Methoxycamptothecin *via* Enamine Annulation

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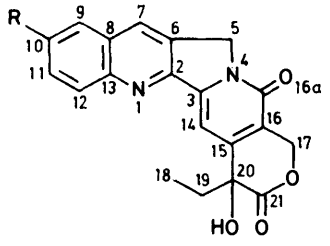
Synthesis of (±)-camptothecin (1) and (±)-10-methoxycamptothecin (2) was achieved *via* enamine annelation as a key step. Condensation of 3,4-dihydro-1-methyl-β-carbolines (9) and (10) with unsaturated tetra-esters (6) and (7) followed by reduction gave the indolo[*a*]quinolizin-4-ones (12) and (13). Photo-oxygenation of (12) and (13) and subsequent base treatment produced the indolizino[1,2-*b*]quinolones (16) and (17), which were converted into the pyridones (20) and (24). The former (20) had been correlated to (±)-camptothecin, while the latter (24) was transformed into (±)-10-methoxycamptothecin by application of the established method.

(+)-CAMPTOTHECIN (1), an alkaloid isolated from the Chinese tree *Camptotheca acuminata* by Wall and co-workers,[2] exhibits potent antileukemic and antitumour activities in animals. However, initial hopes with respect to the possible clinical utility of (1) as an anti-cancer agent were abandoned when it was found to be highly toxic.[3] As a result, there has been considerable effort to synthesize its analogues. Furthermore, (+)-10-methoxycamptothecin (2),[4] (+)-10-hydroxycamptothecin (3) [4] and the related alkaloids [5] were found in the bark of the above plant and *Mappia foetida*.[6] (+)-10-Hydroxycamptothecin (3) was found to be one of the most potent and active compounds of these analogues [7] and is used in the clinical treatment of cancer in the People's Republic of China.[8] We were also interested in the synthesis of camptothecin and derivatives.[9]



(1) R = H
(2) R = OMe
(3) R = OH

Recently our discovery of a one-pot synthesis of benzo[*a*]-quinolizines [10] and indolo[*a*]quinolizines [11] utilizing the enamine character of a 3,4-dihydro-1-methylisoquinoline and a 3,4-dihydro-1-methyl-β-carboline led to total syntheses of *ipecac* alkaloids [12] and an indole alkaloid.[13] Application of this annulation has allowed the development of a short route to the synthetic intermediate of camptothecin by Winterfeldt.[14,15] We now describe a facile synthesis of (±)-camptothecin and (±)-10-methoxycamptothecin [convertible to (3)], along these lines.

RESULTS AND DISCUSSION

Reaction of di-t-butyl malonate (4) and dimethyl methoxymethylenemalonate in the presence of sodium hydride in benzene at room temperature gave a mixture (*ca.* 1 : 1) of two unsaturated tetra-esters (6) and (7) in 76.6% yield. The mixture was used in the subsequent annulation. Thus stirring a mixture of the above esters (6) and (7) and 3,4-dihydro-1-methyl-β-carboline (9) in aprotic solvents at room temperature formed the Michael adduct (11). After evaporation of the solvent, the product was reduced with sodium borohydride in methanol to give the indolo[*a*]quinolizin-4-one (12) with concurrent cyclization, in 80.1% yield from (9). The above addition in acetonitrile was faster than in tetrahydrofuran, but the latter conditions yielded a clean product. When the reaction mixture was stirred for a long period in acetonitrile before the reduction, a considerable amount of 6,7-dihydro-3-methoxycarbonylindolo[2,3-*a*]quinolizin-4-one (14) formed. Although cyclization took place selectively on one of methyl esters, the product was composed of two stereoisomers. However, since the chiral centres on ring D would disappear at the subsequent dehydrogenation stage, the stereochemistry of the products was not further studied and the mixture was subjected to the following reaction without separation.

Transformation of the indolo[*a*]quinolizinone ring to an indolizino[1,2-*b*]quinolone ring was achieved by dye-sensitized photo-oxidation followed by base treatment.[16] Photo-oxygenation of the mixture of (12) in the presence of Rose Bengal as a sensitizer in methanol using a 500-W halogen lamp at 20—25 °C for 2 h yielded the keto-amide (15), which was then treated with aqueous sodium hydrogencarbonate to afford the quinolone (16) in 56.9% overall yield from (12). Since treatment of the above indolo[*a*]quinolizinone with strong bases caused retro-Michael reaction and aromatization to produce (14), the oxidation catalysed with base [14] could not be applied to the above ring transformation.

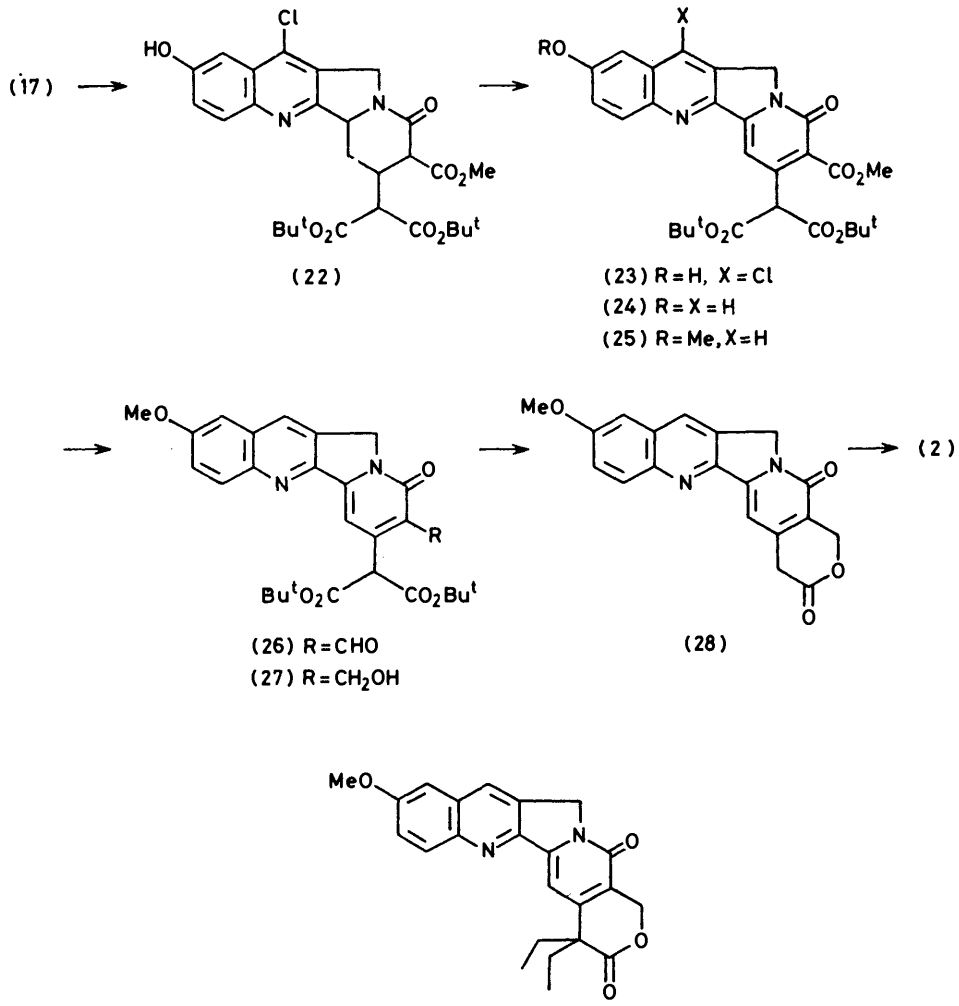
Treatment of (16) with thionyl chloride in dimethyl-

formamide [14] at 0 °C afforded the chloride (18) which was dehalogenated, by hydrogenolysis over palladium–barium sulphate in methanol,[14] to give the quinoline (19) in 85.5% overall yield from (16). N.m.r. and t.l.c. analyses suggested that the above three products [(16), (18), and (19)] were also mixtures of two stereoisomers, as was that of (12). Dehydrogenation of (19) with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in refluxing dioxan produced, in 43% yield, the pyridone (20), the spectral data of which were consistent with those of the ethyl ester (21),[14a] provided by Professor Winterfeldt. This pyridone (20) has been already correlated to (±)-camptothecin.[14b]

(±)-10-Methoxycamptothecin (2) was synthesized in a similar sequence. 6-Acetoxy-3,4-dihydro-1-methyl-β-carboline (10) was prepared by Bischler–Napieralski reaction of the amide (8) [17] with phosphoryl chloride in acetonitrile. Condensation of (10) with a mixture of esters (6) and (7) in acetonitrile for 6 h at room temperature, followed by reduction with sodium borohydride, furnished a stereoisomeric mixture of the indolo[*a*]-quinolizin-4-ones (13) in 69.3% yield. Photo-oxygen-

ation of (13) and subsequent cyclization gave, with the simultaneous hydrolysis of the acetate, the quinone (17) in 56% yield. Chlorination [14] of (17) produced (22) in 87.6% yield, which was oxidized to the pyridone (23) in 74.9% yield. On hydrogenolysis [14] of (23), the phenolic pyridone (24) was obtained in 66.4% yield. After methylation of (24) with diazomethane, the methyl ester of the resulting triester (25) was selectively reduced with di-isobutylaluminium hydride in dimethoxyethane [14] at −60 to −65 °C, leading to a mixture of the aldehyde (26) and the alcohol (27). In order to complete the reduction, the mixture was further reduced with sodium borohydride. The alcohol (27) obtained was treated, without purification, with trifluoroacetic acid [14] at room temperature to produce the lactone (28) in 62.9% overall yield from (25).

Ethylation of (28) was carried out with ethyl iodide in the presence of sodium hydride in dimethylformamide at room temperature giving (±)-10-methoxycamptothecin (2) in 10.7% yield, together with the diethyl compound (29). Oxidation presumably occurred with the dissolving molecular oxygen in dimethylformamide during the ethylation. Under strictly oxygen-free conditions, the corresponding (±)-20-deoxy-10-methoxycamptothecin, which is converted to (2) by oxidation in the presence of copper(II) chloride and dimethylamine in dimethylformamide,[14a] was obtained in trace yield, along with tarry unidentified products.



(22)

(23) R = H, X = Cl
(24) R = X = H
(25) R = Me, X = H

(26) R = CHO
(27) R = CH_2OH

(28)

(29)

The synthetic product was identical with the natural product, donated by Dr. M. C. Wani, in all respects except the optical rotation. (±)-10-Methoxycamptothecin (2) was readily converted into (±)-10-hydroxycamptothecin (3) by heating in concentrated hydrobromic acid.[7]

EXPERIMENTAL

All melting points are uncorrected. U.v. spectra were recorded on a Hitachi 124 spectrophotometer, i.r. spectra on a Hitachi 260-10 spectrophotometer, n.m.r. spectra on JEOL JNM-PMX 60 and PS-100 spectrometers, and mass spectra on Hitachi M-52G and JEOL-JMS-01SG-2 spectrometers.

Methyl α-Methoxycarbonyl-γγ-bis-t-butoxycarbonylcrotonate (6) *and t-Butyl γγ-Bismethoxycarbonyl-α-t-butoxycarbonylcrotonate* (7).—To a solution of t-butyl malonate (4)

(15 g) in benzene (200 ml) was added 50% sodium hydride (4.5 g) in small portions at room temperature and the mixture was stirred for 30 min. Dimethyl methoxymethylenemalonate (5) (15 g) in benzene (30 ml) was then slowly added, and the resulting mixture was stirred for 2 days. The precipitate was then collected by filtration, acidified with 10% aqueous hydrochloric acid, and then extracted with ether. The extract was washed with brine, dried (Na_2SO_4), and evaporated to afford an oily residue, which was applied to chromatography on silica gel. Elution with benzene–n-hexane (7 : 3) gave a mixture of the *tetra-esters* (6) and (7) (19 g, 76.6%) as an oil (Found: C, 56.35; H, 7.35. $C_{17}H_{26}O_8 \cdot 0.25H_2O$ requires C, 56.25; H, 7.35%); $\nu_{max.}$ ($CHCl_3$) 1 730 (CO_2R) cm^{-1}; δ ($CDCl_3$) 1.43—1.63 (18 H, m, 2 × CO_2Bu^t), 3.77—3.93 (6 H, m, 2 × CO_2Me), 4.47 (0.5 H, d, *J* 10 Hz, γ-H), 4.63 (0.5 H, d, *J* 10 Hz, γ-H), 6.95 (0.5 H, d, *J* 10 Hz, β-H), 7.22 (0.5 H, d, *J* 10 Hz, β-H).

Two Stereoisomers of 2-(*Bis-t-butoxycarbonylmethyl*)-1,12b,2,3,6,7-*hexahydro*-3-*methoxycarbonylindolo*[2,3-a]*quinolizin*-4-*one* (12).—A mixture of 3,4-dihydro-1-methyl-β-carboline (9) (500 mg) and tetra-esters (6) and (7) (1 g) in tetrahydrofuran (20 ml) was stirred at room temperature under a nitrogen atmosphere for 2 days. Evaporation of the solvent gave a residue, which was dissolved in methanol (30 ml). After addition of sodium borohydride (105 mg) in small portions, the mixture was stirred at room temperature for 30 min and then acidified with acetic acid. Evaporation of the solvent gave a residue, which was neutralized with saturated aqueous sodium hydrogencarbonate and extracted with methylene chloride. The extract was washed with water, dried (Na_2SO_4), and evaporated to afford a residue, chromatography of which on silica gel [eluting with benzene–acetone (97 : 3)] gave the *tetracyclic compound* (12) (1.15 g, 80.1%) as a syrup (Found: C, 65.8; H, 6.75; N, 5.05. $C_{28}H_{36}N_2O_7$ requires C, 65.6; H, 7.1; N, 5.45%); $\nu_{max.}$ ($CHCl_3$) 3 450 (NH), 1 730 (CO_2R), 1 635 (NCO) cm^{-1}; δ ($CDCl_3$) 1.47 and 1.53 (each 9 H, each s, 2 × CO_2Bu^t), 3.70 and 3.80 (each 1.5 H, each s, CO_2Me), 6.83—7.57 (4 H, m, 4 × Ar-H), and 7.87 and 8.13 (each 0.5 H, br s, NH); *m/e* 512 (M^+).

Two Stereoisomers of 2-(*Bis-t-butoxycarbonylmethyl*)-1,12b,2,3-*tetrahydro*-3-*methoxycarbonyl*-6H-*indolizino*[1,2-b]-*quinoline*-4,7-*dione* (16).—A solution of the tetracyclic compound (12) (2.4 g) and Rose Bengal (100 mg) in methanol (180 ml) was irradiated with a 500-W halogen lamp with a Pyrex filter for 2 h in a current of oxygen at 20—25 °C. After concentration to half its volume under reduced pressure, saturated aqueous sodium hydrogencarbonate (30 ml) was added and the mixture was stirred at room temperature for 2 days. After extraction with methylene chloride, the extract was washed with water, dried (Na_2SO_4), and evaporated to give a residue, which was chromatographed on silica gel. Elution with benzene–methanol (97 : 3) afforded the *indolizino-quinolone* (16) (1.4 g, 56.9%) as a powder (Found: C, 62.75; H, 6.65; N, 4.75. $C_{28}H_{34}N_2O_8 \cdot 0.5H_2O$ requires C, 62.8; H, 6.6; N, 5.25%); $\nu_{max.}$ ($CHCl_3$) 1 735 (CO_2R), 1 670 (NCO), and 1 625 (γ-pyridone) cm^{-1}; δ ($CDCl_3$) 1.40 and 1.43 (each 9 H, s, 2 × CO_2Bu^t), 3.77 and 3.80 (each 1.5 H, s, CO_2Me), 7.16—7.73 (3 H, m, 3 × Ar-H), and 8.27 (1 H, d, *J* 8 Hz, 8-H).

6,7-*Dihydro*-3-*methoxycarbonylindolo*[2,3-a]*quinolizin*-4-*one* (14).—A mixture of the indole (12) (119 mg) and 60% sodium hydride (40 mg) in dimethylformamide (5 ml) was stirred at room temperature under an oxygen atmosphere for 18 h. Excess of ammonium chloride was added to the mixture, which was then extracted with methylene chloride. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a crystalline mass, which was recrystallized from 50% methanol–chloroform to afford the *indoloquinolizinone* (14) (56 mg, 82.5%) as pale yellow needles, m.p. >280 °C (Found: C, 69.1; H, 4.9; N, 9.2. $C_{17}H_{14}N_2O_3$ requires C, 69.35; H, 4.8; N, 9.5%); $\nu_{max.}$ (KBr) 3 300 (NH), 1 710 (CO_2Me), and 1 630 (NCO) cm^{-1}; δ ([$^2H_6$]DMSO) 3.10 (2 H, t, *J* 7 Hz, 7-H_2), 3.73 (3 H, s, CO_2Me), 4.33 (2 H, t, *J* 7 Hz, 6-H_2), 6.70 (1 H, d, *J* 8 Hz, 1-H), 6.90—7.73 (4 H, m, 4 × Ar-H), 8.07 (1 H, d, *J* 8 Hz, 2-H), and 11.77 (1 H, br s, NH); *m/e* 294 (M^+).

Two Stereoisomers of 2-(*Bis-t-butoxycarbonylmethyl*)-1,12b,2,3-*tetrahydro*-3-*methoxycarbonyl*-6H-*indolizino*[1,2-b]-*quinolin*-4-*one* (19).—To a solution of the quinolone (16) (305 mg) in dimethylformamide (10 ml) was added thionyl chloride (0.5 ml) under ice-cooling. The mixture was stirred at 0 °C for 10 min and then poured into ice-cooled saturated aqueous sodium hydrogencarbonate, which was extracted with benzene. The extract was washed with brine, dried (Na_2SO_4), and evaporated to give a residue, which was chromatographed on silica gel. Elution with benzene–acetone (98 : 2) afforded the chloride (18) (290 mg); $\nu_{max.}$ ($CHCl_3$) 1 730 (CO_2R) and 1 650 (NCO) cm^{-1}; δ ($CDCl_3$) 1.50 (18 H, s, 2 × CO_2Bu^t), 3.80 (3 H, s, CO_2Me), and 7.40—8.27 (4 H, m, 4 × Ar-H); *m/e* 544 (M^+).

Without further purification, the chloride (18) was applied to the next reaction. A mixture of the chloride (18) (290 mg) and 5% palladium–barium sulphate (150 mg) in methanol (10 ml) was stirred under a hydrogen atmosphere for 5 h. The catalyst was filtered off and the filtrate was evaporated to give a residue, which was chromatographed on silica gel. Elution with benzene–acetone (96 : 4) afforded the *indolizino-quinoline* (19) [253 mg, 85.5% from (16)] as a syrup (Found: C, 65.3; H, 6.7; N, 5.1. $C_{28}H_{34}N_2O_7 \cdot 0.25H_2O$ requires C, 65.3; H, 6.75; N, 5.45%); $\nu_{max.}$ ($CHCl_3$) 1 735 (CO_2R) and 1 655 (NCO) cm^{-1}; δ ($CDCl_3$) 1.47 and 1.53 (each 9 H, each s, 2 × CO_2Bu^t), 3.80 (3 H, s, CO_2Me), and 7.23—8.33 (5 H, m, 4 × Ar-H and 7-H); *m/e* 510 (M^+).

2-(*Bis-t-butoxycarbonylmethyl*)-3-*methoxycarbonyl*-6H-*indolizino*[1,2-b]*quinolin*-4-*one* (20).—A mixture of the quinoline (19) (253 mg) and 2,3-dichloro-5,6-dicyanobenzoquinone (250 mg) in dioxan (20 ml) was refluxed for 10 min under a nitrogen atmosphere. After cooling, followed by dilution with benzene, the organic layer was washed with saturated sodium hydrogencarbonate and brine, dried (Na_2SO_4), and evaporated to give a residue, which was chromatographed on silica gel. Elution with methylene chloride—methanol (98 : 2) afforded a powder, which was recrystallized from benzene–n-hexane to afford the pyridone (20) [14b] (108 mg, 43.0%) as pale yellow needles, m.p. 203—204 °C; $\nu_{max.}$ ($CHCl_3$) 1 730 (CO_2R) and 1 660 (NCO) cm^{-1}; δ ($CDCl_3$) 1.50 (18 H, s, 2 × CO_2Bu^t), 3.93 (3 H, s, CO_2Me), 4.80 (1 H, s, 2-CH), 5.20 (2 H, s, 6-H_2), and 7.37—8.43 (5 H, m, 4 × Ar-H, 7-H and 1-H); *m/e* 506 (M^+).

6-*Acetoxy*-3,4-*dihydro*-1-*methyl*-β-*carboline* (10).—A solution of the acetamide (8) (2.17 g) and phosphoryl chloride (1.65 g) in acetonitrile (50 ml) was refluxed for 30 min. Evaporation of the solvent and the excess of reagent afforded a residue, which was basified with a saturated aqueous sodium carbonate and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give the β-carboline (10) (2 g, 98%) as a syrup. Its hydrochloride was recrystallized from methanol–

ether as *needles*, m.p. 253—254 °C (Found: C, 60.05; H, 5.4; N, 10.0. $C_{14}H_{15}N_2O_2Cl$ requires C, 60.3; H, 5.4; N, 10.05%); $\nu_{max.}$ ($CHCl_3$) 3 480 (NH) and 1 750 (OAc) cm^{-1}; δ ($CDCl_3$) 2.25 (6 H, s, OAc and 1-Me), 2.77 (2 H, m, 4-H_2), 3.83 (2 H, m, 3-H_2), 7.05 (1 H, dd, *J* 2.5 and 9 Hz, 7-H), 7.20 (1 H, d, *J* 9 Hz, 8-H), 7.22 (1 H, d, *J* 2.5 Hz, 5-H), and 9.73 (1 H, br s, NH); *m/e* 242 (M^+).

Two Stereoisomers of 9-Acetoxy-2-(bis-t-butoxycarbonylmethyl)-1,12b,2,3,6,7-hexahydro-3-methoxycarbonylindolo[2,3-a]quinolizin-4-one (13).—A mixture of the 6-acetoxy-β-carboline (10) (2.0 g) and the tetra-esters (6) and (7) (4.0 g) in acetonitrile (100 ml) was stirred at room temperature under nitrogen atmosphere for 6 h. Evaporation of the solvent afforded a residue, which was dissolved in methanol (100 ml). To this solution was added sodium borohydride (130 mg) in small portions. The mixture was stirred at room temperature for 15 min and then worked-up as described above for compound (12). Chromatography of the resulting residue on silica gel eluting with benzene–acetone (97 : 3) afforded the *tetracyclic compound* (13) (2.8 g, 69.3%) as a syrup (Found: C, 63.65; H, 6.6; N, 4.4. $C_{30}H_{38}N_2O_9$ requires C, 63.15; H, 6.7; N, 4.9%); $\nu_{max.}$ ($CHCl_3$) 3 450 (NH), 1 735 (CO_2R), and 1 635 (NCO) cm^{-1}; δ ($CDCl_3$) 1.47 and 1.50 (each 9 H, s, 2 × CO_2Bu^t), 2.30 (3 H, s, OAc), 3.70 and 3.77 (each 1.5 H, s, CO_2Me), 6.60—7.30 (3 H, m, 3 × Ar-H), and 8.30 and 8.37 (each 0.5 H, br s, NH); *m/e* 570 (M^+).

Two Stereoisomers of 2-(*Bis-t-butoxycarbonylmethyl*)-1,12b,2,3-*tetrahydro-9-hydroxy-3-methoxycarbonyl-6H-indolizino*-[1,2-b]*quinolin-4,7-dione* (17).—A solution of the tetracyclic acetate (13) (1.94 g) and Rose Bengal (100 mg) in methanol (180 ml) was irradiated with a 500-W halogen lamp with Pyrex filter in a current of oxygen for 2 h at 20—25 °C. After concentration to half its volume, saturated aqueous sodium hydrogencarbonate (30 ml) was added to the residual solution. The mixture was stirred at room temperature for 20 h and then extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a residue, which was chromatographed on silica gel. Elution with benzene–methanol (95 : 5) afforded the *hydroxyquinolone* (16) (1.03 g, 56.0%) as a powder (Found: C, 60.3; H, 6.25; N, 4.5. $C_{28}H_{34}N_2O_9 \cdot H_2O$ requires C, 59.9; H, 6.45; N. 5.0%); $\nu_{max.}$ (KBr) 1 740 (CO_2R), 1 640 (NCO), and 1 590 (γ-pyridone) cm^{-1}; δ [$CDCl_3$–CD_3OD (10 : 2)] 1.40 (18 H, s, 2 × CO_2Bu^t), 3.73 and 3.77 (each 1.5 H, s, CO_2Me), and 6.95—7.53 (3 H, m, 3 × Ar-H).

Two Stereoisomers of 2-(*Bis-t-butoxycarbonylmethyl*)-7-*chloro*-1,12b,2,3-*tetrahydro-9-hydroxy*-6H-*indolizino*[1,2-b]-*quinolin-4-one* (22).—To a solution of the quinolone (17) (430 mg) in dimethylformamide (10 ml) was added thionyl chloride (0.2 ml) under ice-cooling. The mixture was stirred for 15 min at 0 °C and worked up as in the case of (18). The resulting residue was chromatographed on silica gel. Elution with benzene–acetone (95 : 5) afforded the *chloride* (22) (390 mg, 87.6%) as a powder (Found: C, 59.5; H, 5.9; N, 4.7. $C_{28}H_{33}N_2O_8Cl$ requires C, 59.95; H, 5.95; N, 5.0%); $\nu_{max.}$ ($CHCl_3$) 1 735 (CO_2R) and 1 650 (NCO) cm^{-1}; δ ($CDCl_3$) 1.40 (18 H, s, 2 × CO_2Bu^t), 3.77 (3 H, s, CO_2Me), 7.17—7.50 (2 H, m, 8- and 10-H), 7.85 (1 H, d, *J* 9 Hz, 11-H), and 9.07 (1 H, br s, OH); *m/e* 561 (M^+).

2-(*Bis-t-butoxycarbonylmethyl*)-7-*chloro*-2-*hydroxy*-8-*methoxycarbonyl*-6H-*indolizino*[1,2-b]*quinolin-4-one* (23).—A mixture of the chloride (22) (390 mg) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (380 mg) in benzene (30 ml) was refluxed for 15 min under a nitrogen atmosphere and, after cooling, poured into a saturated aqueous sodium hydrogencarbonate, which was extracted with methylene chloride. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to chromatography on silica gel. Elution with benzene–methanol (97 : 3) afforded the *indolizino-quinoline* (23) (290 mg, 74.9%) as pale yellow needles, m.p. >280 °C (Found: C, 59.65; H, 5.4; N, 4.5. $C_{28}H_{29}N_2O_8Cl \cdot 0.5H_2O$ requires C, 59.4; H, 5.35; N, 4.95%); $\nu_{max.}$ ($CHCl_3$) 1 720 (CO_2Bu^t), 1 710 (CO_2Me), and 1 650 (NCO) cm^{-1}; δ ($CDCl_3$) 1.63 (18 H, s, 2 × CO_2Bu^t), 4.17 (3 H, s, CO_2Me), 4.93 (2 H, br s, 6-H_2), 5.20 (1 H, s, 2-CH), 6.97—7.43 (3 H, m, 8-, 10-, and 11-H), and 7.80 (1 H, s, 1-H); *m/e* 556 (M^+).

2-(*Bis-t-butoxycarbonylmethyl*)-9-*hydroxy*-3-*methoxycarbonyl*-6H-*indolizino*[1,2-b]*quinolin-4-one* (24).—A mixture of the chloro-pyridone (23) (290 mg) and 5% palladium–barium sulphate (150 mg) in methanol (30 ml) was stirred under a hydrogen atmosphere at room temperature for 4 h. The catalyst was filtered off and the filtrate was evaporated to give a crystalline mass, which was recrystallized from methanol to afford the *indolizino-quinoline* (24) (180 mg, 66.4%) as pale yellow needles, m.p. >280 °C (Found: C, 63.65; H, 5.75; N, 4.8. $C_{28}H_{30}N_2O_8 \cdot 0.5H_2O$ requires C, 63.25; H, 5.9; N, 5.25%); $\nu_{max.}$ (KBr) 1 740 (CO_2Bu^t), 1 720 (CO_2Me), and 1 650 (NCO) cm^{-1}; δ [$CDCl_3$–CD_3OD (2 : 1)] 1.53 (18 H, s, 2 × CO_2Bu^t), 3.97 (3 H, s, CO_2Me), 4.87 (1 H, s, 2-CH), 5.13 (2 H, s, 6-H_2), 7.17 (1 H, d, *J* 2.5 Hz, 8-H), 7.40 (1 H, dd, *J* 2.5 Hz and 9 Hz, 10-H), 7.47 (1 H, s, 7-H), 8.07 (1 H, d, *J* 9 Hz, 11-H), and 8.13 (1 H, s, 1-H); *m/e* 522 (M^+).

2-(*Bis-t-butoxycarbonylmethyl*)-9-*methoxy*-3-*methoxycarbonyl*-6H-*indolizino*[1,2-b]*quinolin-4-one* (25).—To a solution of compound (24) (430 mg) in methylene chloride (20 ml) was added an excess of diazomethane in ether and the mixture was allowed to stand for 4 h. Evaporation of the solvents afforded a crystalline mass, which was recrystallized from benzene–n-hexane to give the *methyl ether* (25) (405 mg, 91.8%) as needles, m.p. 217.5—218.5 °C (Found: C, 64.65; H, 5.9; N, 4.95. $C_{29}H_{32}N_2O_8$ requires C, 64.9; H, 6.0; N, 5.2%); $\nu_{max.}$ ($CHCl_3$) 1 730 (CO_2Bu^t), 1 720 (CO_2Me), and 1 655 (NCO) cm^{-1}; δ ($CDCl_3$) 1.53 (18 H, s, 2 × CO_2Bu^t), 3.97 (6 H, s, 9-OMe and CO_2Me), 4.83 (1 H, s, 2-CH), 5.23 (2 H, s, 6-H_2), 7.12 (1 H, d, *J* 2.5 Hz, 8-H), 7.22 (1 H, d, *J* 2.5 Hz and 9 Hz, 10-H), 7.45 (1 H, s, 7-H), 8.08 (1 H, d, *J* 9 Hz, 11-H), and 8.17 (1 H, s, 1-H); *m/e* 536 (M^+).

20-*Desethyl*-10-*methoxy*-20-*deoxycamptothecin* (28).—To a solution of the methyl ether (25) (580 mg) in dimethoxyethane (60 ml) was added di-isobutylaluminium hydride (20% in toluene) (9 ml) in dimethoxyethane (14 ml) at −60 to −65 °C. The mixture was stirred at this temperature for 1 h under a nitrogen atmosphere and then poured into ice–water, which was acidified with 2N hydrochloric acid. After neutralization with saturated aqueous sodium hydrogencarbonate, the mixture was extracted with methylene chloride. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a crystalline mass, which was, without further purification, dissolved in a mixture of methanol (100 ml) and chloroform (20 ml). To the above mixture was added sodium borohydride (150 mg) in one portion at room temperature, and the mixture stirred for 15 min. Evaporation of the solvent afforded a residue, which, without purification, was stirred with trifluoroacetic acid (10 ml) at room temperature for 1 h. Evaporation of

the solvent afforded a residue, which was chromatographed on silica gel. Elution with methylene chloride–methanol (97 : 3) afforded a powder, recrystallisation of which from 50% methanol–chloroform gave the *lactone* (28) [227 mg, 62.9% from (25)] as needles, m.p. 287—288 °C (Found: C, 67.3; H, 4.55; N, 7.75. $C_{19}H_{14}N_2O_4 \cdot 0.25H_2O$ requires C, 67.35; H, 4.3; N, 8.25%); $\nu_{max.}$ (KBr) 1 720 (lactone) and 1 655 (NCO) cm^{-1}; δ (CF_3CO_2H) 4.10 br (2 H, s, 20-H_2), 4.12 (3 H, s, 10-OMe), 5.77 br (4 H, s, 5 and 17-H_2), 7.53 (1 H, d, *J* 2.5 Hz, 9-H), 7.82 (1 H, s, 13-H), 7.90 (1 H, dd, *J* 2.5 Hz and 9 Hz, 3-H), 8.32 (1 H, d, *J* 9 Hz, 12-H), and 9.10 (1 H, s, 7-H); *m/e* 335 (M^+).

(±)-10-*Methoxycamptothecin* (2).—A mixture of the lactone (28) (124 mg) and 60% sodium hydride (20 mg) in dimethylformamide (20 ml) was stirred at room temperature for 4 h, and at 60 °C for 1 h, under a nitrogen atmosphere; ethyl iodide (100 mg) in dimethylformamide (1 ml) was then added. The resulting mixture was stirred at room temperature for 15 h and then poured into 2N-hydrochloric acid (5 ml). After extraction with chloroform, the extract washed with water, dried (Na_2SO_4), and evaporated to give a residue, which was chromatographed on silica gel. Elution with chloroform–methanol (98 : 2) afforded a powder, which was recrystallized from 50% methanol–chloroform to give the *diethyl compound* (29) (8 mg, 5.5%) as needles, m.p. 257—259 °C (Found: M^+, 390.1612. $C_{23}H_{22}N_2O_4$ requires *M*, 390.1580); $\nu_{max.}$ (KBr) 1 730 (lactone) and 1 655 (NCO) cm^{-1}; δ ([$^2H_6$]DMSO) 0.85 (6 H, t, *J* 7 Hz, 2 × CH_2*Me*), 2.0—2.33 (4 H, m, 2 × CH_2Me), 4.0 (3 H, s, 10-OMe), 5.30 and 5.43 (each 2 H, each s, 5- and 17-H_2), 7.28 (1 H, d, *J* 2.5 Hz, 9-H), 7.34 (1 H, s, 7-H), 7.47 (1 H, dd, *J* 2.5 and 9 Hz, 11-H), 8.06 (1 H, d, *J* 9 Hz, 12-H), and 8.41 (1 H, s, 14-H); *m/e* 390 (M^+).

Further elution with chloroform–methanol (97 : 3) gave a powder, which was recrystallized from 50% methanol–chloroform to afford 10-methoxycamptothecin (2) (15 mg, 10.7%) as needles, m.p. 272—273 °C (lit.,[7] 271—272 °C), the u.v. (MeOH), i.r. (KBr), and n.m.r. ([$^2H_6$]DMSO) spectra of which were identical with those of natural product presented by Dr. M. C. Wani.

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