Synthesis of a Potential Camptothecin Intermediate (1)

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Condensation of dimethyl 1,2-dihydro-2-oxopyridine-4,6-dicarboxylate (IIIb) with methyl acrylate yielded 1,2,3,5-tetrahydro-2,7-dimethoxycarbonyl-1,5-dioxoindolizine (IV), which on hydrolysis and decarboxylation gave 1,2,3,5-tetrahydro-1,5-dioxoindolizine-7-carboxylic acid (VI). Friedländer condensation of VI with 2-aminobenzaldehyde, followed by esterification of the resulting oxoindolizino[1,2-*b*]quinoline-7-carboxylic acid (VIIa), yielded a potential camptothecin intermediate 9,10-dihydro-7-methoxycarbonyl-9-oxoindolizino[1,2-*b*]quinoline (VIIb).

Camptothecin (I), a novel alkaloid isolated by Wall and his co-workers (3) from the stem wood of the Chinese tree, *Camptotheca acuminata Nyssaceae* is an interesting compound because of its unique structure and its potential antitumor and antileukemic activity. The structural elucidation of I reported is mainly based on its spectral data and the X-ray analysis of its iodoacetate (3).

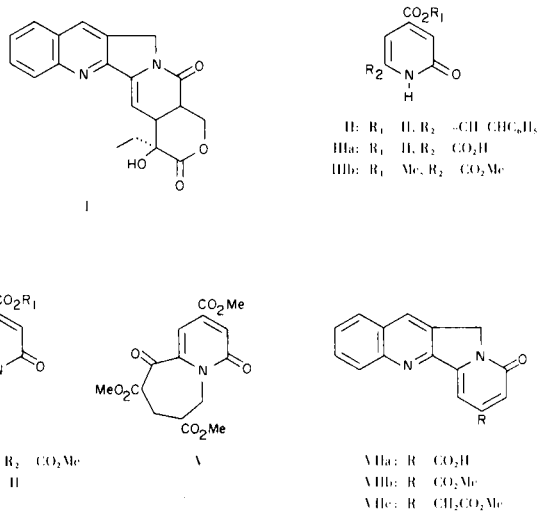
Previously, we reported the synthesis of a camptothecin skeleton (4) and its related compounds (5), but the first total synthesis of (±)-camptothecin was reported by Stork and Schultz (6). Furthermore, three routes for the total synthesis of (±)-camptothecin have been recently reported (7 ~ 9). Herein we wish to report a synthesis of a potential camptothecin intermediate (VIIb).

Treatment of 1,2-dihydro-2-oxo-6-styrylpyridine-4-carboxylic acid (II) (10) with potassium permanganate gave 1,2-dihydro-2-oxopyridine-4,6-dicarboxylic acid (IIIa). After esterification of IIIa in the usual manner, condensation of the diester IIIb with methyl acrylate in dimethylformamide in the presence of sodium carbonate, followed by simultaneously occurring cyclization, afforded a mixture of bicyclic ketoesters IV and V, which could be separated by the difference in solubility.

Hydrolysis of IV followed by decarboxylation yielded 1,2,3,5-tetrahydro-1,5-dioxoindolizine-7-carboxylic acid (VI). Friedländer condensation of VI with 2-aminobenzaldehyde gave a quinoline derivative VIIa, which was esterified to give a potential camptothecin intermediate VIIb.

The compound VIIc occurs in a successful synthesis of camptothecin (7). The carboxylic acid VIIa would be interesting as a potential key intermediate in a formal total synthesis of camptothecin if it were converted to VIIc by the Arndt-Eistert reaction.

SCHEME 1



EXPERIMENTAL (11)

Dimethyl 1,2-Dihydro-2-oxopyridine-4,6-dicarboxylate (IIIb).

A solution of 54 g. of potassium permanganate in 1 liter of water was added to a stirred solution of 50 g. of II (10) and 15 g. of potassium hydroxide in 2 liters of water within 30 minutes and stirring was continued at room temperature for 1 hour. The precipitated manganese dioxide was filtered and washed with 1 liter of hot water on a filter. The filtrate was acidified with concentrated sulfuric acid and evaporated to dryness *in vacuo*. The resulting solid was refluxed with 20 ml. of concentrated sulfuric acid and 2 liters of methanol for 6 hours. Removal of the solvent *in vacuo* gave a brownish oil, which was dissolved in water and extracted with chloroform. The extract was washed with water and dried over sodium sulfate. Evaporation of the solvent afforded 33 g. of the crude product, which was recrystallized from ethanol to give 28 g. of IIIb as colorless needles, m.p. 148°; ir ν max (chloroform): 3260 (NH), 1725 (ester C=O), 1660 cm^{-1} (amide C=O); nmr (deuteriochloroform) δ: 3.92 (s, 3H, CH_3),

3.97 (s, 3H, C*H*$_3$) and 7.41 ppm (s, 2H, Ar*H*).

Anal. Calcd. for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 51.58; H, 4.43; N, 6.95.

Bicyclic Ketoesters IV and V.

A mixture of 4.8 g. of dimethyl 1,2-dihydro-2-oxopyridine-4,6-dicarboxylate (IIIb), 3.0 g. of methyl acrylate, 2.2 g. of sodium carbonate, and 60 ml. of dimethylformamide was stirred at 100° in a current of nitrogen for 4 hours. After being kept aside at room temperature for 16 hours, the mixture was filtered to give a precipitate, which was collected and washed with methanol. A mixture of the precipitate in water was acidified with hydrochloric acid to separate a colorless powder, which was collected and recrystallized from chloroform-ether to yield 500 mg. of IV as pale yellow needles, m.p. 235° dec.; ir ν max (potassium bromide): 3400 (OH), 1725 (ester C=O), 1700 (ketoester C=O), 1660 (amide C=O), 1620 cm^{-1} (C=O); nmr (trifluoroacetic acid) δ: 4.06 (s, 3H, CH$_3$), 4.14 (s, 3H, C*H*$_3$), 5.15 (s, 2H, C*H*$_2$N), 7.90 (s, 1H, Ar*H*), and 7.96 ppm (s, 1H, Ar*H*).

Anal. Calcd. for $C_{12}H_{11}NO_6$: C, 54.34; H, 4.18; N, 5.28. Found: C, 54.09; H, 4.34; N, 5.33.

Three hundred ml. of ether was added to the above filtrate to give a precipitate, which was collected by filtration and dissolved in water. The resulting solution was acidified with concentrated hydrochloric acid to separate a solid, which was collected by filtration and crystallized from ethanol to yield 150 mg. of V as yellow needles, m.p. 165°; ir ν max (chloroform): 1725 (ester C=O), 1700 (ketoester C=O), 1660 cm^{-1} (amide C=O); nmr (deuteriodimethylsulfoxide) δ: 1.81 (t, 2H, J = 7Hz, C-C*H*$_2$-C), 3.43 (s, 3H, C*H*$_3$), 3.75 (s, 3H, C*H*$_3$), 3.87 (s, 3H, C*H*$_3$), 5.70 (t, 1H, J = 3Hz, COC*H*-), 6.87 (s, 1H, ArH), and 6.97 ppm (s, 1H, Ar*H*).

Anal. Calcd. for $C_{16}H_{17}NO_8$: C, 54.70; H, 4.88; N, 3.99. Found: C, 54.48; H, 5.04; N, 4.16.

1,2,3,5-Tetrahydro-1,5-dioxoindolizine-7-carboxylic Acid (VI).

A mixture of 100 mg. of IV and 200 ml. of concentrated hydrochloric acid was refluxed for 1 hour. The solvent was removed *in vacuo* to give a powder, the recrystallization of which from water afforded 60 mg. of VI as brownish needles, m.p. 200° dec.; ir ν max (potassium bromide): 1740 (C=O), 1700 cm^{-1} (carboxyl C=O), m/e 193 (M$^+$), which was used in the following reaction without purification because of its instability. This was changed to a dark resinous material for a while during recrystallization.

9,10-Dihydro-9-oxoindolizino[1,2-*b*]quinoline-7-carboxylic Acid (VIIa).

A mixture of 120 mg. of VI, 150 mg. of 2-aminobenzaldehyde, 50 mg. of sodium hydroxide, and 10 ml. of water was refluxed for 40 hours. The reaction mixture was cooled and acidified with concentrated hydrochloric acid to *p*H 4. The crystalline precipitate was collected by filtration, washed with ether, and recrystallized from methanol-water to afford 50 mg. of VIIa as a yellowish powder, m.p. > 305°; ir ν max (potassium bromide): 1720 (carboxyl C=O), 1660 cm^{-1} (amide C=O).

Anal. Calcd. for $C_{16}H_{10}N_2O_3$: N, 10.07. Found: N, 10.15.

9,10-Dihydro-7-methoxycarbonyl-9-oxoindolizino[1,2-*b*]quinoline (VIIb).

A solution of 100 mg. of VIIa in 100 ml. of methanol saturated with hydrogen chloride gas was refluxed for 6 hours. Removal of the solvent *in vacuo* gave a yellowish powder which was neutralized with aqueous sodium bicarbonate solution and extracted with chloroform. Evaporation of the extract gave a yellowish powder, which was recrystallized from chloroform-ether to give 60 mg. of VIIb as pale yellow needles, m.p. 305°; ir ν max (potassium bromide): 1725 (ester C=O), 1665 cm^{-1} (amide C=O); nmr (trifluoroacetic acid) δ: 4.20 (s, 3H, C*H*$_3$), 5.82 (s, 2H, C*H*$_2$), 7.70 (s, 1H, Ar*H*), 8.00 (s, 1H, Ar*H*), 8.20-8.60 (m, 4H, Ar*H*), and 9.40 ppm (s, 1H, Ar*H*); uv λ max (ethanol) nm (ϵ): 367 (15,000), 254 (22,000), 223 (55,000).

Anal. Calcd. for $C_{17}H_{12}N_2O_3$: C, 69.85; H, 4.14; N, 9.59. Found: C, 69.84; H, 4.26; N, 9.44.

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(11) Ir and uv spectra were recorded on Hitachi EPI-S2 and Hitachi EPI-3 recording spectrophotometers, respectively. Mass spectra were measured on a Hitachi RMU-7 mass spectrometer. Nmr spectra were measured on a Hitachi H-60 using tetramethylsilane as an internal standard.