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STUDIES ON THE SYNTHESES OF HETEROCYCLIC COMPOUNDS—CCCLXXI†

SYNTHETIC APPROACH TO CAMPTOTHECIN

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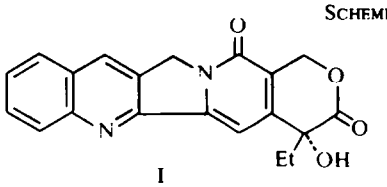
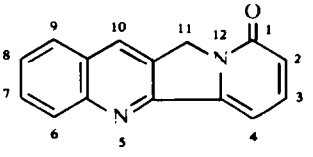
Abstract— Picolinic acid 1-oxide (III) was esterified with thionyl chloride and ethanol to the ester IV, whose treatment with phosphoryl chloride gave ethyl 6-chloropicolinate (V). Hydrolysis of V with hydrochloric acid gave 6-oxo-1,6-dihydropicolinic acid (VI). Simultaneous condensation and cyclisation of the methyl ester of VI with methyl acrylate in the presence of sodium carbonate in dimethylformamide yielded the bicyclic ketoester (VIII). Hydrolysis and decarboxylation of VIII with hydrochloric acid gave 3-keto-pyrrolidino[2.1-*f*]-2-pyridone (IX). Friedländer condensation of IX with 2-aminobenzaldehyde gave the camptothecin analogue II.

CAMPTOTHECIN (I), a novel alkaloid isolated[1] from the stem wood of the Chinese tree, *Camptotheca acuminata* DECSNE., *Nyssaceae*, is an interesting compound because of its unique structure and its potential antitumor and antileukemic activity. The structural elucidation of I reported by Wall *et al.*[1] is mainly based on its spectral data and the X-ray analysis of its iodoacetate. It was also reported by them that camptothecin exhibits an intense blue fluorescence under UV light and is almost

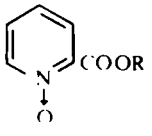
SCHEME I



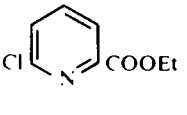
I



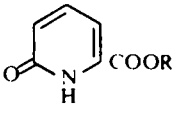
II



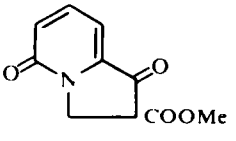
III: R = H
IV: R = Et



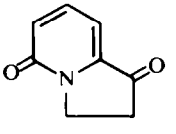
V



VI: R = H
VII: R = Me



VIII



IX

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† Part CCCLXX, T. Kametani, M. Koizumi, and K. Fukumoto, *J. Pharm. Soc. Japan* **90**, 1331 (1970)

nonbasic. Unsuccessful attempts to synthesise I have also been reported.[2,3] As a preliminary synthetic approach, the synthesis of II with a conjugated ring system like camptothecin is described. Esterification of picolinic acid 1-oxide (III) was achieved to give ethyl picolinate 1-oxide (IX). Treatment of IV with phosphoryl chloride (Experimental) gave ethyl 6-chloropicolinate (V) which on hydrolysis gave 6-oxo-1,6-dihydropicolinic acid (VI). This compound (VI) was esterified to yield methyl 6-oxo-1,6-dihydropicolinate (VII) and treatment of VII with methyl acrylate and sodium carbonate in DMF resulted in the condensation, followed by simultaneous cyclisation, to give bicyclic ketoester (VIII). Hydrolysis of VIII followed by decarboxylation afforded 3-oxopyrrolidino[2.1-*f*]-2-pyridone (IX).

Finally, Friedländer condensation of IX with 2-aminobenzaldehyde gave our aimed camptothecin analogue (II) as pale yellow needles, m.p. 263–265°, which showed almost the same UV absorption spectrum as that of camptothecin and an intense blue fluorescence under UV light.

EXPERIMENTAL

NMR spectra were run on a Hitachi H-60 spectrometer using $CDCl_3$ as solvent and TMS as an internal reference. The IR spectra were taken in chloroform soln with a Hitachi EPI-S_2 spectrophotometer, and the UV spectra were taken in MeOH soln on a Hitachi EPS-3 recording spectrophotometer. Mass spectra were measured on a Hitachi RMU-7 mass spectrometer.

Ethyl picolinate 1-*oxide* (IV). Thionyl chloride (69 g) was added dropwise to a soln of picolinic acid 1-oxide[4] (25 g) in EtOH (200 ml) with stirring. After refluxing for 30 min, the solvent was removed and the residue was extracted with chloroform. The extract was washed with sat NaCl aq and dried (Na_2SO_4). After removal of solvent the resulting oil was distilled to give a colourless liquid (29 g; 96%), b.p. 171–176°/6 mm, ν_{max} ($CHCl_3$) 1733 (C=O) cm^{-1}, ppm (in $CDCl_3$) 1·39 (3H, tr, J = 7·0 c/s, C$\underline{H}_3$CH$_2$CO), 4·41 (2H, qu, J = 7·0 c/s, CH$_3$C$\underline{H}_2$CO), 7·2–7·7 (3H, m, C$_3$—$\underline{H}$, C$_4$—$\underline{H}$, C$_5$—$\underline{H}$), 8·18 (1H, C$_6$—H), *m/e* 167 ($\underline{M}^+$).

Ethyl 6-*chloropicolinate* (V). A soln of ethyl picolinate 1-oxide (200 mg) and $POCl_3$ (0·5 ml) in chloroform (5 ml) saturated with HCl was heated at 80° for 7 hr in a sealed tube. After cooling, the solvent was removed under reduced pressure to give a viscous oil, which was neutralised with K_2CO_3 aq and extracted with chloroform. Removal of the solvent gave a yellowish viscous oil, which was distilled to give a colourless oil (150 mg: 69%), b.p. 118–125°/7 mm, ν_{max} ($CHCl_3$) 1724 cm^{-1}, ppm (in $CDCl_3$) 1·41 (3H, tr, J = 6·1 c/s, C$\underline{H}_3$CH$_2$CO), 4·45 (2H, qu, J = 6·1 c/s, CH$_3$C$\underline{H}_2$CO), 7·3–8·1 (3H, m, aromatic protons).

6-*oxo*-1,6-*dihydropicolinic acid* (VI). A soln of V (500 mg) in 36% HCl (20 ml) was heated at 180° for 6 hr in a sealed tube. After cooling, the solvent was removed under reduced pressure to give a colourless powder, which was recrystallised from MeOH to afford colourless needles (300 mg; 81%), m.p. 265°, ν_{max} ($CHCl_3$) 1690 (C=O), 1642 (CONH) cm^{-1}, *m/e* 130 ($\underline{M}^-$) [Found: C, 51·74; H, 3·71; N, 10·91. $C_6H_5NO_3$ requires: C, 51·80; H, 3·62; N, 10·07%].

Methyl 6-*oxo*-1,6-*dihydropicolinate* (VII). A soln of 6-oxo-1,6-dihydropicolinic acid (3·9 g) in MeOH (60 ml) saturated with HCl was refluxed for 5 hr. Removal of the solvent under reduced pressure gave a yellowish oil, which was neutralised with $NaHCO_3$ aq and extracted with chloroform. Evaporation of the solvent gave a colourless powder, which was recrystallised from chloroform-ether to give colourless needles (3 g; 68%), m.p. 105°, ν_{max} ($CHCl_3$) 3340 (NH), 1730 (COOCH$_3$), 1665 (CONH) cm^{-1}, ppm (in $CDCl_3$) 3·98 (3H, s, COOC$\underline{H}_3$), 6·7–7·7 (3H, m, aromatic protons) [Found: C, 54·59; H, 4·79; N, 9·08. $C_7H_7NO_3$ requires: C, 54·90; H, 4·61; N, 9·15%].

Bicyclic ketoerster (VIII). A mixture of methyl 6-oxo-1,6-dihydropicolinate (300 mg), methyl acrylate (1 ml), Na_2CO_3 (200 mg), and DMF (20 ml) was heated at 100° under stirring for 6 hr. After removal of the solvent under reduced pressure, water (10 ml) was added to the residue and the mixture was acidified with HCl to give a colourless powder which was recrystallised from EtOH to yield colourless needles (304 mg; 75%), m.p. 208°, ν_{max} ($CHCl_3$) 1710 (COOC$\underline{H}_3$), 1661 (CON <) cm^{-1} [Found: C, 57·70; H, 3·90; N, 6·72. $C_{10}H_9NO_4$ requires C, 57·97; H, 4·38; N, 6·76%].

3-*Oxopyrrolidino*[2.1-f]-2-*pyridone* (IX). A mixture of VIII (100 mg) and 36% HCl (10 ml) was refluxed for 1 hr. After cooling, extraction with chloroform, followed by evaporation of the solvent, gave a colourless powder, whose recrystallisation from chloroform-hexane afforded colourless needles (50 mg; 69%), m.p. 122°, ν_{max} ($CHCl_3$) 1742 (C=O), 1660 (CON <) cm^{-1}, ppm (in $CDCl_3$) 2·90 (2H, tr, J = 7·0 c/s, $COC\underline{H}_2CH_2N <$), 4·30 (2H, tr, J = 7·0 c/s, $COCH_2C\underline{H}_2N <$), 6·74 (1H, broad s, $C_2\underline{H}$), 7·35 (1H, d, J = 7·5 c/s, $C_4\underline{H}$), 7·60 (1H, d, J = 7·5 c/s, $C_3\underline{H}$) [Found: C, 64·44; H, 4·93; N, 8·94. $C_8H_7NO_2$ requires: C, 64·42; H, 4·73; N, 9·39%].

1-*Oxo-indolizino*-11 H-[1.2-b]*quinoline* (II). A mixture of IX (64 mg), 2-aminobenzaldehyde (51 mg) and NaOH (17 mg) and EtOH (2·5 ml) was allowed to stand for 24 hr at 10–21°. The separated crystals were collected, washed with a small amount of MeOH and recrystallised from EtOH to give pale yellow needles (30 mg; 32% based on IX), m.p. 265°, ν_{max} 1660 (CON <) cm^{-1}, ppm (in $CDCl_3$) 5·16 (2H, s), ($-C\underline{H}_2N <$), 6·5–6·8 (1H, m, pyridone proton), 7·4–8·3 (7H, m, quinoline and pyridone protons), λ_{max} (log ε) 365 (4·19), 285 (3·72), 253 (4·42), 217 (4·44), *m/e* 234 ($\underline{M}^+$, base peak), 206 ($\underline{M}^+$—CO) [Found: C, 76·93; H, 4·25; N, 11·88. $C_{15}H_{10}N_2O$ requires: C, 76·91; H, 4·30; N, 11·96%].

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