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SYNTHETIC APPROACHES TO CAMPTOTHECIN

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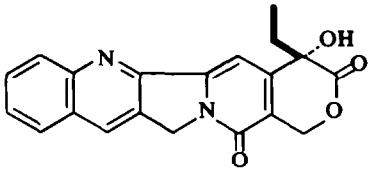
Abstract—3-Pyrrolidinone ethylene ketal (VI) was converted to the ketal amidoester VIII. Mild hydrolysis gave the ketone IX which was cyclized to the hydroxypyridone X. The pentacyclic analog III of camptothecin (I) was then obtained by condensation of X with anthranilaldehyde. Alternatively, VIII could be reduced with $NaBH_4$ to the ketal carbinol XI which through MnO_2 treatment gave the aldehyde XII. The tricyclic ketone XIII derived from XII was condensed with anthranilaldehyde to afford the analog IV.

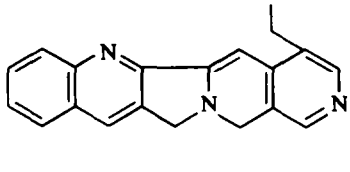
In a separate synthetic sequence, the ketoester XVI was cyclized to the tricyclic base XVII which was subsequently converted to the camptothecin analog V.

THE unusual pentacyclic alkaloid camptothecin (I),[1] isolated from *Camptotheca acuminata* (Nyssaceae), is probably of tryptophane-terpene origin.[2,3] The alkaloid incorporates a number of somewhat unusual structural features, such as an α-hydroxylactone and a pyridone system fused to a five-membered ring, which make for a challenging synthetic problem.

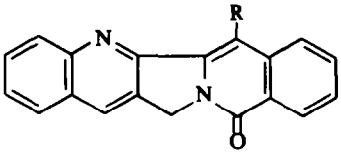
A short time ago Wenkert *et al.* described the preparation of the analog II of camptothecin.[2] It is the purpose of this paper to describe the synthesis of the pentacyclic



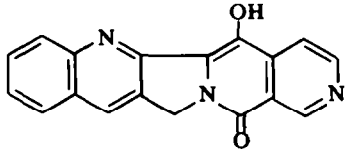
I



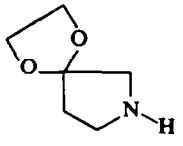
II



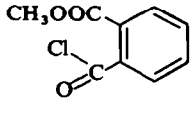
III: R = OH
IV: R = H



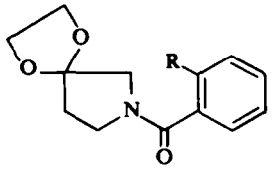
V



VI



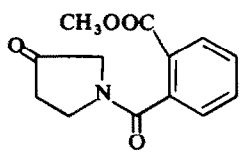
VII



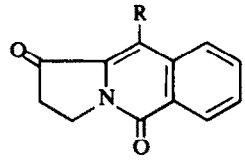
VIII: R = $COOCH_3$
XI: R = CH_2OH
XII: R = CHO

compounds III, IV, and V. The route utilized was appreciably different from that of Wenkert.

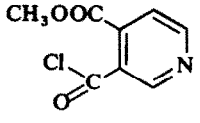
3-Pyrrolidinone is not a stable compound, and has never been isolated. A few N-substituted pyrrolidinones are known, however, and in addition 3-pyrrolidinone ethylene ketal (VI) has recently been prepared.[4] The latter compound was our key starting material. Condensation of VI with the acid chloride of phthalic acid monomethyl ester (VII) yielded the oily ketal aminoester VIII. Deketalization without concomitant hydrolysis of the ester function was achieved by means of polyphosphoric acid or preferably aqueous oxalic acid to afford the ketoester IX. It was expected that a compound such as IX could be easily cyclized to the hydroxypyridone X, and indeed such a reaction occurred by simply refluxing in diphenyl ether.



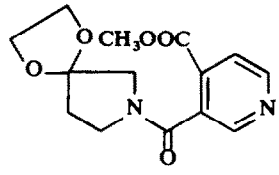
IX



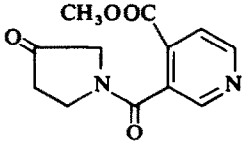
X: R = OH
XIII: R = H



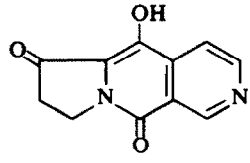
XIV



XV



XVI



XVII

Friedlander condensation of X with anthranilaldehyde in the presence of Triton B in ethanol, gave the greenish yellow crystalline analog III of camptothecin. In analogy with camptothecin, the compound was essentially insoluble in the common organic solvents, and was not even soluble enough in ethanol to allow for the determination of a reliable UV spectrum.

The above straightforward synthetic sequence was also extended to the preparation of the pentacyclic analog IV. Reduction of the oily ketal amidoester VIII with sodium borohydride afforded the crystalline ketal amidoalcohol XI. Oxidation with freshly prepared manganese dioxide in ethanol free chloroform provided a high yield of the corresponding oily aldehyde XII.[5] Facile deketalization as well as cyclization to the

crystalline tricyclic ketopyridone XIII was achieved in one step simply by treating with concentrated sulfuric acid. Finally, the Triton B catalyzed condensation of XII with anthranilaldehyde resulted in the formation of the desired pyridone IV as colorless needles.

In a variation on the above theme, the pentacyclic pyridine derivative V was also prepared. Treatment of 3-pyrrolidinone ethylene ketal (VI) with the known acid chloride of cinchomeronic acid γ-methyl ester (XIV)[6] gave the oily ketal amidoester XV which was selectively hydrolyzed to the crystalline ketoester XVI by means of aqueous oxalic acid.

Cyclization to the hydroxypyridone XVII could be achieved either with Triton B or with sodium ethoxide. Subsequent, condensation of the sodium salt of XPII with anthranilaldehyde in aqueous ethanol followed by acidification with acetic acid gave the desired base V. The yield in this Friedlander condensation was lower than was the case in the formation of the pentacyclic derivatives III and IV, essentially because of the amphoteric character of the tricyclic intermediate XVII and the resultant difficulty in the purification of the pentacyclic base V.

As a result of the present work and Wenkert's published results,[2] the main problem remaining towards a camptothecin total synthesis is the construction and incorporation of the δ-lactone ring as part of the pentacyclic system.

EXPERIMENTAL

Standard procedures. Mps were determined on a Nalge block. The IR spectra were taken on a Beckman IR-5A spectrophotometer using $CHCl_3$ as the solvent. All UV spectra were obtained on a Hitachi-Coleman 124 double-beam instrument. The NMR spectra of $CDCl_3$ solns, with TMS as internal standard, were recorded on a Varian A-60 unit. The mass spectral analyses were carried out using a Nuclide Associates single focus instrument. The elemental analyses were performed by Midwest Microlab, Inc., Indianopolis, Indiana.

3-*Pyrrolidinone ethylene ketal* (VI). The Viscontini procedure was modified as follows:[4]

A soln of 295 g of N-carbethoxy-3-pyrrolidinone ethylene ketal and 232 g KOH in a liter of water was refluxed gently with stirring overnight. The desired product settled out in the darker upper layer. It was separated and dissolved in $CHCl_3$. A second crop of product could be obtained by adding more KOH to the original reaction mixture. Drying over K_2CO_3 and evaporization of the solvent left a dark colored oil which was distilled *in vacuo* to give 147·4 g (80%) of the desired ketal, b.p. 53° at 0·4 mm.

Amide VIII *from 3-pyrrolidinone ethylene ketal and phthalic acid chloride monomethyl ester.* To a soln of 3·87 g of VI and 2·25 g K_2CO_3 in 50 ml water was added at 0° with stirring a soln of 5·94 g VII in 20 ml acetone over 5 min. Stirring was continued for 1 hr at room temp. The reaction mixture was extracted with $CHCl_3$, and the organic layer was washed with dil HCl, dried over $MgSO_4$, and evaporated to dryness. The oily product weighed 7·75 g and exhibited IR bands at 5·81 and 6·10 μ; NMR 3·88 δ singlet (O—Me). The compound was used in the next step without further purification.

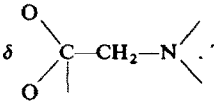
N-(o-*Carbomethoxybenzoyl*) 3-*pyrrolidinone* (IX). A soln of 1·45 g of VIII and 1·26 g oxalic acid in 20 ml water and 10 ml EtOH was refluxed overnight. The reaction mixture was extracted with $CHCl_3$, and the $CHCl_3$ soln washed with water and with $NaHCO_3$aq. After drying and evaporation, 1·16 g of the remaining oil crystallized. Recrystallization from benzene–hexane gave 1·01 g of colorless crystals, m.p. 97–98°. The IR spectrum had bands at 5·68, 5·76 and 6·12 μ; NMR singlet 3·88 δ (OMe). (Found: C, 62·99; H, 5·46. Calc. for $C_{13}H_{13}O_4N$: C, 63·15; H, 5·30%). A 2,4-dinitrophenylhydrazone derivative, recrystallized from EtOAc, melted 207°.

2,3-*Dihydro*-10-*hydroxypyrrolo*[1.2-b]*isoquinoline*-1,5-*dione* (X). To a boiling 50 ml portion of diphenyl ether was added 3·0 g of IX, and the mixture boiled for 20 min. After cooling, the soln was diluted with an equal volume of benzene, and extracted with 1·5 g NaOH in 50 ml water. The organic layer was extracted once more with 50 ml water, and the combined aqueous extracts were acidified with dil HCl. The yellow

crystalline compound was filtered off, washed with water, and dried. Decolorization with Norit and recrystallization from EtOH gave 2·0 g of light yellow needles m.p. 175–176°. IR bands at 5·89 and 6·08 μ; NMR triplets 2·88 δ and 4·14 δ (J = 8 c/s) (—CH_2—CH_2—); λ_{max}^{EtOH} 258 and 365 mμ (log ε 3·52 and 3·45). M^+ at m/e 215 (calc. 215). (Found: C, 67·12; H, 4·44. Calc. for $C_{12}H_9O_3N$: C, 66·97; H, 4·21%).

6-*Hydroxybenz*[6.7]*indolizino*[1.2-b]*quinolin*-11(13H)*one* (III). A mixture of 107 mg of X, 500 mg of a 40% methanolic soln of Triton B, 73 mg of freshly prepared anthranilaldehyde,[7] and 10 ml EtOH was heated to boiling for 6 hr. The EtOH was evaporated, and the reaction mixture acidified with dil HCl. The mixture was now extracted twice with $CHCl_3$. The $CHCl_3$ was evaporated, and the residue was triturated with ether. The ether was then decanted off to give 0·067 g of the desired product, yellow needles from pyridine, m.p. near 300° with dec. IR spectral bands at 6·14 and 6·25 μ. M^+ at m/e 300 (calc. 300). (Found: C, 75·66; H, 4·29. Calc. for $C_{19}H_{12}N_2O_2$: C, 75·99; H, 4·02%).

N-(o-*Hydroxymethylbenzoyl*)-3-*pyrrolidinone ethylene ketal* (XI). A mixture of 500 mg of IX and an equal weight of $NaBH_4$ in 15 ml EtOH was stirred overnight at room temp. The reaction mixture was decomposed with 5 ml water and extracted with $CHCl_3$. After evaporation of the $CHCl_3$ soln, 310 mg of crystals were obtained, m.p. 90° after recrystallization from benzene–hexane. IR bands at 2·93, and 6·2 μ; NMR singlet 4·56 δ (carbinol methylene). (Found: C, 64·13; H, 6·42. Calc. for $C_{14}H_{17}O_4N$: C, 63·86; H, 6·51%).

N-(o-*Formylbenzoyl*)-3-*pyrrolidinone ethylene ketal* (XII). A mixture consisting of 263 mg of XI, 2·63 g of freshly prepared MnO_2,[5] and 20 ml EtOH free $CHCl_3$, was stirred overnight. The reaction mixture was filtered, and the MnO_2 washed with warm $CHCl_3$. The organic solns were combined and evaporated. The residue consisted of 241 mg of an oil which gave a quantitative yield of a 2,4-dinitrophenylhydrazone derivative, m.p. 241–242°. IR bands at 5·89 and 6·14 μ; NMR singlet 4·01 δ  . The oil was used without further purification in the subsequent synthetic step.

2,3-*Dihydropyrrolo*[1.2-b]*isoquinoline*-1.5-*dione* (XIII). Into 9 ml conc. H_2SO_4 was dissolved 900 mg of XII, the process being exothermic. After standing overnight, the soln was diluted with ice and water, and the product extracted with $CHCl_3$. Evaporation of the solvent yielded 380 mg of yellow crystals, m.p. 186°. After recrystallization from EtOH and decolorization with Norit the colorless plates melted 191–192°. IR bands at 5·77, 6·07 and 6·24 μ; λ_{max}^{EtOH} 334 and 250 mμ (log ε 4·08 and 3·98); NMR triplets at 2·93 δ and 4·39 δ (J = 7·5 c/s) (—CH_2—CH_2). M^+ at m/e 199 for $C_{12}H_9O_2N$ (calc. 199). (Found: C, 72·50; H, 4·86. Calc. for $C_{12}H_9O_2N$: C, 72·35; H, 4·55%). A red 2,4-dinitrophenylhydrazone was obtained, which does not melt below 326°.

Benz[6.7]*indolizino*[1.2-b]*quinolin*-11(13H)-*one* (IV). A mixture of 119 mg of XIII, 79 mg anthranilaldehyde,[7] and 116 mg 40% methanolic Triton B, in 10 ml EtOH, was heated to mild reflux for 1 hr. Evaporation of the solvent gave 105 mg of yellow needles, m.p. 284°. A $CHCl_3$ soln of the compound was decolorized with Norit, and the solvent then evaporated. Recrystallization from EtOH gave long, colorless needles, m.p. 294°. IR bands at 6·02, and 6·15 μ; λ_{max}^{EtOH} 376, 363 and 283 mμ (log ε 4·52, 4·49 and 4·34); M^+ at m/e (calc. 284). (Found: C, 80·36; H, 4·31. Calc. for $C_{19}H_{12}ON_2$: C, 80·26; H, 4·25%).

Amide XV *from* 3-*pyrrolidinone ethylene ketal and cinchomeronic acid* γ-*methyl ester*. A soln of 9·28 g of the acid chloride of XIV[6] in 20 ml acetone was added to a mixture of 7·2 g K_2CO_3 in 100 ml water and 4·6 g of VI at 0° with stirring. Stirring was continued at room temp for 2 hr. The reaction mixture was extracted 3 times with $CHCl_3$, and the organic layer dried and evaporated. The residue consisted of 8·34 g of a yellow oil, pure by TLC, which was used without further purification in the next step. IR bands at 5·77 and 6·12 μ.

Selective hydrolysis of ketal amide XV *to ketone* XVI. A mixture consisting of 2·8 g of XV, 2·5 g oxalic acid, 10 ml EtOH and 20 ml water was heated to gentle boiling overnight. After extraction with $CHCl_3$, drying and evaporation, 2·3 g of crude ketone solidified, m.p. 130–132° after recrystallization from benzene–hexane. IR bands at 5·67, 5·76, and 6·12 μ; NMR singlet 3·91 δ (Me). (Found: C, 58·22; H, 5·01. Calc. for $C_{12}H_{12}O_4H_2$: C, 58·06; H, 4·87%). The compound gives a yellow 2,4-dinitrophenylhydrazone, m.p. 153° (MeOH).

Cyclization of ketone XVI *to* 7,8-*dihydro*-5-*hydroxypyrrolo*-[1.2-b][2.7]*naphthyridine*-6,10-*dione* (XVII). A mixture of 62 mg of XVI and 250 mg of a 40% MeOH Triton B soln in 10 ml MeOH was refluxed for 75 min. A soln of 50 mg of 2,4-dinitrophenylhydrazine in 10 ml MeOH and 2 ml conc HCl was then added, and the mixture heated for 2 min. A dark red 2,4-dinitrophenylhydrazone ppt appeared, 65 mg, m.p. 225–226°. (Found: C, 51·23; H, 2·85. Calc. for $C_{17}H_{12}O_6N_6$: C, 51·52; H, 3·05%).

5-*Hydroxyquino*[2′.3′:3.4]*pyrrolo*[1.2-b][2.7]*naphthyridin*-14(12H)-*one* (V). The sodium salt of XVII

was first prepared by dissolving the crude product XVII in EtOH and adding an equivalent amount of NaOEt in EtOH, then evaporating to dryness *in vacuo* at 40°. The crude Na salt, 1·88 g, was dissolved in 15 ml water and an ethanolic soln of 1·36 g anthranilaldehyde[7] was added. The mixture was refluxed for 5 hr. Evaporation of the solvent left 1·1 g of a new Na salt. The material was washed with MeOH, suspended in a mixture of 25 ml water and 30 ml $CHCl_3$, and acidified with AcOH. Some undissolved material remained. The $CHCl_3$ soln was separated, washed with $NaHCO_3$, and evaporated to dryness. The residue was the desired pentacyclic compound which is too insoluble for recrystallization from the usual organic solvents, m.p. near 300° (dec.). IR bands at 6·07, and 6·26 μ. M^+ at *m/e* 301 for $C_{18}H_{11}O_2N_3$ (calc. 301).

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