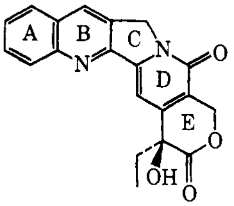
stituted cumenes currently in progress in the near future.

Dietmar Seyferth,* Ying Ming Cheng
Department of Chemistry, Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
Received June 18, 1971

The Total Synthesis of *dl*-Camptothecin

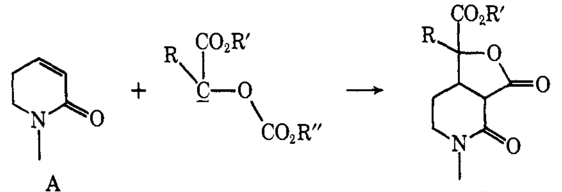
Sir:

Outstanding work by Wall and his associates[1] has led to the establishment of structure **1** for the antileukemic and antitumor alkaloid (+)-camptothecin, isolated from the tree *Camptotheca acuminata*, Nyssaceae, native to China.



1

We now wish to report the first total synthesis of (±)-camptothecin. The keystone of the synthesis was the possibility that one might effect the fusion of a lactone ring by addition–cyclization of the carbonate of an α-hydroxy ester to an α,β-unsaturated lactam (*e.g.*, A → B). Such an annelation would introduce all of the necessary atoms of the camptothecin E ring,

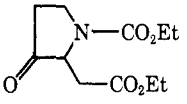


A

B

leaving only necessary changes in oxidation states to be performed. The approach proved to be very successful and the transformation A → B represents a new annelation of α,β-unsaturated carbonyl compounds which will probably prove of general utility.

The known[2] tricyclic quinoline acid **2**, mp 180–182° (reported[2] mp 184–186°), was obtained in $\sim$50% yield by the condensation of *o*-aminobenzaldehyde with the pyrrolidone **3**[3] in the presence of dilute sodium hydroxide. Hydrolysis of **2** by refluxing its solution in 50% hydriodic acid for 14 hr, followed by evaporation and subsequent esterification with ethanolic hydrogen chloride, afforded the amino ester **4** (isolated as an oil), ir 3.00 and 5.78 μ.[4] Reaction of **4** with the half-acid chloride of diethyl malonate[5] (benzene–aqueous sodium bicarbonate) gave the diesteramide **5**, ir 5.75 and 6.00 μ, which was cyclized on heating with 1.1 equiv of sodium ethoxide in 1:5 ethanol–toluene to the tetracyclic material **6**, mp 185–190°. Hydrolysis and decarboxylation of **6** occurred smoothly upon refluxing $\sim$4 hr with 10% aqueous acetic acid to give the β-ketoamide **7** in 72% overall yield from **2**. Infrared absorptions at 5.78 and 6.02 μ and a parent ion at *m/e* 252 support the structural assignment of **7**.



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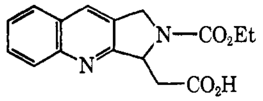

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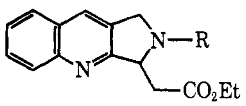
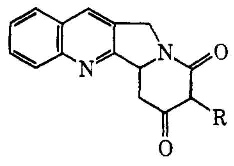
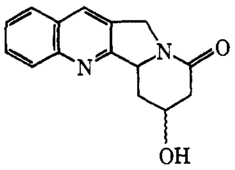


4, R = H
5, R = COCH₂CO₂Et



6, R = CO₂Et
7, R = H

Reduction of **7** with sodium borohydride in ethanol gave the β-hydroxy lactam **8**, mp 220–225° dec, in 95% yield. Treatment of **8** with refluxing acetic anhydride saturated with sodium acetate, under carefully deoxygenated conditions, gave in high yield the required unsaturated lactam **9**: mp 187–192°; *m/e* 236.0948; ir 6.00 and 6.04 μ.



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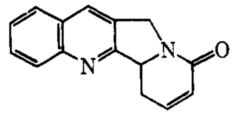

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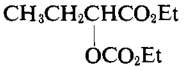
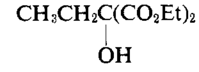
The other necessary component, the ester carbonate **10**, bp 110–111° (25 mm), was prepared in 95% yield from the reaction of ethyl α-hydroxybutyrate[6] with ethyl chloroformate in pyridine.



$\mathrm{CH_3CH_2\underset{OCO_2Et}{\underset{|}{C}}HCO_2Et}$

10



$\mathrm{CH_3CH_2\underset{OH}{\underset{|}{C}}(CO_2Et)_2}$

11

Formation of the anion of **10**, using 1 equiv of lithium diisopropylamide in tetrahydrofuran (THF) at room temperature, resulted in an expected facile rearrangement to the tartronic ester **11**. The anion of **10** proved, however, to be moderately stable at Dry Ice–acetone temperature; when a solution of the unsaturated lactam **9** in THF was added rapidly to a solution of 5 equiv of the lithium salt of **10**, generated in THF at −70°, yields as high as 85% of the pentacyclic lactone **12** (isolated as a glass) could be realized. Infrared absorption at 5.55, 5.72, and 6.00 μ and a parent ion at *m/e* 394 support the structural assignment of **12**. The overall yield from diethyl maleate (the precursor of **3**) to the lactam **12** approaches 20%. Dehydrogenation of **12** with either dichlorodicyanoquinone (DDQ) in refluxing *p*-dioxane, or lead tetraacetate in glacial acetic acid at room temperature, gave in high yield the pyridone **13**, mp 285–289° dec, *m/e* 390.1217, which has all the carbon, oxygen, and nitrogen atoms of the desired camptothecin.

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(1) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. I. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, **88**, 3888 (1966).

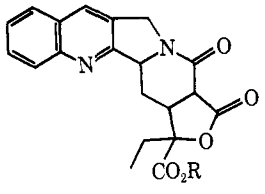
(2) J. A. Kepler, M. C. Wani, J. M. McNaull, M. E. Wall, and S. J. Levine, *J. Org. Chem.*, **34**, 3853 (1969).

(3) J. W. Clark-Lewis and P. I. Mortimer, *J. Chem. Soc.*, 189 (1961).

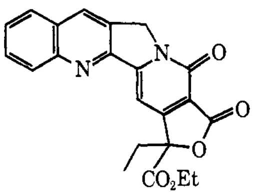
(4) All intermediates had ir and nmr spectra in agreement with the assigned structures. Key compounds were further characterized by exact masses and/or low-resolution mass spectra, as indicated in the text.

(5) L. Gol'dfarb, S. Z. Taits, and V. N. Bulgakova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 7, 1299 (1963).

(6) L. Schreiner, *Justus Liebigs Ann. Chem.*, **197**, 1 (1879).

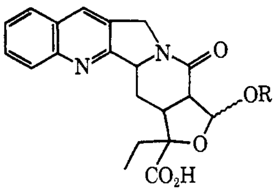


12, R = Et
14, R = H

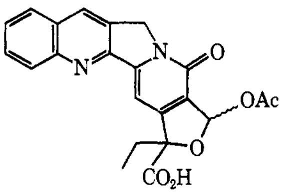


13

Hydrolysis of the ethyl ester function in **12** was accomplished in high yield by refluxing ~2 hr with concentrated hydrochloric acid. The carboxylic acid **14**, isolated as the crude amine hydrochloride, was treated with excess sodium borohydride in ethanol at room temperature (20 hr), to form the hemiacetal **15**. Reaction of **15** with excess acetic anhydride in pyridine resulted in the formation of acetylated hemiacetal **16**, ir 3.0–4.0, 5.75, and 6.05 μ. Dehydrogenation of **16** with 2 equiv of DDQ in refluxing *p*-dioxane (4 hr) gave the pyridone **17**, which was converted to *dl*-camptothecin (**1**) by successive treatment with (1) 0.1 *M* aqueous sodium hydroxide (0.5 hr, room temperature), followed by (2) addition of excess sodium borohydride (room temperature, 6 hr), and finally (3) acidification with dilute hydrochloric acid, followed by chromatography (silica gel–chloroform) and crystallization from acetonitrile–methanol. The tlc properties, low-resolution mass spectra, and 300-MHz spectra (in CF_3CO_2H) of synthetic (±)-camptothecin, mp 287–288° dec, *m/e* 348.1098, were identical with those of the natural material.[7,8] The attempted resolution of *dl*-camptothecin is currently in progress.



15, R = H
16, R = Ac



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Acknowledgment. We wish to thank the National Science Foundation and the National Institutes of Health for their support of this work.

[7] We wish to thank Mr. L. Cary of Varian Associates, Palo Alto, Calif., for taking the 300-MHz nmr spectra. The high-resolution mass spectra were obtained through the courtesy of Hoffmann La Roche, Inc., Nutley, N. J.

[8] A sample of authentic natural camptothecin was kindly supplied by Dr. Robert B. Ing of the Cancer Chemotherapy National Service Center, National Cancer Institute.

Gilbert Stork,* Arthur G. Schultz
Department of Chemistry, Columbia University
New York, New York 10027

Received April 28, 1971

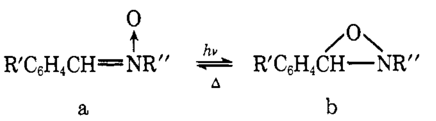
Orbital Symmetry Control in the Nitrone–Oxaziridine System. Nitrone Photostationary States

Sir:

Recently the orbital symmetry rules[1] have been shown to apply to heteroatom systems such as nitrone thermal cycloaddition reactions[2] and the thermal and photochemical aziridine ring cleavage at the C–C bond.[3] The concerted photocyclization is disrotatory and the reverse thermal cleavage is conrotatory in these molecules with four π electrons.[1]

In contrast to the azomethine ylide–aziridine system, the stereochemistry of the nitrone photocyclization to oxaziridine can only be observed on carbon and nitrogen atoms because the oxygen atom has lone-pair electrons instead of substituents. For the reverse thermal ring opening of oxaziridine to the nitrone, the two possible conrotatory motions of C–O bond cleavage should result in a mixture of the cis and trans isomers of the nitrone,[4] in contrast to the photoclosure which should be stereospecific.

Boyd, *et al.*,[5] recently reported the formation of mixtures of *cis*- and *trans*-oxaziridines from the irradiation of *trans*-nitrones. However, there has been some evidence for the stereospecific formation of oxaziridine from nitrones.[6] We wish to report our results obtained from the photolysis of several nitrones at −60°,[7] including IIIa and IVa which were studied by Boyd, *et al.*,[5] at room temperature, and the thermolysis of Ib at −8°. Under these conditions thermal isomerization of the oxaziridine and nitrone isomers was suppressed.



$$\underset{\text{a}}{R'C_6H_4CH{=}\overset{\overset{O}{\uparrow}}{N}R''} \underset{\Delta}{\overset{h\nu}{\rightleftharpoons}} \underset{\text{b}}{R'C_6H_4\overset{\quad O \quad}{CH{-}NR''}}$$

I, R′ = $(CH_3)_2N$; R″ = CH_3
II, R′ = H; R″ = CH_3
III, R′ = NO_2; R″ = CH_3
IV, R′ = NO_2; R″ = CH_2CH_3

The nmr spectra of these nitrones at −60° indicated the presence of only one nitrone isomer, the trans configuration as discussed by Koyano and Suzuki.[8] Irradiation of *trans*-Ia and -IIa at −60° in CD_3OD and $CDCl_3$ yielded exclusively *trans*-oxaziridines,[9] as observed by nmr at −60°. However, under the same conditions in CD_3OD, *trans*-IIIa and -IVa yielded a mixture of 69% *cis*–31% *trans*-oxaziridines, which was in contrast to the predominantly *trans*-oxaziridines found by Boyd, *et al.*[5] With successive partial irradiations of *trans*-IVa at −60°, the presence of *cis*-IVa was demonstrated by nmr,[10] and a photostationary state of 37% *cis*–63% *trans*-IVa was reached at approximately 15% conversion to oxaziridines. The *cis*-IVa rapidly

[1] R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1969.

[2] R. Huisgen, H. Seidl, and I. Brüning, *Chem. Ber.*, **102**, 1102 (1969).

[3] R. Huisgen, W. Scheer, and H. Huber, *J. Amer. Chem. Soc.*, **89**, 1753 (1967).

[4] J. S. Splitter and M. Calvin, *J. Org. Chem.*, **30**, 3427 (1965). An oxaziridine was found to cleave at least partially to a *cis*-nitrone.

[5] D. R. Boyd, W. Jennings, and R. Spratt, *Chem. Commun.*, 745 (1970). Photochemical or thermal equilibration of *cis*- and *trans*-IIIb and -IVb was shown to occur only on prolonged irradiation or on prolonged heating at 130°.

[6] (a) H. Ono, Ph.D. Dissertation, University of California, Berkeley, Calif., 1969; (b) G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, **70**, 231 (1970).

[7] Solutions (10^{-2} *M*) were irradiated in the nmr tube in the presence of oxygen with a Hanovia 450-W medium-pressure mercury lamp, Pyrex filter. The oxaziridines remained unchanged under these conditions of irradiation. Nmr spectra were recorded on a Varian 220-MHz spectrophotometer; uv spectra on a Cary-14 spectrophotometer.

[8] K. Koyano and H. Suzuki, *Tetrahedron Lett.*, 1859 (1968); *Bull. Chem. Soc. Jap.*, **42**, 3306 (1969). These authors presented nmr evidence which was used to distinguish *cis*- and *trans*-nitrone isomers.

[9] According to the assignment of D. Jerina, D. Boyd, L. Paolillo, and E. Becker, *Tetrahedron Lett.*, 1483 (1970).

[10] *trans*-IVa: α-CH, τ 1.82; $-CH_3$, τ 8.49 (t). *cis*-IVa: α-CH, τ 1.75; $-CH_3$, τ 8.46 (t).