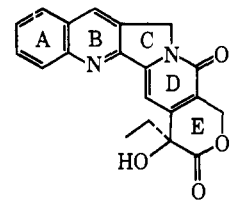
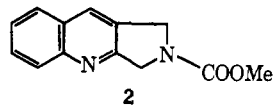
Dehydrogenation of **8** with dichlorodicyanoquinone in refluxing *p*-dioxane (4 hr) proceeded in high yield to give the pyridone **10**[16] (mp >310°). Reduction of **10**



1



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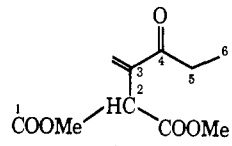

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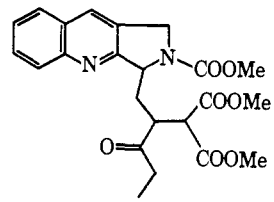

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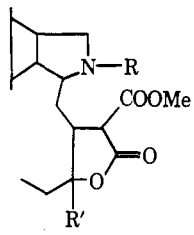
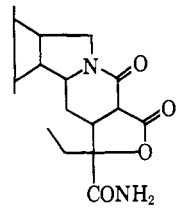


5, R = COOMe; R′ = CN
6, R = COOMe; R′ = $CONH_2$
7, R = H; R′ = $CONH_2$



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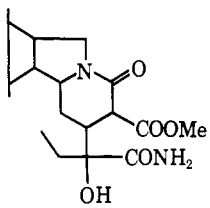

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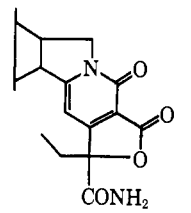

10

with lithium borohydride in refluxing (6 hr) tetrahydrofuran, followed by acidification with dilute hydrochloric acid and heating (0.5 hr) on a steam bath, gave *dl*-camptothecin whose tlc properties and low-resolution mass spectrum were identical with those of the natural material.

Acknowledgments. We wish to thank Dr. David Rosenthal and Mr. Fred Williams of the Research Triangle Center for Mass Spectrometry for mass spectral data. Their work was supported by the Biotechnology Resources Branch, Division of Research Resources, National Institutes of Health, under Grant No. PR-330. We wish also to thank Mr. J. B. Thompson for expert technical assistance. Dr. Campbell was supported by NIH Grant No. CA 08673-05.

(16) For preparative purposes the sequence of reactions leading to the synthesis of **10** from **4** could be accomplished without chromatography.

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Plant Antitumor Agents. X. The Total Synthesis of a Ring DE Analog of Camptothecin[1]

Sir:

Since the initial communication from this laboratory on the isolation, structure, and antitumor activity of the novel alkaloid, camptothecin[2] (**1**), there has been much interest in the chemistry and synthesis of this interesting compound culminating in three recent total syntheses.[1,3,4] Several years ago Wall[5] reviewed the structure–function activity in the camptothecin series and showed that the α-hydroxy lactone moiety in camptothecin was an absolute requirement for antitumor activity. In an attempt to delineate the parameters of the molecule required for activity we have instituted a systematic approach to the synthesis of camptothecin analogs which will incorporate the requisite α-hydroxy lactone moiety. This report presents the first total synthesis of a ring DE analog **13** which has also potentialities for further elaboration to **1** and also describes the preparation of intermediates useful for a variety of syntheses in the camptothecin series.

3-Pentanone was brominated in aqueous bromine in the presence of potassium chlorate[6] to yield the known 2-bromo-3-pentanone,[7] which on treatment with potassium dimethyl malonate in dimethylformamide yielded methyl 2-carbomethoxy-3-methyl-4-oxohexanoate[8] (**2**), bp 69–70° (0.005 mm), in 85% yield. Bromination of **2** as the sodium salt under special anionic conditions[9] in the presence of sodium hydride in dimethoxyethane smoothly yielded the 2-bromo ketone[10] **3**, which without purification[11] was immediately dehydrobrominated in refluxing pyridine, giving a mixture of the exo olefin **4** and the endo olefin **5**, ratio 65/35[12] (bp 79–82° (0.02 mm)) in 50% yield from **2**. The olefinic mixture was suitable for the next step which involved a Michael condensation of nitromethane with the olefin mixture in the presence of Triton B in re-

(1) Previous paper in this series: M. C. Wani, H. F. Campbell, G. A. Brine, J. A. Kepler, M. E. Wall, and S. G. Levine, *J. Amer. Chem. Soc.*, **94**, 3631 (1972).

(2) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *ibid.*, **88**, 3888 (1966).

(3) G. Stork and A. Schultz, *ibid.*, **93**, 4074 (1971).

(4) R. Volkmann, S. Danishefsky, J. Eggler, and D. M. Solomon, *ibid.*, **93**, 5576 (1971).

(5) M. E. Wall, Abstracts, 4th International Symposium on the Biochemistry and Physiology of Alkaloids, Halle, DDR, Academic Press, Berlin, 1969, p 77.

(6) J. R. Catch, D. F. Elliott, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 272 (1948).

(7) H. Pauly, *Chem. Ber.* **34**, 1771 (1901).

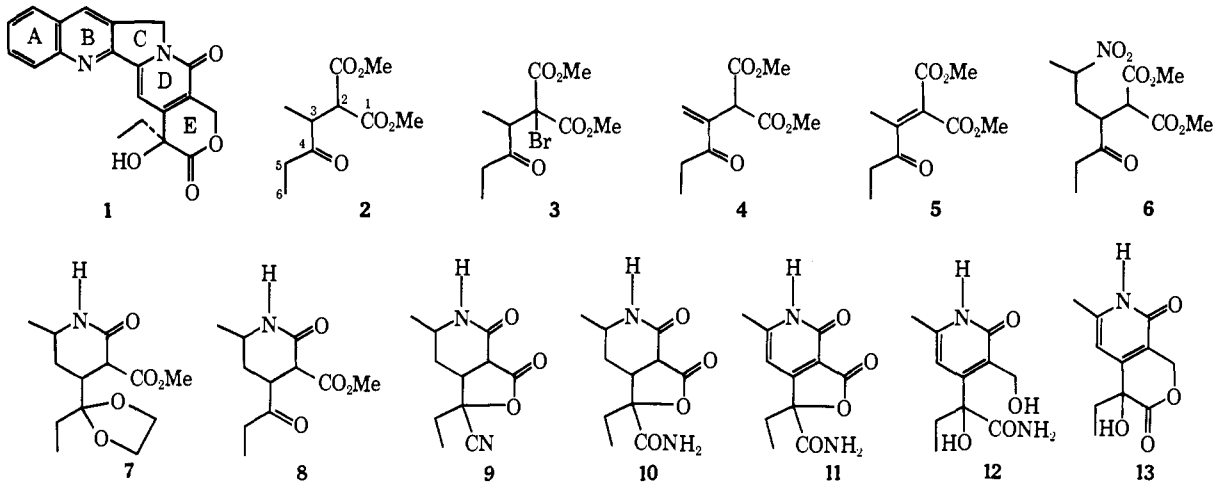
(8) The ir, nmr, and high-resolution mass spectra of all new compounds are consistent with assigned structures.

(9) Specific reaction conditions: a solution of **3** in dry dimethoxyethane (DME) is added to a 15–20% excess of sodium hydride in DME chilled in an ice bath. After hydrogen evolution ceases, an equivalent quantity of bromine in DME is added dropwise. As soon as bromine color persists, the addition of bromine is stopped, salts are filtered, and solvent is evaporated *in vacuo* at room temperature.

(10) For our purposes either the 2-bromo or 3-bromo derivative of **2** was suitable for conversion to the requisite olefin **4** or **5**. Under standard acidic bromination conditions only the undesired 5-bromo derivative was obtained contrary to the general expectation that substitution of bromine adjacent to a ketone takes place on the most substituted carbon atom (*cf.* H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 146–147). In this case steric hindrance at position 3 may rationalize the observed findings.

(11) The bromo ketone **3** was unstable and could not be distilled without extensive decomposition.

(12) The olefinic mixture could not be separated by fractional distillation; the ratio of the isomers was readily determined by pmr spectroscopy.



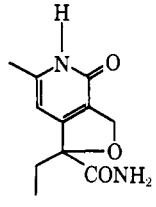
fluxing ether, giving a 90% yield of **6**. Prior to reductive cyclization, the ethylene ketal of **6** was prepared[13] which was then reduced with hydrogen–platinum oxide at 50 psi to give **7** in 50% yield from **6** (crystals from EtOAc–Et_2O, mp 134–136°). Removal of the ketal with trityl fluoroborate[14] in methylene chloride gave **8** as an oil in 90% yield. Treatment of **8** with liquid hydrogen cyanide gave the cyanolactone **9** in 50% yield[1,15] which on hydrolysis in anhydrous HCl–MeOH gave the amide lactone **10** in 98% yield. Dehydrogenation of **10** in the presence of dichlorodicyanoquinone in refluxing dioxane gave a quantitative yield of the pyridone **11** (crystals from MeOH–$CHCl_3$, mp 262–265° dec). Reduction of **11** with lithium borohydride in refluxing THF formed the corresponding diol **12** as a borate ester which was not isolated. Heating **12** with HCl gave the desired camptothecin analog **13** (crystals from CH_2Cl_2, mp 242–243°) in 40% yield from **11**.[16] Compound **13** is a weak but not inactive cytotoxic agent; it is about 1/100th the potency of **1**.[17]

(13) It was found that direct reduction of **6** resulted in formation of the Δ^1-pyrroline *N*-oxide. The 4-oxo moiety of **6** was unreactive under standard ketalization conditions; however, ethylene glycol in the presence of $BF_3 \cdot Et_2O$ at room temperature gave a 90% yield of the desired ketal.

(14) D. H. R. Barton, P. D. Magnus, G. Smith, and D. Zurr, *J. Chem. Soc. D*, 861 (1971).

(15) About 50% unreacted starting material 8 was found which could be readily separated from **9** by chromatography and recycled.

(16) The major by-product in this reaction is the ether



which could be formed either directly from **11** by hydride reduction or during subsequent acid treatment of **12**. This reaction is being further investigated.

(17) Cytotoxicity was determined by the procedures described in *Cancer Chemother. Rep.*, **25**, 1 (1962). The values for **1** and **13** determined at the same time were, respectively, 3×10^{-2} and 4×10^{0}. Potency is determined in terms of the number of micrograms required to give an ED_{50} response; the lower the value, the more potent the compound. The data would indicate that **1** was approximately 100 times more potent than **13**. Allowing for the fact that **13** was racemic and assuming that one of the racemates was inactive, **13** might be regarded as about 1/50th as active as **1** in this assay. The relationship between cytotoxicity and antitumor or antileukemia activity is not, as yet, well established. It is planned to test **13** in P-388 and L-1210 mouse leukemia as soon as a sufficient quantity has been prepared.

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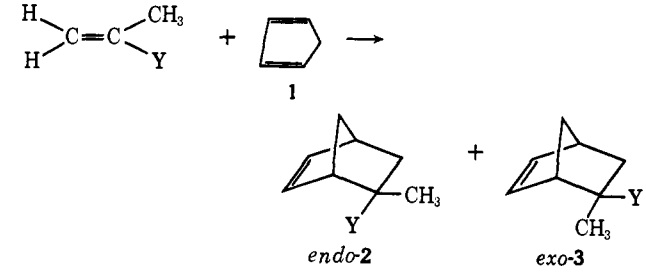
The Role of Attractive Interactions in Endo–Exo Stereoselectivities of Diels–Alder Reactions

Sir:

In the study of Diels–Alder reactions of methyl-substituted dienophiles with cyclopentadiene (**1**), we found that the methyl group shows a greater tendency toward endo orientation than most of the electron-withdrawing polar substituents Y, thereby leading to preferential formation of exo Y adducts (**3**).[1] We



Y = CN, $COOCH_3$, $COCH_3$, CHO, COOH

wish to report evidence that the attractive van der Waals forces between the methyl group in dienophiles and the unsaturated center of dienes play a significant role in the stabilization of the exo Y transition state.

(1) Y. Kobuke, T. Fueno, and J. Furukawa, *J. Amer. Chem. Soc.*, **92**, 6548 (1970).