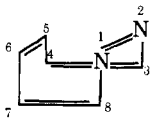
clearly arise by initial valence tautomerization to the bicyclo[4.2.0]octatrienes **4–8**, followed by cleavage to the aromatic radical cations of benzene, pyridine, and pyridazine. The formation of pyridine as the major fragment is in accord with energy considerations. Thus, the bond isomer **3** should be greatly preferred to **3a**[11] and it should cyclize preferentially to valence isomer **5**. 1,2-Diazacycloocta-2,4,6,8-tetraene is stable in solution



3a

below room temperature and decomposes to tars slowly in solution at room temperature and rapidly in the neat.

The photochemical decomposition of **1** stands in stark contrast to the thermal decomposition. Scheme II provides a rationale for these observations. Note that benzene arises only indirectly as a secondary photolysis product of **3**. Indeed, support for this interpretation arises from consideration of the product ratios as a function of photolysis time (*vide supra*). Formation of benzene as the exclusive photoproduct of **3** demands the intermediacy of the bicyclic isomer **4** which subsequently loses nitrogen presumably also by a photochemical step.[12,13]

Thus the photoexcited state of **1** dissipates energy to only a minor extent by nitrogen disengagement to diradical **9**. This species either collapses to Dewar benzene or diradical **10**, the precursor of benzvalene.[14] The major process for energy dissipation is the allowed 2 + 2 reversion to the diazabicyclo[4.2.0]octatriene (**8**). Even at −78° this compound rearranges to **3** in striking contrast to bicyclo[4.2.0]octa-2,4,7-triene which is quite stable at this temperature.[15] The lower activation energy for the rearrangement of **8** to **3** compared to the all-carbon system presumably reflects the stability gained in terms of bond energies in generating the azine moiety. A concerted pathway is conceivable for the conversion of **1** to the bond shift isomer of **3** (*i.e.*, **3a**); this would be a formal $[_{\sigma}2_s + {}_{\sigma}2_a + {}_{\sigma}2_a]$ cycloreversion, photochemically forbidden by orbital symmetry considerations.

Acknowledgment. We wish to express our appreciation to the National Science Foundation for their generous support of our programs.

(11) Similar behavior has been noted for derivatives of 1,2-diazacycloocta-1,3,7-triene which prefer to exist as 3,4-diazabicyclo[4.2.0]-octa-2,4-dienes: G. Maier and F. Seidler, *Chem. Ber.*, **99**, 1236 (1966).

(12) Compare the photolysis of cyclooctatetraene and bicyclo[4.2.0]-octa-2,4,7-triene to benzene and acetylene: H. E. Zimmerman and H. Iwamura, *J. Amer. Chem. Soc.*, **92**, 2015 (1970), and references therein. For azine photolysis see R. W. Brinkley, *J. Org. Chem.*, **34**, 931 (1969).

(13) $\Delta^{1,2}$-Diazetines have been shown to be remarkably stable thermally: N. Rieber, J. Alberts, J. A. Lipsky, and D. M. Lemal, *J. Amer. Chem. Soc.*, **91**, 5668 (1969).

(14) This process is comparable to the presumed intermediates in the di-π-methane rearrangement. For a leading reference, see H. E. Zimmerman and A. C. Pratt, *ibid.*, **92**, 6267, 6259, 1407, 1409 (1970).

(15) E. Vogel, H. Kiefer, and W. R. Roth, *Angew. Chem.*, 76, 432 (1964).

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Nucleophilic Additions to Allenes. A New Synthesis of α-Pyridones

Sir:

A 1,3-dicarboalkoxyallene might be expected to serve as a powerful receptor toward Michael addition since the resultant anion would be a highly stabilized glutaconate system.[1,2] Surprisingly, the synthetic applications of such allenes[3] have been limited to Diels–Alder reactions.[4] With a total synthesis of camptothecin[5] as our orienting goal, we studied the feasibility and utility of Michael additions to compound I (R = Et).[6–8]

Condensation of equimolar quantities of I with ethyl *trans*-β-aminocrotonate in the presence of 1 equiv of triethylamine gives an adduct which, when heated in 1:1 acetic acid–toluene at 100 for 5 hr, gives pyridone III, mp 128–130°, in 70% overall yield. The structure of III follows from its monohydrolysis product (2 equiv of NaOH ethanol, reflux 3 hr) IV which smoothly decarboxylates at its melting point (195°) to give the known[9] 4,6-dimethyl-5-carbethoxy-α-pyridone (V). Interestingly, treatment of IV with chloromethyl methyl ether in acetic acid gave lactone VI, mp 233–235°,[10,11] in 31% yield. While we have not carried compound VI further, the demonstration of the feasibility of this type of insertion played a crucial role in formulating a strategy for synthesizing camptothecin.[12]

Allene I is also attacked by monoenamines of β-diketones. Thus, condensation of 4-aminopent-3-en-4-one[13] with I using the conditions described above gave VIII, mp 141–143°,[10,11] in 48% yield. This new synthesis of α-pyridones may be executed with preservation of acid-sensitive functionality. Carbomethoxylation of 3,3-diethoxybutanone[14] (sodium hydride–dimethyl carbonate–benzene) gives β-keto ester VIII,[10,11] which is converted in 50% yield to enamine IX. Condensation of the latter with allene I in ethanol containing 1 equiv of triethylamine at room temperature gives pyridone X, mp 123–127°,[10,11,15] in 36% yield. Half-saponi-

(1) The full stabilization of the glutaconate system at the level of the transition state of addition requires a rotation about the C_2–C_3 bond. This argument has already been set forth in the context of the addition of amines to 1-cyanoallene.[2]

(2) P. M. Greaves and S. R. Landor, *Chem. Commun.*, 322 (1966).

(3) For a most unusual reaction in the addition of 1-morpholinocyclohexane with cyanoallene, see W. Reid and W. Kaepeller, *Justus Liebigs Ann. Chem.*, **687**, 183 (1965).

(4) G. Büchi and J. A. Carlson, *J. Amer. Chem. Soc.*, **90**, 5336 (1968).

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

(6) The correct structures of the parent diacid and dimethyl ester were established by E. R. H. Jones, G. H. Mansfield, and M. C. Whiting, *J. Chem. Soc.*, 3208 (1954).

(7) The method of preparing I was that of J. C. Craig and M. Moyle, *ibid.*, 5356 (1963).

(8) A new route to derivatives of allenedicarboxylic acid has recently been developed by J. Ficini and J. Pouliquen, *J. Amer. Chem. Soc.*, **93**, 3295 (1971).

(9) J. N. Collie, *J. Chem. Soc.*, 297 (1897).

(10) Molecular formulas were verified by either combustion analyses or in the case of compounds III–VII by high-resolution mass spectrometry.

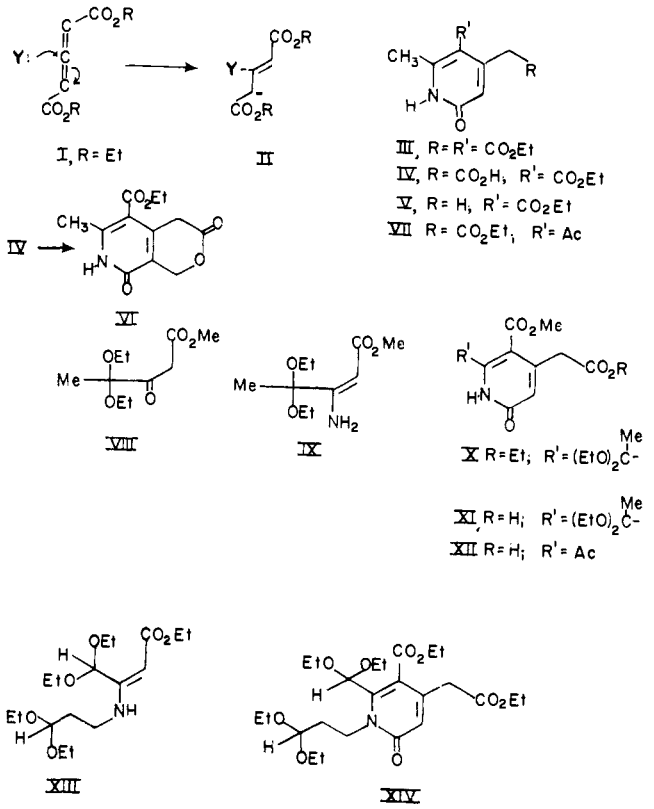
(11) The assigned structure is consistent with the ir, nmr, and mass spectra of the product.

(12) R. Volkmann, S. Danishefsky, J. Eggler, and D. M. Solomon, *J. Amer. Chem. Soc.*, **93**, 5576 (1971).

(13) For a related reaction of this enamine with dimethyl acetylenedicarboxylate, see: C. Heubner, L. Dorfman, M. M. Robinson, E. Donoghue, and P. Straehen, *J. Org. Chem.*, **28**, 3134 (1963).

(14) For ethoxyalylation, see: H. Muxfeldt, M. Weigele, and V. Rheenen, *ibid.*, **30**, 3573 (1965).

(15) The use of hydroxylic solvent tends to promote one-step cycliza-



fication affords acid XI,[10,11] mp 195–199° dec, which is smoothly converted (TsOH–acetone–H_2O, room temperature) to 4-carboxy-5-carbomethoxy-6-acetyl-α-pyridone (XII),[10,11] mp 195–199° dec.

The synthesis may be applied to the construction of N-substituted α-pyridones. Treatment of ethyl 3-amino-4,4-diethoxycrotonate[16] (XIII) with allene I in ethanol containing triethylamine gives an adduct which cyclizes through the action of sodium ethoxide to give pyridone XIV[10,11] in 40% yield.

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tion to the pyridone though in some cases subsequent treatment with strong base is necessary. The precise structural factors which favor one-step cyclization (*cf.* enamines VIII and XIII) have not as yet been defined.

(16) R. Bloch, *Ann. Chim.*, **10**, 583 (1965).

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A Total Synthesis of *dl*-Camptothecin

Sir:

Structure XIV was assigned by Wall and coworkers to the alkaloid camptothecin.[1] Early reports ascribing promising antitumor properties to camptothecin[2] coupled with its difficult availability have generated considerable enthusiasm for assembling this compound in the laboratory. This synthetic challenge has been accepted in a variety of laboratories[3a–j] culminating in the first total synthesis of Stork and Schultz.[4] In this paper we report a total synthesis of *dl*-camptothecin using a new pyridone synthesis which we have recently developed.[5]

Enamino diester I[6] (bp 135–138° (0.1 mm)) was produced in 67% yield from the uncatalyzed addition of β-aminopropionaldehyde diethyl acetal to dicarbomethoxyacetylene in ether. Condensation of I with dicarbethoxyallene[5] in methanol containing 1 equiv of triethylamine at room temperature gave the pyridone triester, II,[6,7] mp 50–52°, in 45% yield which, upon deacetalization (HCl–acetone–water), gave quantitatively aldehyde III,[6,7] mp 86–87°. The latter was transformed by oxidation (CrO_3–H_2SO_4–acetone–water) to the acid IV[6] and thence by esterification and transesterification (methanolic HCl, room temperature) to the tetramethyl ester V,[6,7] mp 89–91°, in 86% yield.

The C ring of camptothecin was now established by a Dieckmann closure[8] (3 equiv of sodium methoxide–methanol, reflux 12 hr). These conditions led, reproducibly, in 81% yield to the enolic acid ester VI,[6] 195–197° dec, through some, as yet undefined, hydrolytic pathway. The latter is most readily characterized through its methyl ester VII,[6,7] mp 178–180°. Hydrolysis and selective decarboxylation of VI (4% aqueous HCl, reflux 3 hr) gave in crude form keto acid VIII[6] which was subjected directly to Friedlander condensation (3 equiv of sodium hydroxide, 2 equiv of *o*-aminobenzaldehyde–water, reflux 36 hr). These conditions sufficed to hydrolyze the carbomethoxyl group at the 5 positions of the pyridone ring, and afforded the tetracyclic diacid IX,[6] mp >310°. Without purification this was converted into acid ester X, mp >300° dec, which was decarboxylated by pyrolysis (239–244°, 4 min) over 0.3 equiv of cuprous oxide to give the tetracyclic methyl ester XI,[6,7] mp 209–211°, in 29% yield from VI. Ethylation of XI (1 equiv of sodium hydride dimethoxyethane, excess ethyl iodide (room

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

(2) J. A. Gotlieb, A. M. Quarino, J. B. Call, V. T. Oliverio, and J. B. Block, *Cancer Chemother. Rep.*, **54**, 461 (1970).

(3) (a) E. Wenkert, K. G. Dave, R. G. Leives, and P. W. Sprague, *J. Amer. Chem. Soc.*, **89**, 6471 (1967); (b) J. A. Keppler, M. C. Wani, J. N. McNaull, M. E. Wall, and S. G. Levine, *J. Org. Chem.*, **34**, 3853 (1969); (c) M. C. Wani, J. A. Keppler, J. B. Thompson, M. E. Wall, and S. G. Levine, *Chem. Commun.*, 404 (1970); (d) M. Shamma and L. Novak, *Tetrahedron*, **25**, 2275 (1969); (e) M. Shamma and L. Novak, *Collect. Czech. Chem. Commun.*, **35**, 3280 (1970); (f) T. Kametani, J. Nemoto, H. Takeda, and S. Takano, *Tetrahedron*, **26**, 5753 (1970); (g) E. Winterfeldt and H. Radunz, *Chem. Commun.*, 374 (1971); (h) T. K. Lias, W. H. Nyberg, and C. C. Cheng, *J. Heterocycl. Chem.*, **8**, 373 (1971); (i) M. Wojcik, Ph.D. Thesis, Harvard University, 1970; (j) A. S. Kende, R. W. Draper, I. Kubo, and M. Joyeux, Abstracts, 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, No. ORGN 10.

(4) G. Stork and A. Schultz, *J. Amer. Chem. Soc.*, **93**, 4034 (1971).

(5) S. Danishefsky, S. J. Etheredge, R. Volkmann, J. Eggler, and J. Quick, *J. Amer. Chem. Soc.*, **93**, 5575 (1971).

(6) The nmr and mass spectra of this compound are consistent with the assigned structure.

(7) Carbon, hydrogen, and nitrogen combustion analyses within 0.3% of theory were obtained for this compound.

(8) Clearly some subtle and, as yet undefined, factors are involved in the success of this reaction relative to β elimination of the pyridone group [*cf.* ref 3a and 3i]. We encountered the β elimination problem in the reaction of pyrrolidine on aldehyde III. This gave, cleanly, 4-carbethoxymethyl-5,6-dicarbomethoxy-α-pyridone,[6,7] mp 105–106°.