

it by an independent route¹² and demonstrating it to be unreactive under the reaction conditions employed, thus we suggest the intermediate is **5**. Unfortunately, all of our attempts to synthesize **5** have failed, as indeed did the attempts of others¹⁵⁻¹⁷ in trying to prepare this and similar intermediates. However its accepted¹⁵⁻¹⁷ chemistry is consistent with that required by this mechanism.

Acknowledgment. We thank Dr. Gary Gray for helpful discussions. We also thank the Natural Sciences and Engineering Research Council of Canada for support of this work.

(12) Nitration ($\text{HNO}_3/\text{H}_2\text{SO}_4$) of *p*-nitrobenzyl chloride gave 2,4-dinitrobenzyl chloride that was converted into 2,4-dinitrobenzyl methyl sulfide by treatment with methyl mercaptan essentially according to ref 13. Oxidation of this product to 2,4-dinitrobenzyl methyl sulfoxide was achieved with *m*-chloroperbenzoic acid essentially according to ref 14. Satisfactory spectral and analytical data were obtained for all compounds.

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Cyclic Conjugated Eneidyne Related to Calicheamicins and Esperamicins: Calculations, Synthesis, and Properties

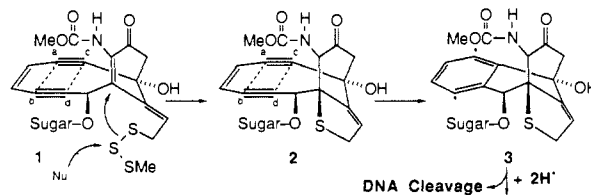
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Received February 25, 1988

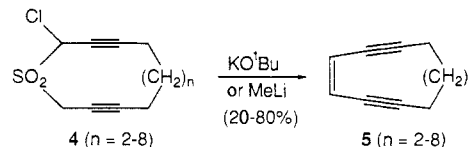
A series of novel naturally occurring compounds with powerful biological properties, the calicheamicins, were recently isolated by Lederle scientists.¹ This new class of compounds isolated from *Micromonospora echinospora ssp. calichensis*, includes calicheamicin γ_{1A} (**1**), whose structure was determined on the basis of chemical and spectroscopic data and an X-ray crystallographic analysis on a partial structure. A similar group of natural products, the esperamicins, was simultaneously reported by a Bristol-Myers group.² The phenomenal biological profile of the calicheamicins and esperamicins includes the following: (a) subpicogram potency against Gram positive bacteria, (b) activity in the biochemical induction assay at very low concentrations, (c) high potency against a number of animal tumor models, and (d) induction of double-stranded DNA cleavage with minimal concurrent single-stranded breakage. A fascinating hypothesis regarding the mode of action of these compounds has been advanced.^{1,2} According to this mechanism (Scheme I), after recognition and appropriate interaction with DNA, the aglycon framework of the molecule **1** undergoes an intramolecular con-

Scheme I^a



^a Presumed DNA-cleaving mechanism of calicheamicin γ_{1A} (**1**).

Scheme II^a



^a Synthesis of eneidyne **5** ($n = 2-8$).

jugate addition to tricycle **2** followed by a Bergman cyclization³ leading to a highly reactive benzenoid diradical **3** which damages DNA. Intrigued by the novel architecture and mode of action of these potent biomolecules, we initiated a program directed toward the understanding of their chemistry and the investigation of strategies for their total synthesis. In this communication, we report (a) calculations on structural parameters of cyclic conjugated eneidyne relating to calicheamicins and esperamicins, (b) methodology for the construction of these systems, (c) the application of this strategy to the first synthesis of cyclodecenediynone **5** ($n = 2$), the parent molecule of the active skeleton of these natural products, and (d) the properties of **5** ($n = 2$), including its thermal cyclization to a benzenoid diradical analogous to the species postulated in the biological mode of action of these compounds.⁴

Crucial for the cascade of Scheme I is the geometrical change in going from structure **1** to **2**. Specifically, it was hypothesized that saturation of the double bond in **1** after the conjugate addition (**1** \rightarrow **2**) must result in shortening of the distance between the acetylenic groups (Scheme I, distances *ab* and *cd*).⁵ Indeed, molecular mechanics calculations (MacroModel, MM2)⁶ on the aglycons of **1** and its cyclic product (entries 6 and 7, Table I) revealed that the distances *ab* and *cd* shortened in going from structures of type 1 to structures of type 2. In particular, *cd* goes from 3.35 to 3.16 Å, which apparently is close enough for spontaneous cyclization to take place (Scheme I, **2** \rightarrow **3**). Table I also includes a number of other, known model systems and their calculated *ab* and *cd* distances. Inspection of these values leads to the conclusion that the crucial turning point from stability to spontaneous cyclization must be in the *cd* range of 3.31–3.20 Å. Examples of compounds with lower than 3.20 Å *cd* values have been claimed as transient intermediates, suffering spontaneous cyclization to benzenoid systems (Table I, entries 1–3).^{7,8} On

(3) (a) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25. (b) Lockhart, T. P.; Gomita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091. (c) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660.

(4) For some other elegant studies in this area, see synthetic: (a) Schreiber, S. L.; Kiessling, L. L. *J. Am. Chem. Soc.* **1988**, *110*, 631. (b) Magnus, P.; Carter, P. A. *J. Am. Chem. Soc.* **1988**, *110*, 0000. Theoretical: Houk, K. N. *J. Am. Chem. Soc.*, submitted for publication. We thank these authors for sharing their results with us prior to publication.

(5) This is a simplifying assumption, since obviously other considerations such as strain energies of substrates, transition states, and products may play a role in complex systems. The distances between the acetylenic groups, however, seems to correlate well with the rates of cyclization of all eneidyne mentioned in this work.

(6) We thank Professor W. C. Still, Columbia University, for supplying this program to us. The values in Table I were obtained by using standard MM2 force field parameters. Using the altered *sp* bending constants (Allinger, N. L.; Pathiaseril, A. *J. Comput. Chem.* **1987**, *8*, 1225) resulted in only small changes in the *cd* distance and a comparable fit to the X-ray derived parameters for **5** ($n = 3$).

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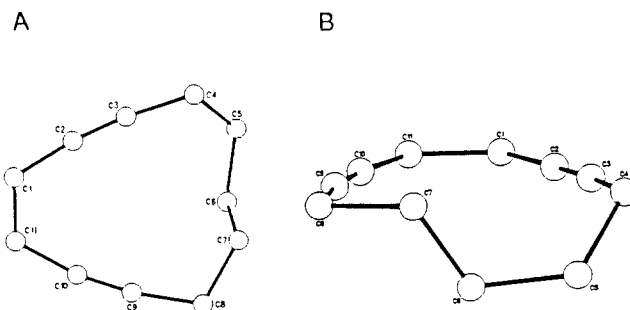
Table I. Calculated^a Strain Energies and Distances Between Acetylenic Carbons in Cyclic Conjugated Eneidyne.

Entry	Compound	Ring Size	Strain Energy (kcal/mole)	ab (Å)	cd (Å)	Stability	Ref
1		10	21.2	2.51	2.99	spontaneous cyclization	7
2		10	19.71	2.54	3.01	spontaneous cyclization	7
3		10	16.50	2.58	3.03	spontaneous cyclization	8
4		10	15.52	2.56	3.17	should cyclize at 25 °C	unknown
5		10	16.42	2.65	3.36	should be stable at 25 °C	unknown
6	2	10	22.67	2.55	3.16	spontaneous cyclization	1
7	1	10	23.25	2.65	3.35	stable at 25 °C	1
8		—	0.43	2.86	4.12	stable at 25 °C	3
9		—	5.38	2.76	3.94	stable at 25 °C	3
10		12	2.79	2.74	3.77	stable at 25 °C	9
11	5 (n = 1)	9	14.80	2.51	2.84	should cyclize	unknown
12	5 (n = 2)	10	11.40	2.60	3.25	cyclization at 25 °C	this work
13	5 (n = 3)	11	8.96	2.72	3.61	stable at 25 °C	this work
14	5 (n = 4)	12	7.60	2.80	3.90	stable at 25 °C	this work
15	5 (n = 5)	13	7.37	2.87	4.14	stable at 25 °C	this work
16	5 (n = 6)	14	8.21	2.87	4.15	stable at 25 °C	this work
17	5 (n = 7)	15	8.39	2.93	4.33	stable at 25 °C	this work
18	5 (n = 8)	16	11.35 ^b	2.88 ^b	4.20 ^b	stable at 25 °C	this work

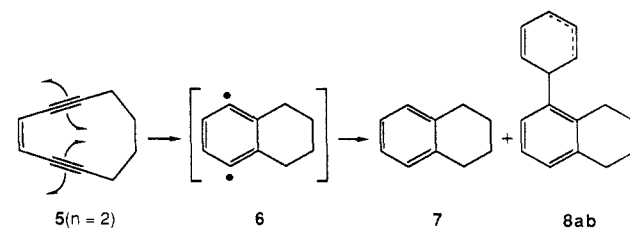
^aMM2 calculations were performed by using MacroMode.⁶ ^bThe origin of this seemingly anomalous result is unknown at present.

the other hand, numerous examples of systems with higher than 3.31 Å cd values are known, and they are quite stable at 25 °C (e.g., entries 8–10).^{3,9} A number of other designed model systems are also included in Table I (entries 4, 5, and 11–18) with calculated cd values and predictions regarding their stability at 25 °C. Thus, the compounds of entries 4 and 11 with a cd value below 3.20 Å should suffer spontaneous ring closure, whereas the compounds of entries 5 and 13–18 with cd values higher than 3.31 Å cd values ought to be stable toward cyclization at ambient temperatures. Quite interesting is the parent 10-membered ring system of entry 12 (Table I) whose cd distance of 3.25 Å falls right in the middle of the critical range (3.31–3.20 Å), and, therefore, no safe prediction as to its behavior at ambient temperatures could be made. The synthesis of this 10-membered ring eneidyne and its homologs was, therefore, undertaken in order to test the above hypothesis and to facilitate further investigations in this area of biomedical relevance.

Scheme II outlines the general strategy used for the synthesis of the cyclic conjugated eneidyne **5** (entries 13–18, Table I) which relies on the Ramberg–Backlund reaction.^{10,11} All these com-

**Figure 1.** ORTEP drawing of **5** (n = 3): A, top view; B, side view.**Table II.** Calculated and Experimental Parameters of Eneidyne **5** (n = 3).

Method	C1-C11(Å)	C2-C10(Å) (ab value)	C3-C9(Å) (cd value)	C1-C2(Å)	C4-C8(Å)	C4-C3-C2(°)
MM2	1.34	2.72	3.61	1.43	4.41	175.3
X-Ray	1.327(5)	2.778(5)	3.661(5)	1.410(5)	4.357(6)	173.2(4)
Method	C3-C2-C1(°)	C2-C1-C11(°)	C1-C11-C10(°)	C11-C10-C9(°)	C10-C9-C8(°)	
MM2	174.6	119.1	119.2	172.1	171.9	
X-Ray	172.6(4)	121.1(3)	120.3(3)	169.4(4)	170.5(4)	

Scheme III^a^aBergmann cyclization of eneidyne **5** (n = 2).

pounds except for the 10-membered ring eneidyne (vide infra) proved to be thermally quite stable at ambient temperatures as theoretically predicted from the data in Table I.

Luckily, the 11-membered eneidyne **5** (n = 3)¹² crystallized nicely in large colorless plates, mp 36–36.5 °C (from pentane). An X-ray crystallographic analysis of this compound was, therefore, carried out¹³ in order to compare experimentally obtained molecular parameters with the calculated ones. Figure 1 shows two ORTEP drawings of **5** (n = 3), whereas Table II compares calculated and found values for some selected geometrical parameters of this compound. The agreement of the experimentally derived values with those obtained by calculations is remarkable and enhances our degree of confidence in using the MM2 program for these systems.⁶ Quite interesting is the planar arrangement of all but two carbons in **5** (n = 3) as seen from the side view ORTEP drawing B (Figure 1).

Eneidyne **5** (n = 2) exhibited the expected spectral¹⁴ and thermal properties. While at ambient temperatures **5** (n = 2) is sufficiently stable for purification and characterization purposes,

(10) For an extensive review of the Ramberg–Backlund reaction, see: Paquette, L. A. *Org. React.* **1977**, *25*, 1. More details on the preparation of these compounds and their precursors can be found in Supplementary Material.

(11) All new compounds exhibited satisfactory spectral and analytical and/or exact mass data. Yields have not been maximized and refer to spectroscopically and chromatographically homogeneous materials.

(12) This compound was mentioned as a byproduct in a solvolysis reaction without any data: Hanack, M.; Rieth, R. *Chem. Ber.* **1987**, *120*, 1659.

(13) We thank Dr. Patrick Carrol of this department for this X-ray crystallographic analysis.

(14) **5** (n = 2): ¹H NMR (500 MHz, CD₂Cl₂) δ 5.80 (s, 2 H, olefinic), 2.38 (m, 4 H, propargylic), 1.91 (m, 4 H, CH₂); ¹³C NMR (125 MHz, CD₂Cl₂) δ 123.6 (olefinic), 104.7 (acetylenic) 82.6 (acetylenic), 29.4, 21.9; UV (Et₂O) λ_{max} 282, 263, 259 (sh) nm; HRMS calcd for C₁₀H₁₀ 130.0786, (M⁺), found 130.0783.

it slowly decomposes upon standing in solution or neat. Kinetic studies on the cyclization of **5** ($n = 2$) (Scheme III) were carried out in the presence of 1,4-cyclohexadiene in benzene in order to determine its rate of cyclization to a benzenoid diradical at various temperatures and to define its energy of activation (E_a). As expected from Bergman's elegant studies,³ under these conditions, **5** ($n = 2$) led to tetralin (**7**) and the two adducts **8a** and **8b** via benzenoid diradical **6** (Scheme III). At 37 °C the cyclization of **5** ($n = 2$) (Scheme III) proceeded with a half life ($t/2$) of 18 h and a rate constant (k_r) of 6.4×10^{-4} /min. The energy of activation (E_a) for this reaction was determined to be 23.8 kcal/mol.¹⁵ Thus, it appears that structure **5** ($n = 2$) may serve as a useful "warhead" in damaging molecular or cellular structures such as DNA and tumor cells, without further activation.

Applications of the gathered knowledge to further studies in this area using computer design, synthesis, and biotechnology should be forthcoming and may prove therapeutically useful.

Acknowledgment. We thank Drs. May D. Lee, Ving J. Lee, and Robert Babine (Lederle Laboratories) and Professors Ralph Hirschmann and W. S. Dailey of this department for stimulating and helpful discussions. Our many thanks are also due to Drs. Patrick Carrol, George Furst, and John Dykins of this department for their superb assistance and helpful comments regarding X-ray crystallography, NMR, and mass spectroscopy, respectively. This work was financially supported by the National Science Foundation, Lederle Laboratories, Merck Sharp and Dohme, and the University of Pennsylvania.

Supplementary Material Available: ¹H NMR data for compounds **5** ($n = 3-8$), X-ray data for **5** ($n = 3$), kinetic data for **5** → **6**, and details for the synthesis of **5** ($n = 2-8$) (7 pages). Ordering information is given on any current masthead page.

(15) Calculations were made on the assumption of complete conversion of enediyne **5** ($n = 2$) to diradical **6** (at half life for the 37 °C run the material balance was ca. 95.5%). Reactions at 37, 50, 60, and 70 °C were carried out in degassed benzene solutions at 0.01 M concentrations of **5** ($n = 2$) and 100 mol equiv of 1,4-cyclohexadiene. The kinetics were followed by HPLC with diphenyl ether as internal standard. Further details can be found in the Supplementary Material.

Novel Chemistry of Dithiatopazine

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Received March 22, 1988

We have recently reported the synthesis of the first stable 1,2-dithietane compound, dithiatopazine (**1**).¹ In this communication, we wish to disclose some novel chemistry of this remarkable molecule including (i) a number of unique skeletal rearrangements, (ii) the synthesis of some unusual structures, and (iii) the transfer of sulfur atoms from dithiatopazine to suitable acceptors.

Scheme I depicts the transformations taking place when **1** is exposed to NaBH₄ in EtOH at 25 °C for 10 min, followed by quenching with excess MeI. The three products **2**, **3**, and **4** were isolated in 35, 28, and 12% yields, respectively, by preparative

(1) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Carrol, P. J. *J. Am. Chem. Soc.* 1987, 109, 3801.

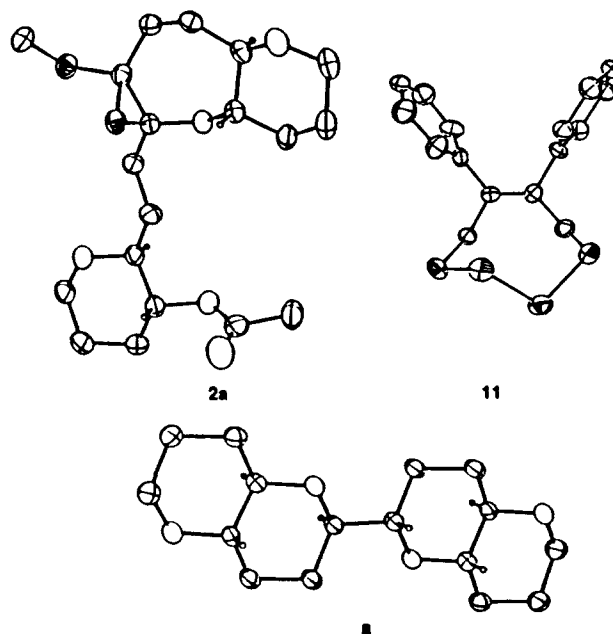
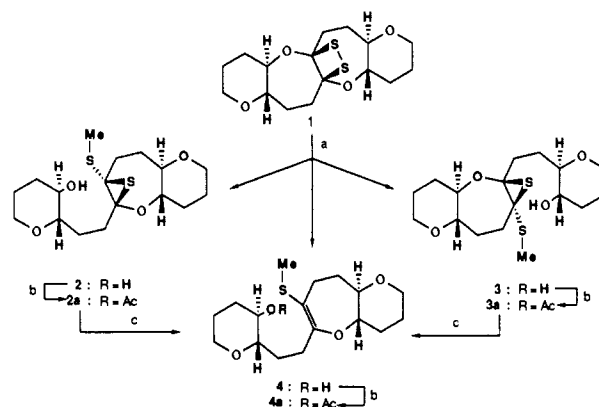


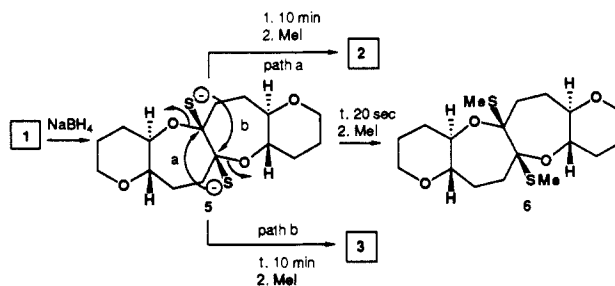
Figure 1. ORTEP drawings of **2a**, **8**, and **11**.

Scheme I^a



^aReagents and conditions: (a) 2.0 equiv of NaBH₄, EtOH, 0 °C, 10 min, then 15.0 equiv of MeI, 30 min, **2** (35%), **3** (28%), **4** (12%); (b) 2.0 equiv of Ac₂O, 2.2 equiv of Et₃N, 0.1 equiv of DMAP, CH₂Cl₂, 0 °C, **2a** (85%), **3a** (80%), **4a** (81%); (c) 4.0 equiv of Ph₃P, CH₂Cl₂, 50 °C, 24 h, **2a**, **4a** (87%), **3a**, **4a** (80%).

Scheme II^a



^aPresumed mechanism for the formation of **2** and **3** from **1**.

thin layer chromatography (R_f values, silica, 30% EtOAc in benzene, **2**: 0.27, **3**: 0.23, **4**: 0.20).² The structures of these novel compounds were based on spectroscopic and chemical data. Thus, these three compounds yielded, upon acetylation with excess

(2) All new compounds exhibited satisfactory spectral and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.