Bimanes. 24. Synthesis, Structure, and Dynamic Properties of Zero-Bridged Bimanes, 3,7-Dimethyl- and 3,7-Dichloro-4,6-(1′,2′-dimethylene)-1,5-diazabicyclo[3.3.0]-octa-3,6-diene-2,8-diones [μ-0-*syn*-(CH_2,CH_3 or Cl)B]

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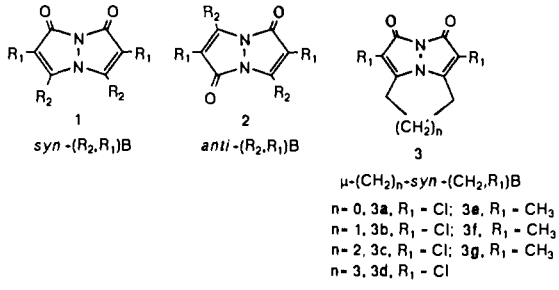
Abstract: Conversion of the dibromo compound, 4,6-bis(bromomethyl)-3,7-dimethyl-1,5-diazabicyclo[3.3.0]octa-3,6-diene-2,8-dione (*syn*-($BrCH_2$,CH_3)B) or the related 3,7-dichloro derivative (*syn*-($BrCH_2$,Cl)B) to a 4,6-sulfone-bridged bimane via oxidation of a 4,6-thiatrimethylene derivative is described. Elimination of SO_2 via thermolysis of the sulfones at 525 °C in a quartz reactor yields the strained tricyclic bimanes containing a 4,6-dimethylene group ("zero-bridge") μ-0-syn-(CH_2,CH_3)B (**3e**) and μ-0-syn-(CH_2,Cl)B (**3a**). The structure of the 3,7-dimethyl derivative, μ-0-syn-(CH_2,CH_3)B, has been established by X-ray crystallography. The absorption maxima (**3a**, 324 nm; **3e**, 315 nm) are at much shorter wavelengths than those of compounds with longer "bridges", but the positions of the fluorescence maxima are similar. The NMR spectrum at room temperature shows only one signal for CH_2, the hydrogens being equilibrated by flipping of the bimane ring. The coalescence temperature for the 3,7-dimethyl derivative is at 205 K; that for the 3,7-dichloro derivative is somewhat below 181 K. The rate constant ($(6-8) \times 10^5$ s^{-1}) and activation energy (11 ± 1 kcal/mol) for the flipping process in **3e** have been estimated by simulation of NMR spectra at different temperatures. The structure of μ-(S)-*syn*-(CH_2,Cl)(**5a**) has been confirmed by X-ray analysis. Thermolysis of the sulfone at temperatures somewhat higher than 525 °C leads to the loss of a CH_2=S fragment and formation of *syn*-(H,Cl)(CH_3,Cl)B.

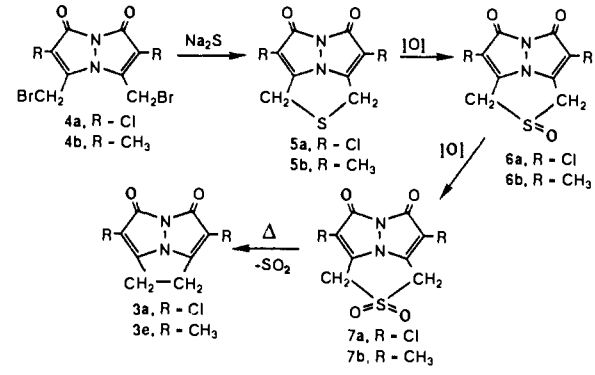
Introduction

The discovery of a simple synthesis for both *syn*- and *anti*-1,5-diazabicyclo[3.3.0]octadienediones (*syn*-(**1**) and *anti*-9,10-dioxabimanes(**2**)) ("bimanes") made a variety of these 5:5 bicyclic systems available.[2,3] Bimanes have fascinating chemical,[3-7] photophysical,[8-12] and photochemical properties[13,14] and have found wide use as labeling and thiol analytical agents for biological thiols, proteins, cells, and tissues.[15-19] In the course of our studies, we noted the substantial differences between the absorption maxima for simple derivatives, i.e., *syn*-(CH_3,CH_3)B (**1**, $R_1 = R_2 = CH_3$) and bridged 4,6-methylene compounds like μ-(NCH_3)-*syn*-(CH_2,CH_3)B. It was of interest to increase the restrictions on the shape and motion of the 9,10-dioxabimane molecule through shortening the link between the 4- and 6-methylene groups. With the "zero-bridged" *syn*-9,10-dioxabimane (**3**, n = 0) added to the



series of tricyclic bimanes (**3**, n = 0-3), we would expand our understanding of the relationship between the bimane ring-ring dihedral angle[20,21] and photophysical properties. Derivatives of **3**, n = 1 substituted on the central atom or with a heteroatom in place of the central carbon can be prepared easily.[5] Only recently have we developed a convenient method for preparing the compound with n = 1 and an unsubstituted central CH_2,[22] especially good for tricyclic bimanes with n = 2 and satisfactory for compounds in which n = 3. However, the synthesis fails at the last stage for compounds with n = 0, for which we used the classical thermal elimination of SO_2 from bridged sulfones. We now report

Scheme I. Synthesis of Zero-Bridged Bimane, μ-0-*syn*-(CH_2,CH_3)B



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(1) Kosower, E. M.; Pazhenchevsky, B.; Hershkowitz, E. *J. Am. Chem. Soc.* **1978**, *100*, 6516-6518.
(2) Kosower, E. M.; Pazhenchevsky, B. *J. Am. Chem. Soc.* **1980**, *102*, 4983-4993.
(3) Kosower, E. M.; Ben-Shoshan, M.; Faust, D.; Goldberg, I. *J. Org. Chem.* **1982**, *47*, 213-221.
(4) Kosower, E. M.; Pazhenchevsky, B.; Dodiuk, H.; Kanety, H.; Faust, D. *J. Org. Chem.* **1981**, *46*, 1666-1673.
(5) Kosower, E. M.; Pazhenchevsky, B.; Dodiuk, H.; Ben-Shoshan, M.; Kanety, H. *J. Org. Chem.* **1981**, *46*, 1673-1679.
(6) Radkowsky, A. E.; Kosower, E. M. *J. Am. Chem. Soc.* **1986**, *108*, 4527-4531.
(7) Radkowsky, A. E.; Kosower, E. M.; Eisenberg, D.; Goldberg, I. *J. Am. Chem. Soc.* **1986**, *108*, 4532-4541.
(8) Kosower, E. M.; Hermolin, J.; Ben-Shoshan, M.; Faust, D. *J. Org. Chem.* **1981**, *46*, 4578-4580.
(9) Kosower, E. M.; Kanety, H.; Dodiuk, H. *J. Photochem.* **1982**, *21*, 171-182.
(10) Kosower, E. M.; Kanety, H.; Dodiuk, H.; Hermolin, J. *J. Phys. Chem.* **1982**, *86*, 1270.
(11) Giniger, R.; Huppert, D.; Kosower, E. M. *Chem. Phys. Lett.* **1985**, *118*, 240-245.
(12) Kosower, E. M.; Giniger, R.; Radkowsky, A. E.; Hebel, D.; Shusterman, A. *J. Phys. Chem.* **1986**, *90*, 5552-5557.

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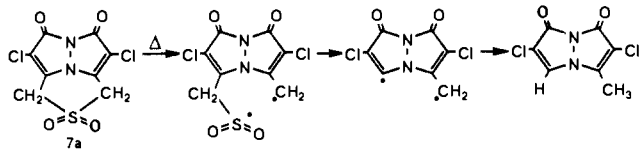
Scheme II. Decomposition of μ-(SO_2)-*syn*-$(CH_2,Cl)B$



the synthesis and the interesting properties of two "zero-bridged" tricyclic bimanes, **3a** and **3e**.

Results

Synthesis. Certain dibromobimanes (**4**, R_1 = Cl or CH_3) are converted into thia-bridged compounds μ-(S)-*syn*-$(CH_2,R_1)B$ (**5**, R_1 = CH_3 or Cl) by reaction with sodium sulfide, using a two-phase system with a phase-transfer catalyst. The yield of the thia-bridged compound **5a** μ-(S)-*syn*-$(CH_2,Cl)B$, is quite low (6–16%) due to the predominance of reduction, a side reaction previously noted with the thiol tripeptide, glutathione, in the course of kinetic studies.[6] A more effective synthesis (80% yield) of **5a** is achieved through the reaction of the dibromide **4a** with bis-(tributyltin) sulfide, $[(C_4H_9)_3Sn]_2$.[23]

Oxidation of the cyclic sulfide (**5**) to the sulfone (**7**) is effected with 3-chloroperbenzoic acid or magnesium peroxyphthalate. The sulfoxide (**6b**, R_1 = Cl) is relatively insoluble and can escape attention if this fact is ignored. Thermolysis of the sulfones[24] in a quartz reactor at 525 °C produces the zero-bridged bimanes in reasonable yields. The structure of the methyl derivative **3e** has been confirmed by an X-ray determination. Mass spectra of the compounds show clear parent peaks at (M^+) 190 (**3e**) or 230, 232, and 234 (**3a**). The reactions are summarized in Scheme I.

If the thermolysis of the chloro sulfone **7b** is carried out at somewhat higher temperatures and pressures, elimination of $CH_2{=}S$ was observed, leading to *syn*-$(H,Cl)(CH_3,Cl)B$. (Scheme II)

Preliminary thermolysis of the sulfone **5b** so that the product condensed onto the cold sapphire window in a thin-film spectroscopic apparatus (designed for trapping pyridinyl radicals at 77 K)[25] showed that no significant spectroscopic changes occurred on warming the film of **3e** from 77 K to 25 °C. The zero-bridged compounds could thus be handled without special precautions with respect to temperature or light and proved to be quite stable in air. However, the chloro compound, **3a**, may be somewhat unstable over moderate periods at room temperature.

UV and Fluorescence Spectra. The UV absorption maximum for the methyl zero-bridged bimane **3e**, in thin films at 77 K is at 308 nm, slightly different than that for a CH_3CN solution (315 nm) at 25 °C. The absorption maximum for **3a** in CH_3CN is at 324 nm.

The fluorescence maxima for **3a** and **3e** are at 444 and 448 nm, respectively, in acetonitrile. The excitation maxima are similar to the absorption maxima, at 327 nm for **3a** and at 315 nm for **3e**.

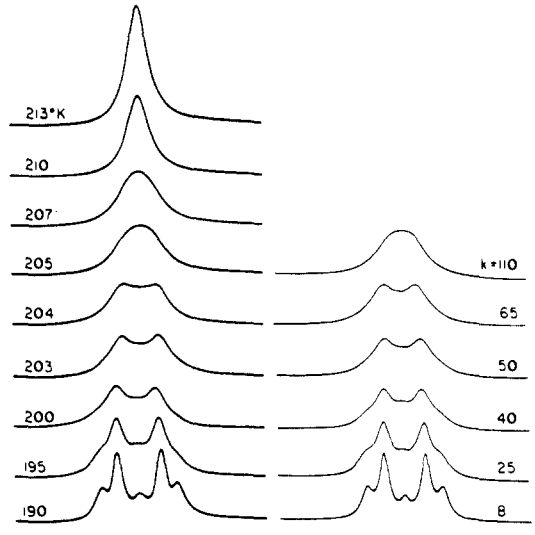


Figure 1. Experimental (left) and simulated (right) NMR spectra for μ-0-*syn*-$(CH_2,CH_3)B$ at various temperatures. The kinetic constants needed to match the simulated and experimental spectra are noted (right) along with the temperatures at which the spectra were measured (left). The small center singlet of the simulated spectrum was added in the calculation (see text).

NMR Spectra and Kinetics. The NMR spectrum of the CH_3-μ-0 (**3e**) shows two singlets (1.79 and 3.29) in the ratio of 3:2. With decreasing temperature, the singlet at 3.29 becomes broader and is finally split into a complex but symmetrical set of signals. The coalescence temperature is 205 K. The NMR spectra are simulated by the standard method. A plot of log k vs $1/T$ gives a straight line, corresponding to an E_{act} of 11 ± 1 kcal/mol. While ΔG^* (205 K) is 10.0 ± 0.2 kcal/mol, a rate constant can be estimated by extrapolation to be from (2–30) × 10^5 s^{-1} at 25 °C. Sufficient broadening of the 4,6-methylene signals is noted for Cl-μ-0 (**3a**) at 181 K to indicate that the coalescence temperature was somewhat lower than that value.

The Low-Temperature Spectrum. ^1H NMR spectra are obtained with a Bruker AM-360 spectrometer at 360 MHz in a temperature-controlled 5-mm probe. The resonances representing the four bridge methylene hydrogens are shown in Figure 1 (left). The experimental spectrum has a digital resolution of 0.5 Hz/point and is further broadened by a 0.5 Hz sensitivity enhancement filter. We attempted to simulate the line shape by using the PANIC program in the Bruker software package, and assuming a four-spin AA'BB' system. Limiting ourselves to reasonable values of the various coupling constants, it soon became evident that the entire line shape could not be properly simulated, but a good fit (not shown) could be achieved if the small central peak in the experimental spectrum is ignored, utilizing the following parameters:

$$\delta_{AB} = 45 \text{ Hz } (0.125 \text{ ppm})$$

$$J_{A'B'} = J_{AB} = -14 \text{ Hz}$$

$$J_{AB'} = J_{A'B} = 3.8 \text{ Hz}$$

$$J_{BB'} = J_{AA'} = 2.5 \text{ Hz}$$

and an intrinsic Lorentzian line width of 5.5 Hz which represents contributions from the digital filter, spin–spin relaxation, and magnetic field inhomogeneities. We therefore conclude that the central peak results from an additional conformation, assumed by a small fraction of the molecules, in which the four hydrogens have nearly identical chemical shifts. If the same line width of 5.5 Hz is assumed for this central peak, then its integrated area

(13) Kanety, H.; Dodiuk, H.; Kosower, E. M. *J. Org. Chem.* **1982**, *47*, 207–213.
(14) Melis, A.; Kosower, N. S.; Crawford, N. A.; Kirowa-Eisner, E.; Schwarz, M.; Kosower, E. M. *Photochem. Photobiol.* **1986**, *43*, 583–589.
(15) Kosower, N. S.; Kosower, E. M.; Newton, G. L.; Ranney, H. M. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 3382–3386.
(16) Kosower, N. S.; Kosower, E. M. *Methods Enzymol.* **1987**, *143*, 76–84.
(17) Kosower, N. S.; Kosower, E. M.; Radkowsky, A. E.; Zipser, J. In *Molecular biology of neuroreceptors and ion channels*; Maelicke, A., Ed.; NATO-ASI Series, Vol. H32; Springer Verlag: Berlin, 1989; pp 381–391.
(18) Kosower, N. S.; Zipser, J.; Radkowsky, A. E.; Kosower, E. M. *J. Cell. Biol.* **1988**, *107*, 355a.
(19) Kosower, E. M.; Kosower, N. S.; Radkowsky, A. E.; Zipser, J. *J. Cellular Biochem.* **1989**, *13B*, Suppl. 222.
(20) Goldberg, I.; Bernstein, J.; Kosower, E. M.; Goldstein, E.; Pazhenchevsky, B. *J. Hetero. Chem.* **1982**, *20*, 903–912.
(21) Goldberg, I.; Bernstein, J.; Kosower, E. M. *Acta Cryst.* **1982**, *B38*, 1990–2000.
(22) Marciano, D.; Baud'huin, M.; Zinger, B.; Goldberg, I.; Kosower, E. M. Bimanes 25. *J. Am. Chem. Soc.*, third of three papers in this issue.
(23) Harpp, D. N.; Ginigras, M.; Aida, T.; Chan, T. H. *Synthesis* **1987**, *12*, 1122–1124.
(24) Vögtle, F.; Rossa, L. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 515–529.
(25) Hermolin, J.; Levin, M.; Ikegami, Y.; Sawayanagi, M.; Kosower, E. M. *J. Am. Chem. Soc.* **1981**, *103*, 4795–4800. Hermolin, J.; Levin, M.; Kosower, E. M. *J. Am. Chem. Soc.* **1981**, *103*, 4801–4807.

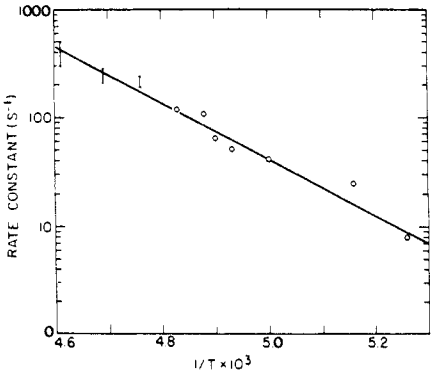


Figure 2. Logs of the kinetic constants derived from simulation of NMR spectra at given temperatures for the zero-bridged bimane, μ-0-*syn*-(CH_2,CH_3)B are plotted against the reciprocal of the temperature, yielding the activation energy.

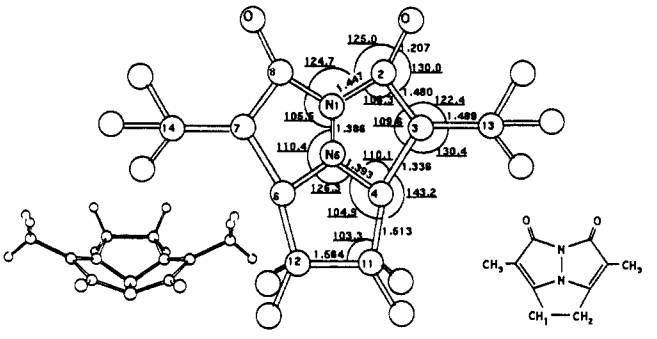


Figure 3. Structure, bond distances (estimated standard deviation 0.002–0.003 Å) and angles (estimated standard deviation 0.1–0.2°) for the zero-bridged bimane, μ-0-*syn*-(CH_2,CH_3)B.

represents 9% of the total molecular population. Flexing of the dimethylene group above and below the mean plane of the group is plausible, accounting for the chemical shift and perhaps for its change with temperature.

The Dynamic Study. The resonance of the methylene protons at various temperatures is shown in the left part of Figure 1. Since one of the coupling constants is much larger than the other two, the experimental line shape closely resembles an AB pattern, and the spectral resolution is insufficient to allow unique and accurate determination of the smaller coupling constants. Furthermore, the fine structure due to these small couplings is averaged out after heating by only a few degrees. We therefore wrote a program for simulation of the dynamic spectra on the basis of an AB pattern subject to motion which interchanges the chemical identity of A and B.[27] The program also allowed us to include a singlet at the center frequency, representing the small peak which could not be accounted for by the static AA'BB' simulation. The simulated spectra are shown in the right side of Figure 1, and the values of the interconversion constant k which yielded the best fit to the experimental spectra are indicated. In all simulations, δ_{AB} = 45 Hz, and J_{AB} = −14 Hz. The intrinsic Lorentzian line width is 7.5 Hz and the intensity of the singlet at the center gradually decreases from 9% at 190 K to 0 at 205 K.

A plot of log k vs $1/T$ is shown in Figure 2. At temperatures below coalescence, the exact choice of the intrinsic line width does not have a strong influence on the best fitting value of k. However, after the signal has collapsed to a single line, the uncertainty in this intrinsic line width introduces some uncertainty into the value for k, as reflected in the error bars on the figure. A least-squares fit to the points yields an E_a of 11.7 kcal/mol and a k(298 K) of 7.3 × 10^5 s^{-1}. With the uncertainties in some of the rate

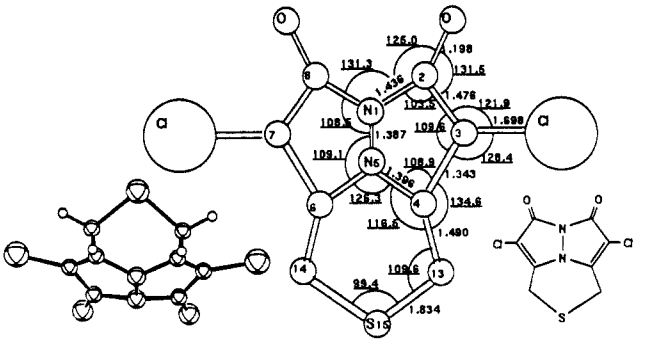


Figure 4. Bond distances (estimated standard deviation 0.002–0.003 Å) and angles (estimated standard deviation 0.1–0.2°) and the structure for μ-(S)-*syn*-(CH_2,Cl)B.

constants taken into account, E_a is 12.0 ± 1.5 kcal/mol, and k(298 K) (2–30) × 10^6 s^{-1}.

Crystal Structure. The molecular structure of **3e** is characterized by an ideal C_s symmetry, as the molecules are located on crystallographic mirror planes. The asymmetric unit of the structure corresponds to half of the molecule. The structure revealed a beautifully symmetrical cup-shaped molecule corresponding to the expected formula, shown along with the bond angles and bond lengths in Figure 3. The atomic coordinates and the thermal parameters for **3e** are given in Tables 1a and 1b (supplementary material), respectively.

The thermal motion of the tricyclic framework can be formulated to a very good approximation by a rigid-body model (in terms of libration, translation, and screw tensors),[28] in contrast to the dynamical behavior revealed by the NMR studies. It appears that the dense packing of the crystal accounts for the "rigid-body" behavior. As in other dioxabimane structures,[20] specific C–H···O interactions appear to contribute significantly to the lattice energy; the relevant nonbonding distances are C(8)···O(6) (at $^1/_2 - x$, $^1/_2 + y$, z) = 3.319 Å and H(8)···O(6) = 2.30 Å.

The molecular structure of μ-(S)-(CH_2,Cl)B is shown in Figure 4 (More details are given in Table 3, supplementary material). The crystal structure of μ-(S)-*syn*-(CH_2,Cl)B is characterized by $P2_1/n$ symmetry. The bimane framework, bent at the central N–N bond, has a dihedral angle between the mean planes of the five-membered rings of 146.3°. The atomic parameters, and the thermal parameters are given in Tables 2a and 2b (supplementary material), respectively. As already noted for most bimanes, the vibrational amplitudes of nitrogen atoms N1 and N5 in a direction perpendicular to the mean plane of the bimane framework are significantly larger than those in directions parallel to this plane. Components of the vibrational tensors are 0.044 Å^2 and 0.041 Å^2 for N1 and N5, respectively, along the perpendicular axis as compared to 0.023 Å^2 and 0.028 Å^2 for N1 and 0.019 Å^2 and 0.023 Å^2 for N5 along the other axes. The crystal packing arrangement of μ-(S)-*syn*-(CH_2,Cl)B is stabilized by van der Waals forces and apparent hydrogen bonds between neighboring molecules (H(13A)···O(10), H(14B)···O(9), 2.38 Å).

Discussion

Three significant points can be made about zero-bridged (μ-)[29] bimanes. First, zero-bridged bimanes are clearly strained, as indicated by the unusually long 11–12 bond and the reactivity of **3e** toward hydroxide ion. Second, the fluorescence maxima for zero-bridged bimanes are not very different from those of

(26) Shannon, V. L.; Strauss, H. L.; Kosower, E. M. Unpublished results.
(27) Steigel, A. In *NMR-Basic Principles and Progress*; Diehl, P.; Fluck, E., Kosfeld, R., Ed.; Springer 1978; Vol. 15, (Mechanistic Studies of Rearrangements and Exchange Reactions by Dynamic NMR Spectroscopy), pp 1–53.

(28) Schomaker, V.; Trueblood, K. N. *Acta Cryst.* **1968**, *B24*, 63.
(29) The nomenclature (9,10-dioxa-*syn*-bimanes, 4,6-bridged (or μ-)-9,10-dioxa-*syn*-bimanes, and 9,10-dioxa-*anti*-bimanes) which we have developed for efficient discussion of the 1,5-diazabicyclo[3.3.0]octadienediones has been thoroughly discussed in ref 2. The "9,10-dioxa" prefix is often omitted for brevity. The use of μ- as an abbreviation in the names for the bridged compounds, about which one may read in ref 4, is done in analogy with the usage of μ- for bridged inorganic compounds. The μ- is used to designate the connecting link (or "bridge") between the 4- and 6-methylenes. The formal name in the title includes 4,6-(1′,2′-dimethylene) to designate this part of the molecule as a substituent of the bimane.

bimanes lacking a bridge between the 4,6-methylenes, although the absorption maxima are at much shorter wavelengths. Third, the NMR spectra show that zero-bridged bimanes are more flexible than an innocent might guess from the formula and the crystal structure.[30]

The zero-bridged compound **3e** was somewhat unstable on thin-layer chromatograms, disappearing after several hours. The reaction with hydroxide ion which leads to opening of one five-membered ring, could be followed easily at pH 10.8 (carbonate buffer) and is about 50 times as fast as the hydroxide ion reaction at the same pH with *syn*-(CH_3,CH_3)B.[31] The strain in **3e** is thus reflected in the high rate of reaction with hydroxide ion.

The C_{11}–C_{12} dimethylene bridge, linking positions 4 and 6 of the 9,10-dioxabimane[29] framework, makes the molecule strained, with a C_{11}–C_{12} bridge bond of 1.564 Å and a rather small dihedral angle of 129° between the two symmetry-related halves of the dioxabimane system. This dihedral angle is the smallest found so far in crystal structures of dioxabimanes. For example, the dihedral angle in μ-C(CN)$_2$)-*syn*-(methylene,methyl)-9,10-dioxabimane,[21] which has a 1-carbon bridge, is greater than that of CH_3-μ-0 by about 10°.

The ground-state flexibility exhibited by the bimanes is slightly greater than that of the saturated 1,5-diazabicyclo[3.3.0]octane, a bicyclic hydrazine.[32] The 3,3,7,7-tetramethyl derivative exhibits coalescence temperatures of −29 °C for the CH_2 signal and −55 °C for the CH_3. The transition-state free energy estimated for flipping at 244 K is 12 kcal/mol, somewhat greater than the value of 9.8 kcal/mol at 244 K derived from our data for **3e**. Since the coalescence temperature for the bimanes is lower, the difference seems reasonable. Bimanes without the bridge would no doubt exhibit higher flipping rates, but this remains to be demonstrated. The Cl-μ-0 (**3a**) absorbs at longer wavelengths in the UV and is thus presumably more planar than **3e**. The coalescence temperature for the NMR spectrum of **3a** is well below that of **3e**, suggesting a higher flipping rate for **3a**. Crystals of Cl-μ-0 suitable for X-ray structural analysis have not yet been obtained.

The excited state is much more flexible than the ground state, as shown by the rapid conversion of the bent state to the quasi-planar state in times, between 200–300 ps, controlled by the longitudinal dielectric relaxation time of the solvent.[11] A limiting case for the excited state is the radical cation derived from the saturated 1,5-diazabicyclo[3.3.0]octane, for which the flipping rates are much higher, with a rate constant of 10^{11} s^{-1} estimated for room temperature.[33] The excited state of μ-0-bimanes must resemble that of other unbridged bimanes since the position of the emissions are similar, e.g., 444 nm for **3a**, 448 nm for **3e**, and 446 nm for *syn*-(CH_3,CH_3)B in CH_3CN.[9] We infer that the excited state of μ-0-bimanes must be much more planar than the ground state.

The mechanism of the "flipping" interconversion is of some interest. If the bimane ring were planar, there would be considerable repulsion between the adjacent p orbitals, assuming an sp^2 + p arrangement for both nitrogens. Rehybridization would decrease the repulsion but would introduce strain into the five-membered rings because of the change toward tetrahedral bonding around nitrogen. A somewhat twisted but bent ground state in which, partially, p orbitals point in somewhat different directions might be the best compromise for one of the structures. The flipping process would almost certainly have to be simultaneous because of the strain involved in lengthening any of the bonds in a five-membered ring, if each nitrogen moved through the plane independently.

The observed conformation of the μ-(S)-*syn*-(CH_2,Cl)B system reflects a strain similar to that of similarly bridged bimanes as μ-(S)-*syn*-(CH_2,CH_3)B and μ-(SO_2)-*syn*-(CH_2,CH_3)B, with dihedral angles around N–N of 142 and 139°, respectively). However, the slightly less bent structure in this chloro derivative (dihedral angle 144.3°), was anticipated after a comparison of the absorption spectra of μ-(S)-*syn*-(CH_2,Cl)B and μ-(S)-*syn*-(CH_2,CH_3)B. The absorption maxima for acetonitrile solutions are 360 and 345 nm, respectively, implying a more planar system for μ-(S)-*syn*-(CH_2,Cl)B. A similar comparison lead us to the prediction that μ-(S)-*syn*-(CH_2,Cl)B should be more bent than μ-(CH_2CH_2)-*syn*-(CH_2,Cl)B(Cl-μ-C_2) (λ_{max} 374 nm in acetonitrile, dihedral angle of 150°).

Experimental Section

General. Instruments used are as follows: ^{1}H NMR spectra, (Chemical shifts are δ values referred to $(CH_3)_4Si$ as 0.00) Bruker WH-90, 200, and AM-360 spectrometers; ultraviolet and visible spectra, Cary Model 17 spectrophotometer; fluorescence spectra, Hitachi Perkin-Elmer MPF-4 fluorescence spectrometer; mass spectra, DuPont 21–491B mass spectrometer; IR spectra, Perkin-Elmer Model 177 or Nicolet 5DX FTIR spectrophotometer.

Solvents and Materials. Dichloromethane, acetonitrile, and 2-propanol (Anal., Merck) were used without further purification. Dimethylformamide (DMF) was dried by refluxing over calcium hydride. Tetrahydrofuran (THF) was distilled from the sodium ketyl of benzophenone. Absorption and emission spectra were measured in Spectrograde acetonitrile or dioxane.

X-ray Crystallographic Determination of Structure. The X-ray diffraction data were measured at room temperature on an Enraf-Nonius CAD-4 diffractometer equipped with a graphite monochromator, employing Mo Kα radiation (λ = 0.7107 Å) and using $\omega - 2\theta$ scan technique. The scan rate varied according to the detected intensity between 1.0 and 4.0° min^{-1}. Possible deterioration of the crystal under examination was tested by frequent measurement of the intensities of standard reflections and found to be negligible. The data were not corrected for absorption and extinction effects. Final refinements of the structural model was based only on those observations that satisfied the conditions $F_o^2 > 3\sigma(F_o^2)$.

All crystal structures were solved by a combination of direct methods and Fourier techniques (MULTAN78 and MULTAN80). The refinements were carried out by full-matrix least-squares, including the positional and anisotropic thermal parameters of all the non-hydrogen atoms. All hydrogens were located in electron density difference maps at an intermediate stage of the refinement, and were assigned isotropic temperature factors. Their atomic parameters were not refined, except for a partial adjustment of the coordinates with low-order data below $\sin\theta/\lambda = 0.50$ $Å^{-1}$. The least-squares calculations were based on the experimental weights ($w = 1/\sigma^2(F_o)$), the quantity minimized being $w(\Delta F)^2$.

Summary of Crystal Data and Experimental Parameters. μ-0-*syn*-(CH_2,CH_3)B (3e). $C_{10}H_{10}N_2O_2$, M_r = 190.2, orthorhombic, a = 4.216 (1), b = 13.428 (1), c = 15.602 (2) Å, V = 883.3 $Å^3$, Z = 48 d_c = 1.430 gcm^{-3}, $F(000)$ = 400, μ(Mo Kα) = 1.10 cm^{-1}, space group *Pbnm*. Data collection: 2θ limits 0–60°; scan range $(0.80 + 0.20 \tan\theta)$°; number of unique observations above zero, 1077. Refinement: 67 parameters refined by using 701 reflections with $I > 3\sigma_I$. Final R = 0.043, R_w = 0.051, gof = 1.37 e.

μ-(Thia)-*syn*-(methylene,chloro)-9,10-dioxabimane (5a). $C_8H_4N_2O_2S$, M_r = 263.1, a = 8.698 (1), b = 13.343 (1), c = 8.702 (1) Å, β = 93.7 (1)8, V = 1007.9 $Å^3$, Z = 4, d_c = 1.734 gcm^{-3}, $F(000)$ = 528, μ(Mo Kα) = 8.21 cm^{-1}, space group $P2_1/n$. Data collection: 2θ 0–54°; scan range $(0.9 + 0.3 \tan\theta)$°; number of unique data > 0, 1636. Refinement: 136 parameters refined against 1441 observations above threshold. Final R = 0.047, R_w = 0.051, gof = 1.74 e.

Synthesis of Bridged Compounds. The synthesis of μ-(S)-*syn*-(CH_2,CH_3)B (**5b**) has been reported.[5] The preparation of μ-(S)-*syn*-(CH_2,Cl)B is more difficult because the system is more reactive toward nucleophiles and subject to attack by base. The procedure given below is reasonably successful, as are oxidations to sulfoxide and sulfone, described for the chloro derivative.

μ-(S)-*syn*-(CH_2,Cl)B (5a). A solution of *syn*-(CH_3,Cl)B (78 mg, 0.2 mmol) and bis(tributyltin) sulfide[23] (366 mg, 0.6 mmol) in dichloroethane is refluxed overnight under nitrogen. After evaporation of the solvent, the residue is flash chromatographed on silica gel (eluants, petroleum ether, dichloromethane, dichloromethane/ethyl acetate (1:1)) to yield crude μ-(S)-*syn*-(CH_2,Cl)B. A second chromatography (dichloromethane) is necessary to remove tributyltin bromide (Bu_3SnBr) to give μ-(S)-*syn*-(CH_2,Cl)B, 42 mg (0.16 mmol) (80% yield) as a yellow solid, mp 205 °C dec.

Alternate Procedure. Phosphate buffer, pH 6.5 (Na_2HPO_4, KH_2PO_4) (15 mL), was added to *syn*-($BrCH_2$,Cl)B (391 mg, 1 mmol) in benzene

(30) A less than perspicacious referee for a grant proposal in which was noted the flexibility of the "zero-bridged" bimanes, insisted that this was clearly impossible. Unfortunately, the circumstances did not permit one to respond with the words of the famous Italian, "Eppur si muove".

(31) Kanety, H.; Kosower, E. M. *J. Org. Chem.* **1982**, *47*, 4222–6.

(32) Kintzinger, J. P.; Lehn, J. M.; Wagner, J. *Chem. Commun.* **1967**, 206–207.

(33) Nelsen, S. F.; Weisman, G. R.; Hintz, P. J.; Olp, D.; Fahey, M. R. *J. Am. Chem. Soc.* **1974**, *96*, 2916–2923.

(70 mL) followed by $Na_2S·9H_2O$ (240 mg, 1 mmol). Hexadecyl trimethylammonium bromide (40 mg) was then added as a phase-transfer catalyst (PTC), whereupon the clear yellow two-phase system became black and inhomogeneous. After 3 h, more PTC (40 mg) was added and the whole stirred for another hour. The benzene layer was separated, the water phase extracted with benzene, the combined dark solutions filtered through Celite, and the yellow filtrate evaporated to yield μ-(S)-*syn*-(CH_2,Cl)B, 128 mg (16% yield) as a yellow solid. A reaction carried out with 20 mmol of **4a** gave only 6% of μ-(S)-*syn*-(CH_2,Cl)B. μ-(S)-*syn*-(CH_2,Cl)B: ^{1}H NMR ($CDCl_3$) δ 3.86 (s) ppm; UV(CH_3CN) λ_{max} (ϵ_{max}) 360 nm (1800), 260 (sh) (1100), 238 (4300); mass spectrum, *m/e* 266 (14), 264 (64), 262 (100) (M^+), 228 (19).

μ-(SO)-*syn*-(CH_2,Cl)B. *m*-Chloroperbenzoic acid (*m*-CPBA) (200 mg, 1.16 mmol) was added to a solution of μ-(S)-*syn*-(CH_2,Cl)B (263 mg, 1 mmol) in dichloromethane (30 mL). After a few minutes, μ-(SO)-*syn*-(CH_2,Cl)B precipitated and was filtered off 30 min later to yield μ-(SO)-*syn*-(CH_2,Cl)B, 206 mg (0.74 mmol), a yellow solid (74% yield). The filtrate contained some product which could not be easily separated from *m*-CPBA and from the remaining starting material. The yield of the sulfoxide varied with the purity of the starting sulfide. μ-(SO)-*syn*-(CH_2,Cl)B: ^{1}H NMR (CD_3CN) 4.28, 4.32, 4.42, 4.46 ppm; mass spectrum, (*m/e*) 282 (11), 280 (73), 278 (100) (M^+); thin-layer chromatography on silica gel 60 (Merck) (eluant, ethyl acetate) gave an R_f = 0.34, much less than that of μ-(S)-*syn*-(CH_2,Cl)B, which has an R_f = 0.86.

μ-(SO_2)-*syn*-(CH_2,Cl)B. Method 1. A mixture of μ-(SO)-*syn*-(CH_2,Cl)B (112 mg, 0.4 mmol) and magnesium monoperphthalate (MgMMPP) (918 mg, 2 mmol) in acetonitrile (50 mL) was stirred for 5 h at room temperature. The reaction mixture was filtered, the filtrate evaporated, and the residue extracted with dichloromethane at room temperature. The extract was evaporated to afford 118 mg (0.4 mmol) μ-(SO_2)-*syn*-(CH_2,Cl)B (100% yield) in pure form. Repetition of the procedure with a larger quantity of sulfoxide led to product contaminated with 10% MMPP. The MMPP (dec 93 °C) does not interfere with the subsequent pyrolysis of the sulfone to the zero-bridged bimane, in contrast to *m*-CPBA which sublimes together with the zero-bridged bimane.

Reaction of the sulfide with MMPP in acetonitrile gave a mixture of sulfoxide and sulfone which was not changed in ratio by use of excess MgMMPP.

Method 2. A mixture of μ-(SO)-*syn*-(CH_2,Cl)B (50 mg, 0.18 mmol) and *m*-CPBA (300 mg, 1.74 mmol) in acetonitrile was stirred at room temperature for several hours. The solvent was evaporated and the residue chromatographed on silica gel 60. One fraction gave 53 mg (0.18 mmol) μ-(SO_2)-*syn*-(CH_2,Cl)B, a yellow solid (100% yield), mp 300 °C dec. An experiment involving 615 mg μ-(SO)-*syn*-(CH_2,Cl)B gave 272 mg sulfone (42% yield). μ-(SO_2)-*syn*-(CH_2,Cl)B: ^{1}H-NMR (CD_3CN) 4.780 ppm; mass spectrum, *m/e* 296 (33), 294 (44) (M^+); thin-layer chromatography on silica gel 60 (Merck) (eluant, ethyl acetate) showed an R_f = 0.84.

Thermolysis of Sulfones. (High vacuum) A modest quantity of sulfone (120 mg) is placed into a cylindrical bulb sealed to a quartz reactor via a graded seal and the entry tube sealed off. The quartz tube has numerous internal projections to make more effective the heat exchange between the reactant gas and the high temperature produced by electrical heating tape used to heat the tube; a probe with a digital readout is used to measure the temperature. The collection bulb is attached to a high vacuum system (10^{-4} torr). The sulfone was vaporized by heating the sample bulb between 250–270 °C; the reactor was maintained between 510 and 530 °C. The pyrolysis product was chromatographed on silica and crystallized from CH_3CN to yield, in the case of **3e**, white crystals, mp 219 °C. (Moderate vacuum) The apparatus described above is connected through a condenser cooled to −78 °C to an efficient oil pump (5×10^{-2} torr). Pyrolysis of 106 mg μ-(SO_2)-*syn*-(CH_2,Cl)B at ca 600 °C yielded *syn*-(CH_3,Cl)(H,Cl), 23 mg (28% yield), mp 275 °C: ^{1}H NMR ($CDCl_3$) δ 2.503 (s, 3 H), 7.701 (s, 1 H) ppm, identical by NMR and a TLC comparison with material synthesized by another route.[34] The quantities of μ-0-*syn*-(CH_2,Cl)B (**3a**) produced were quite small (ca. 6 mg) due to the difficulty in preparing the sulfone and in converting the sulfone to **3a**. Extensive study of **3a** was thus precluded.

μ-0-*syn*-(CH_2,CH_3)B (3e): IR (KBr) 2992, 2951, 2927, 1770, 1696, 1648, 1450, 1389, 1329, 1249, 1150, 1114, 1074 cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ 1.79 (s, 3 H), 3.29 (s, 2 H) ppm; UV (CH_3CN) λ_{max} (ϵ_{max}) 315 nm (4800); fluorescence (CH_3CN) 448 nm (excitation maximum corresponding to the absorption maximum at 315 nm); mass spectrum, *m/e* (M^+) 190.

μ-0-*syn*-(CH_2,Cl)B (3a): IR (KBr) 2963, 2923, 1762, 1712, 1628, 1448, 1314, 1199, 1059, 991, 750, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.24 (s) ppm; UV (CH_3CN) λ_{max} (ϵ_{max}) 324 nm (5000); mass spectrum, *m/e* (M^+) 230, 232, 234.

The "direct synthesis" of μ-(S)-*syn*-(CH_2,Cl)B was unsuccessful. The bis-β-keto ester ($CH_3O_2CCH_2COCH_2$)S was prepared from thiodiacetyl chloride and potassium methyl malonate. The keto ester was a yellow oil: ^{1}H NMR ($CDCl_3$) 3.349 (s, 2 H), 3.513 (s, 2 H), 3.781 (s, 3 H) ppm; mass spectrum, *m/e* 244 (3) (M^+), 243 (32), 211 (100), 180 (49). The bispyrazolinone was prepared by adding hydrazine to the β-keto ester in methanol. The pale yellow solid (mass spectrum *m/e* 226 (100) (M^+)) decomposes in the presence of chlorine.

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Supplementary Material Available: Tables of atomic coordinates and isotropic thermal parameters, anisotropic thermal parameters for non-hydrogen atoms for μ-0-*syn*-(CH_2,CH_3)B and μ-(S)-*syn*-(CH_2,Cl)B, and bond lengths and angles for μ-(S)-*syn*-(CH_2,Cl)B (5 pages). Ordering information is given on any current masthead page.

(34) Ben-Shoshan, M. Ph.D. Thesis, Tel-Aviv University, 1989; Chapter 6 p 211.