Cage Aza Polycyclics. An Investigation of the Cyclization Oriented to Twisted—or Nontwisted—Tricyclic Aza Bridged Molecules. Synthesis and Structure Determination by 250-MHz Nuclear Magnetic Resonance Spectroscopy

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Analysis of the 250-MHz NMR spectrum of *N*-methyl-2-azatwistane and of its azahomobrendane isomer, which have been synthesized independently, allows the assignment of twisted—or nontwisted—structure to this type of cage compounds.

The synthesis of cage polycyclics, and particularly of twisted derivatives, is of interest in the carbocyclic and heterocyclic series.[1-3] We recently have described the cyclization of *N*-chloro-*N*-methylaminobicyclo[2.2.2]oct-5-ene (**1**) (Scheme I), and assigned a "homobrendane" [28] structure to the tricyclic derivative **2** thus obtained.[4] However, a twistane structure has since been proposed by others[5] for the same product.

Similarly, we have studied the cyclization of *N*-chloroamine **5** under the conditions of the well-known Hofmann–Loeffler–Freytag reaction,[6] where a similar structural problem arises (Scheme II). The regioselectivity of the Hofmann–Loeffler–Freytag reaction has been explained on the basis of steric arguments (such as lining up of C–H---N atoms), and energetic considerations (minimum steric interactions in the transition state[7,8]). Accordingly, cyclization generally occurs in the δ position relative to nitrogen; however, some exceptions are known,[9] when the conformation of the molecule is more favorable to γ or ϵ cyclization.

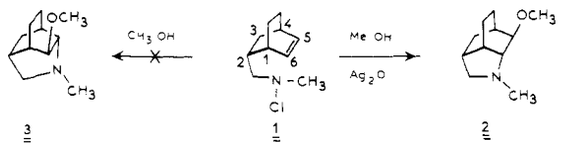
With both substrates **1** and **5** (Schemes I and II), it is clear from inspection of molecular models that the cyclization can occur "frontwise", to yield a homobrendane type structure (**2** or **6**), or "crosswise" to give a twistane derivative (**3** or **7**). A "frontwise" cyclization would lead to products where about all C–C and C–H bonds are in energetically disfavored conformations. This is particularly clear in the case of the *N*-chloro amine **5**, where a twisted or a nontwisted conformation can be considered for the bicyclo[2.2.2]octane skeleton.[10] In order to obtain the homobrendane structure **6**, a cyclization on the δ position, which implies a transition state such as **8b**, must occur. However, the strong eclipsing interactions apparently involved in this transition state should disfavor it relative to transition state **8a**, the latter leading to a twistane structure via a cyclization in ϵ position.

Undoubtedly, prediction of the cyclization direction will be problematical and risky. The situation is quite similar for the cyclization reaction of the ethylenic *N*-chloro amine **1**, where the nitrogen–carbon bond can be formed at both ends of the double bond.

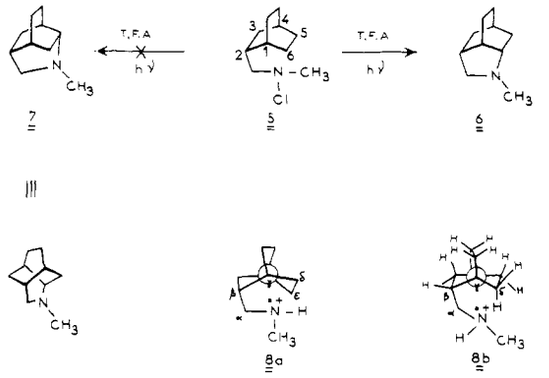
However, in each of these reactions, *only one* cyclized product is formed. Consequently their structures have to be exactly determined in order to have information on the reaction regioselectivity. This question is of interest as a similar problem occurs in the formation of lactones having this type of structure, where erroneous structural assignments have led to questionable theoretical conclusions.[11]

In order to determine the exact structure (homobrendane or twistane) of compound **2** (from **1**) and **6** (from **5**), we examined their 250-MHz NMR spectra. This led us to the conclusion that the spectra analysis was not sufficient to make unambiguous structure assignments. It appeared necessary to prepare model compounds using unequivocal synthetic pathways. Nontwisted **6** and twisted **7** were synthesized independently, respectively from **9** and **13** (Scheme III). Using decoupling experiments, the 250-MHz NMR spectra of the azatricyclic amines **6** and **7** were carefully analyzed in detail. This comparative study enabled us to assign a homobrendane structure to the intramolecular cyclization product **2** of the olefinic *N*-chloroamine **1**.[4]

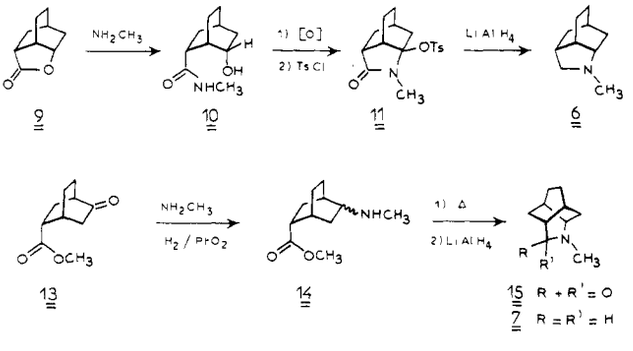
Scheme I



Scheme II



Scheme III



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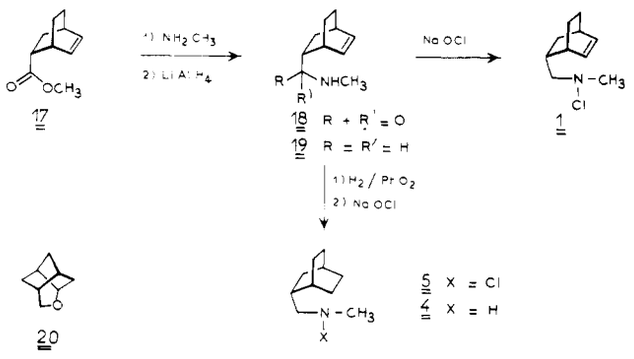
Scheme IV



It is the purpose of this paper to describe (1) the synthesis of tricyclic amines **2**, **6**, and **7**; (2) the 250-MHz NMR spectral analysis of these compounds and the use of these spectral data for structure assignment to the cyclization product of unsaturated *N*-chloroamine **1**.

Results and Discussion

A. Synthesis. Independent synthesis of tricyclic amines **6** and **7**, as well as preparation of *N*-chloroamines **1** and **5**, respectively, are shown in Schemes III and IV.[4,12] Details will be found in the Experimental Section. The 250-MHz NMR features of **6** and **7** (**7** obtained from **13**) and the signal assignments are described below.

Cyclization of *N*-Chloroamine 5 (Scheme II). Although two structures **6** or **7** may be predicted, a single compound is obtained when *N*-chloroamine **5** is submitted to the conditions of the Hofmann–Loeffler–Freytag reaction. Its structure is identical with the nontwisted model **6** obtained from **9** (Scheme III).

Cyclization of *N*-Chloroamine 1 (Scheme I). Similarly, a unique product which might have structure **2** or **3** is obtained in good yield (75%) when *N*-chloroamine **1** is treated for 3 h with silver oxide in boiling methanol. The same compound is formed (56%) besides five other products (18%) and starting amine (26%) when **1** is treated in boiling methanol for 36 h. The mechanisms of these reactions will be discussed elsewhere.[13]

The comparison of the NMR spectrum of **2** with those of **6** and **7** (see below) allows us to assign without any doubt a "nontwisted" homobrendane structure **2**[14] to the solvolysis product of *N*-chloroamine **1**.

B. 250-MHz NMR Spectroscopy. As there has been some disagreement in signal assignments, for instance on compound **2**,[5,14] or for octahydroindol[15,16] derivatives, the analyses we propose for the different spectra are essentially based on spin decoupling experiments, which allow unambiguous signal assignments to the various protons (see Tables I–III).

Compound 6 (Spectra 1a, 1b, 1c, Figure 1, Table I). The recording of the spectrum of this compound is of particular interest, as we have observed a variation of its aspect with the time. Spectrum 1a is obtained when the recording is carried out immediately after dissolution of the sample in deuteriochloroform. First-order analysis on this spectrum is very difficult, and the interpretation of decoupling experiments would have been problematic. When a drop of trifluoroacetic acid is added to the solution, spectrum 1c is obtained, and six protons can quite easily be identified (see Table I and discussion below). The general aspect of the spectrum is in between these two extreme situations, when the recording is carried out on a deuteriochloroform solution which has been left standing for a certain time. For example, spectrum 1b was obtained on a 3 weeks old solution. The explanation is as follows: in presence of trifluoroacetic acid, the amine is rapidly and totally protonated,[17] whereas in deuteriochloroform, the protonation—in fact deuteration—is only partial. In the latter case the phenomenon is due to DCl formed by slow decomposition of deuteriochloroform.[18] The NMR spectra clearly show that these protonations are clean reactions. Furthermore, it is always possible to recover unchanged tricyclic amine from the solutions (when trifluoroacetic acid is used an alkaline treatment is needed). Consequently, molecular

Table I. Analysis of Spectrum 1c

Chemical shift, δ	Integration	Multiplicity	Assignments	Coupling constants
3.37	1H	dd	H_6	$J_{H_6,H_{5exo}} = 8$ Hz $J_{H_6,H_1} = 5$ Hz $J_{H_6,H_{5endo}} \leq 1$ Hz $J_{H_6,H_2} \leq 1$ Hz
3.15	1 H	dd	H_{8a}	$J_{H_{8a},H_{8b}} = 10$ Hz $J_{H_{8a},H_2} = 5$ Hz
3.06	1 H	d	H_{8b}	$J_{H_{8b},H_{8a}} = 10$ Hz $J_{H_{8b},H_2} \leq 1$ Hz
2.72	3 H	s	CH_3	
2.36	1 H	m	H_2	$J_{H_2,H_{3exo}} = 11$ Hz $J_{H_2,H_{8a}} = 5$ Hz $J_{H_2,H_{8b}} \leq 1$ Hz $J_{H_2,H_1} = 4.5$ Hz $J_{H_2,H_6} \leq 1$ Hz
2.13	1 H	m	H_1	$J_{H_1,H_6} = 5$ Hz $J_{H_1,H_2} \simeq 4.5$ Hz $J_{H_1,H_9} \simeq 4$ Hz
1.36–2.02	9 H	m		

Table II. Analysis of Spectrum 2

Chemical shift, δ	Integration	Multiplicity	Assignments	Coupling constants
2.89	1 H	dd	H_{7b}	$J_{H_{7b},H_{7a}} = 9$ Hz $J_{H_{7b},H_2} = 3.5$ Hz
2.62	1 H	dd	H_5	$J_{H_5,H_{10exo}} = 5$ Hz $J_{H_5,H_4} = 5$ Hz
2.30	3 H	s	CH_3	
2.26	1 H	d	H_{7a}	$J_{H_{7a},H_{7b}} = 9$ Hz $J_{H_{7a},H_{3exo}} = 2$ Hz
2.06	1 H	m	H_4	$J_{H_4,H_5} = 5$ Hz
1.84	1 H	m	H_2	$J_{H_2,H_{7b}} = 3.5$ Hz
1.32–1.80	8 H	m		
1.17	1 H	dd	H_{10exo}	$J_{H_{10exo},H_1} = 0$ $J_{H_{10exo},H_{10endo}} = 12$ Hz $J_{H_{10exo},H_5} = 5$ Hz

Table III. Analysis of Spectrum 3

Chemical shift, δ	Integration	Multiplicity	Assignments	Coupling constants
3.35	3 H	s	OCH_3	
3.27	1 H	d	H_5	$J_{H_5,H_4} = 4.5$ Hz
2.64	1 H	dd	H_{8a}	$J_{H_{8a},H_{8b}} = 9$ Hz $J_{H_{8a},H_2} = 4.5$ Hz
2.56	1 H	d	H_6	$J_{H_6,H_1} = 5$ Hz
2.50	3 H	s	NCH_3	
2.44	1 H	d	H_{8b}	$J_{H_{8a},H_{8b}} = 9$ Hz
2.10	1 H	m	H_2	
1.91–1.60	5 H	m		
1.17	2 H	m	H_{3exo} H_{10a}	

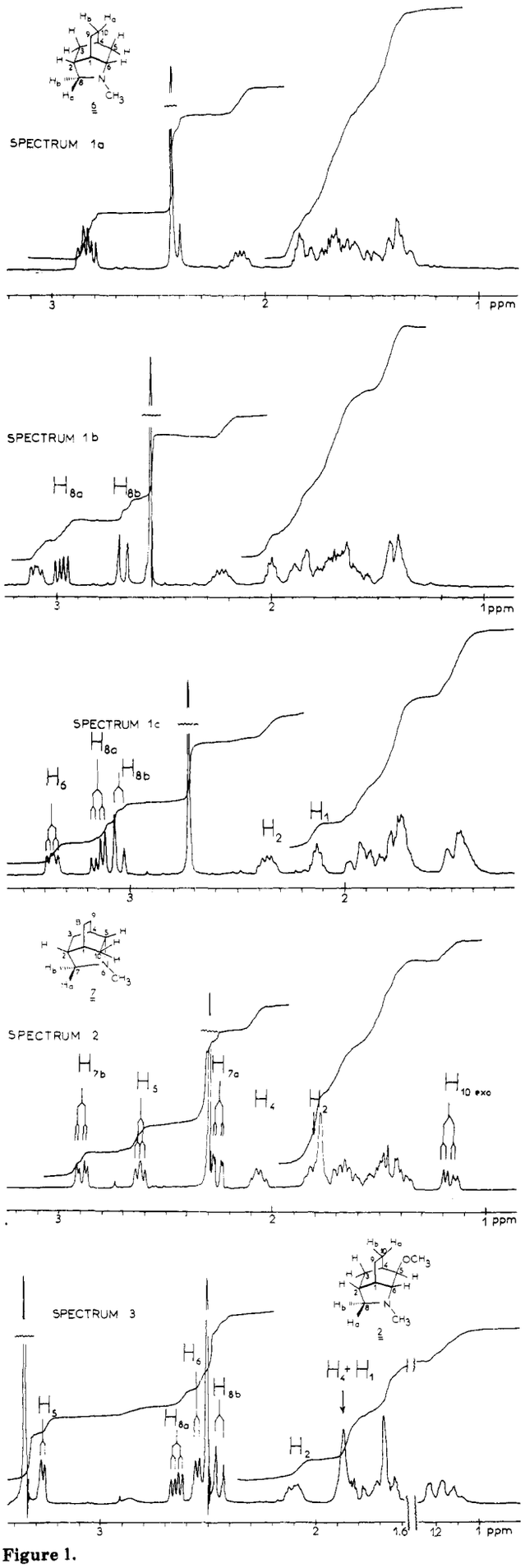


Figure 1.

modifications can be definitely excluded. We report, in Table I, the detailed analysis of easily reproducible spectrum 1c, resulting from complete protonation at the nitrogen atom.

As can be seen on spectrum 1b, the low-field signals centered at 2.98 and 2.69 ppm are the typical AB part of an ABX system, deshielded by nitrogen. These A and B signals are spread apart in spectrum 1a, but the low-field multiplet results from the overlap of two signals due to different protons (see below). The A and B signals start merging together in spectrum 1b, to get even closer in spectrum 1c. Similar signals have been reported in various azapolycyclic compounds such as octahydroindol derivatives[15] or decahydroquinolines.[19] Furthermore, polycyclic ethers, having structures similar to **6**, exhibit comparable spectra.[20] As spectrum 1b easily permits spin decoupling on each signal of the above mentioned ABX system, all the decoupling experiments necessary to allow signal assignments to the various protons have been conducted on the corresponding solution.

The ABX structure is confirmed by irradiation of the doublet of doublets centered at 2.98 ppm, which transforms the doublet at 2.69 ppm into a singlet, and sharpens the signal at 2.23 ppm. However, a small perturbation is also observed around 1.6 ppm, and is very likely due to partial irradiation of the signal at 3.1 ppm (assigned to H_6, see below) which is quite near the irradiated signal. The only protons which can correspond to signals having these fine structure and chemical shifts, in molecule **6**, are protons H_{8a} and H_{8b} (AB) and H_2 (X). Molecular models clearly show the 90° dihedral angle between C_8H_{8b} and C_2H_2, which results in a practically zero value for the corresponding coupling constant. Therefore, the signal at 2.69 ppm can be assigned to H_{8b}. According to these experiments, the signal at 3.10 ppm, which is strongly deshielded, can only be due to proton H_6, expected to exhibit a long-range coupling with H_2. Indeed, the irradiation of the signal centered at 3.10 ppm (H_6) does not perturb the signal at 2.69 ppm assigned to H_{8b}; but the signals at 2.23 (H_2) and 1.98 ppm are sharpened, whereas a modification is observed in the 1.6-ppm region. Consequently the signal at 1.98 ppm is assigned to proton H_1. Even so, the signals centered at 2.23 and 1.98 ppm are pretty close; one observes that irradiation of H_2 (at 2.23 ppm) modifies the fine structure of the signal at 1.98 ppm due to H_1. Accordingly, the proton which gives a signal around 1.6 ppm can only be due to exo H_5 (endo H_5 and H_6 form a dihedral angle of about 90°).

The irradiation of H_2 (2.23 ppm) also transforms the doublet of doublets at 2.98 ppm (H_{8a}) into a simple doublet and sharpens the signal centered at 3.10 ppm (H_6), showing the existence of a small long-range coupling. The spectrum analysis and the spin decoupling experiments are self-consistent and in perfect agreement with the structure of compound **6**.

Compound 7 (Spectrum 2, Figure 1, Table II). With the exception of the high-field doublet of doublets centered at 1.17 ppm, the general aspect of this spectrum is somewhat similar to the one of spectrum 1c; in particular, there are three low-field signals at 2.26, 2.62, and 2.89 ppm which are very likely to be due to the three protons next to the nitrogen atom (H_{7a}, H_{7b}, and H_5). However, their fine structure is quite different from the one observed in spectrum 1c but similar to the one reported for the twisted ether **20**[21] (Scheme IV). The two peaks at 1.84 and 2.06 ppm are more delicate to assign on the basis of the chemical shifts; by analogy with spectrum 1c, they could be due to H_2 and H_1 but, because of the twisted structure, proton H_4 (see model) (which is now pretty close to nitrogen) could also appear in this area. All these observations clearly show that decoupling experiments are absolutely necessary to make unequivocal signal assignments.

The first decoupling experiments are meant to identify the ABX system due to protons H_{7b}, H_{7a}, and H_2 (which appear

respectively at 2.89, 2.26, and 1.84 ppm). Irradiation of the signal centered at 2.89 ppm transforms the doublet of doublets at 2.26 ppm into a doublet (with a small coupling constant), and perturbs the signal centered at 1.84 ppm; this irradiation does not affect the signals at 2.62 and 2.06 ppm. Therefore, neither of these two latter signals corresponds to protons H_2. At this point, we would like to emphasize that, if the assignment of the signal at 2.06 ppm had been made by analogy with spectrum 1c, it should have been related with proton H_2. The above mentioned decoupling experiments show that this is definitely not correct. In fact, this signal corresponds to proton H_4 (see below).

According to the above mentioned decoupling experiments, proton H_2 is most likely to appear at 1.84 ppm. Irradiation of the signal at 1.84 ppm (H_2) leads to the collapse of the signal at 2.89 ppm into a simple doublet, but does practically not perturb the signal at 2.26 ppm. As the Dreiding models clearly show that the C_2H_2–C_7H_{7a} dihedral angle is very close to 90°, the signal at 2.26 ppm must be assigned to H_{7a}. The doublet of doublet at 2.89 ppm can therefore only be due to H_{7b}. A small long-range coupling (probably with exo H_3) is at the origin of the fine structure of the signal of H_{7a} at 2.26 ppm.

The remaining low-field signal at 2.62 ppm can now only be assigned to proton H_5. Indeed, when it is irradiated, the *only* modifications observed are as follows: the signal at 2.06 ppm collapses into a wide triplet, whereas the doublet of doublets at 1.17 ppm is transformed into a doublet. As the C_5H_5–$C_{10}H_{10\ endo}$ dihedral angle is practically equal to 90°, the doublet of doublets at 1.17 ppm can only be assigned to proton exo H_{10} coupled with endo H_{10} and H_5. Consequently the multiplet at 2.06 ppm must be due to H_4. This is confirmed by irradiation at 2.06 ppm (H_4) which leads to the collapse of the H_5 triplet (at 2.62 ppm) into a doublet. It was not possible to locate precisely the other vicinal protons (H_3 and H_9) which appear between 1.3 and 1.8 ppm.

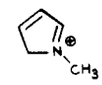
It can be seen from the above discussion that, in order to effect unambiguous proton–signal correlations, it was absolutely necessary to carry out detailed analysis and spin decoupling experiments on samples of known structure. This clearly shows that it was not possible to determine the structure of an unknown compound (such as **2**) on the sole basis of its NMR spectrum, without any reference spectra. These are needed because similar signals in the spectrum of compounds **6** and **7** correspond to different protons. For instance, the chemical shift of the H_2 proton of each tricyclic amine are quite different (2.12 ppm in spectrum 1a and 1.84 ppm in spectrum 2; the signal which appears at 2.06 ppm in spectrum 2 is due to proton H_4).

Having these analyses in hand, it is now possible to compare the spectrum of compound **2** to those of **6** and **7**, and thus to deduce the structure of methoxy amine **2**.

Compound 2 (Spectrum 3, Figure 1, Table III). Spectrum 3 of compound **2** (Table III) is much more similar to spectrum 1b of tricyclic amine **6** than to spectrum 2 of 2-azatwistane **7**. In spectrum 3, the AB part of the ABX system, assigned to H_{8a} (at 2.64 ppm) and to H_{8b} (at 2.44 ppm), exhibits the same fine structure as in spectrum 1b, and is clearly different from the corresponding signals of H_{7a} and H_{7b} in spectrum 2 of compound **7**. As these features seem to be characteristic of the azahomobrendane structure, we therefore assigned—and confirmed by decoupling experiments (see below)—this type of skeleton to compound **2**. Furthermore, on the basis of chemical arguments, the methoxy group was expected to be exo.[13] Consequently proton H_6 should appear as a doublet (90° dihedral angle between C_5H_5 and C_6H_6) which must be the one at 2.56 ppm. The signal at 3.27 ppm can only be due to proton H_5 deshielded by the methoxy group.

Irradiation experiments completely agree with these signal assignments (presented in Table III). As in tricyclic amine **6**, irradiation of the signal at 2.44 ppm (H_{8b}) transforms the doublet of doublets at 2.64 ppm (H_{8a}) into a simple doublet. Irradiation at 2.10 ppm (H_2) transforms this same signal (H_{8a}) into another doublet. Finally, irradiation at 1.84 ppm (H_1 and H_4) leads to collapse of the doublets centered at 2.56 (H_6) and 3.27 ppm (H_5) into singlets, and also perturbs the signals centered at 2.10 ppm.

Mass Spectrometry. The mass spectrometry fragmentations observed for compounds **2, 6,** and **7** are not in disagreement with the proposed structures. In particular, the spectra of compounds **2** and **6** exhibit a fragment at *m/e* 82 (respectively 26 and 44%), which possibly corresponds to an ion of type **21.** This kind of ion has been observed for similar compounds.[22-24] Interestingly enough, this type of ion does not exist in the spectrum of **7.** Although not a proof of structure by itself, this is a supplementary clue for the determination of the twisted—or nontwisted—structure of this type of cage compound.



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Experimental Section

Infrared spectral data were obtained from a Perkin-Elmer 257 spectrophotometer. Routine nuclear magnetic resonance spectra were obtained from a Varian XL 100 WG spectrometer, and 250-MHz spectra were obtained from a Cameca spectrometer. Mass spectra were obtained from a Varian MAT CH 5 and from a Varian MAT 111 spectrometer. All melting points and boiling points are uncorrected.

Lactone 9. This lactone has been prepared by the method described by Wagner and co-workers.[25]

Amido Alcohol 10. Lactone **9** (5 g, 33 mmol) is dissolved in a 30% methanol–methylamine solution and kept for 2 days at normal temperature in a stoppered flask. The solvent is distilled under reduced pressure, to give crude amido alcohol **10.** This is recrystallized in cyclohexane to yield 5.5 g of product (90%): mp 125–130 °C; M^+ *m/e* 183; IR ($CHCl_3$) 3460, 3300, 2940, and 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.1–2.65 (m, 11 H), 2.8 (d, 3 H), 3.8 (m, 1 H), 5.59 (d, 1 H), and 6.52 (m, 1 H).

A solution of this compound (4.5 g, 24 mmol) in 40 mL of CH_3COOH is treated with stirring by slow addition of a solution of 2.8 g of CrO_3 in 36 mL of CH_3OH/H_2O (90%). After 4 h at room temperature the solvents are distilled under vacuum and one adds 40 mL of water. The aqueous solution is continuously extracted with $CHCl_3$ for 24 h. The organic phases are washed successively with a 10% aqueous $NaHCO_3$ solution, then with brine, and dried over magnesium sulfate. Stripping the solvent gives 4 g of crude product, purified by chromatography on an alumina column (pentane–methylene chloride). One gets 2.6 g (14 mmol) of lactam **10** (58%): mp 60–65 °C; M^+ *m/e* 181; IR ($CHCl_3$) 1675 cm^{-1}; NMR δ 1.2–3 (m, 14 H) (with a singlet at 2.7), 5.2 (s, 1 H).

Tosylate 11. *p*-Toluenesulfonyl chloride (1 g) is added in small portions to a 500-mg solution of **10** in 3 mL of pyridine cooled in an ice bath. After 24 h at room temperature, pyridine is stripped under reduced pressure. Water (10 mL) is added and extracted with three portions of 10 mL of chloroform. The organic phase is washed with a 10% solution of sodium bicarbonate, then with brine, and dried over magnesium sulfate. Evaporation of the solvent gives 500 mg of tosylate **11** (30%): NMR (CCl_4) δ 7–8 (m, 4 H), 1.1–3.5 (m, 17 H) with two singlets at 2.28 and 2.4.

Amine 6. This tosylate is directly reduced by action of 200 mg of lithium aluminum hydride in 30 mL of dry tetrahydrofuran (15 h reflux). After normal workup one gets 80 mg of amine **6,** which proves to be identical in all points with the compound obtained by photocyclization of **5** (see below) (yield 50%): M^+ *m/e* 151; picrate mp 264–265 °C; NMR, see the 250-MHz NMR spectra previously described.

Keto Ester 13. This keto ester was prepared following the method described by Lee.[26]

Amine 14. A suspension of PtO_2 (200 mg) in 15 mL of methanol is placed under hydrogen for 0.5 h. Keto ester **13** (3.64 g) and 3.45 mL of a 30% methanol solution of methylamine are added. The solution

is kept under hydrogen with efficient stirring, until absorption of the stoichiometric quantity of hydrogen. The catalyst is then filtered and the solvent stripped under reduced pressure. One gets 3.4 g of amine **14** (87%): IR (CCl_4) 3340 cm^{-1}; NMR ($CDCl_3$) δ 3.34 (s, 3 H), 2.30 (m, 2 H), 2.19 (s, 3 H), 2.19–1.0 (m, 11 H).

Amide 15. Amino ester **14** (5.3 g) placed in a small distillation apparatus is heated by means of a metallic bath to 250–270 °C for 1.5 h. Methanol slowly distills. The residue is taken off with chloroform and passed through a 30-g column of silica gel (chloroform elution). The solvent is stripped to yield 2.89 g of practically pure lactam **15** (65%). This can be purified further by preparative GC on a 3% SE-30, 3-m column at 140 °C: IR ($CHCl_3$) 1680 cm^{-1}; NMR (CCl_4) δ 3.40 (m, 1 H), 2.75 (s, 3 H), 2.48 (m, 1 H), and 2.25–1.10 (m, 11 H). This spectrum proves to be identical with the one kindly supplied by Professor Tichy.[27]

***N*-Methyl 2-azatwistane.** Lactam **15** (2.89 g) is reduced by reaction with 1.3 g of lithium aluminum hydride in 50 mL of refluxing dry ether for 15 h. After normal workup and distillation (68 °C, 5 mm), one gets 2.15 g of *N*-methyl-2-azatwistane **7** (78%): picrate mp 245–258 °C dec; NMR (CCl_4) δ 2.9–0.9 (m, 14 H), 2.19 (s, 3 H); high-resolution mass spectrum M^+ 151.1358 (calcd for $C_{10}H_{17}N$, 151.1360).

***N*-Chloroamines.** The *N*-chloroamines have been obtained by following the usual procedure as follows. The amine is placed in about ten times its volume of methylene chloride, and this solution is vigorously stirred in the dark with an excess of 1–1.5 M commercial bleach for 1.5 h and then extracted with three portions of methylene chloride. The organic phases are washed with brine, then water, and dried over magnesium sulfate. The solvent is stripped under vacuum without heating, in the dark. The yield of *N*-chloroamine is practically quantitative and its purity, which can be checked by iodometry, is around 95–98%.

Solvolysis of 1 in the Presence of Silver Oxide. Chloroamine **1** (3 g) is dissolved in 100 mL of dry methanol. The flask is flushed with nitrogen and 3 g of silver oxide is added. The mixture is heated to boiling under vigorous stirring for 3 h.

After cooling, the solution is passed through a short Florisil column. The solvent of the filtrate is then stripped to yield 2.3 g of **2** (75–77%): bp 49–51 °C (0.7 mm); high-resolution mass spectrum M^+ found 181.146755 (calcd, 181.146156); picrate mp 175–176 °C; IR ($CHCl_3$) 1098 cm^{-1}; NMR, see description of the 250-MHz spectrum.

5-Carbomethoxybicyclo[2.2.2]octene (17). Freshly distilled methyl acrylate (10 g) is placed in a sealed tube together with 13.5 g of 1,3-cyclohexadiene and 100 mg of hydroquinone. The solution is heated at 90 °C for 36 h. The product is distilled under vacuum to give 16.3 g of adduct **17** (70%): bp 90–94 °C (10 mm); IR 3040, 2940, 1680, and 600 cm^{-1}; NMR (CCl_4) δ 5.9–6.4 (m, 2 H), 3.55 (s, 3 H), 2.34–3 (m, 3 H), 1–1.9 (m, 6 H).

Carboxamide 18. This ester (10 g) is dissolved in 100 mL of a 30% methylamine solution in methanol and placed in a stoppered flask. After 5 days, the solvent is stripped and the residue is recrystallized in cyclohexane to give 7.9 g of **18** (80%): mp 140 °C; IR ($CHCl_3$) 3460, 2940, and 1650 cm^{-1}; NMR ($CDCl_3$) δ 6.1–6.58 (m, 2 H), 5.65 (s, 1 H), 2.75 (d, 3 H), and 1–3 (m, 9 H).

Amine 19. This amine is obtained by usual reduction of **18** by means of lithium aluminum hydride in boiling tetrahydrofuran. After normal workup and distillation under vacuum (58–61 °C 2 mm) one gets amine **19** (70% yield): IR (CCl_4) 3640, 3350, 3040, 2940, 2860, and 695 cm^{-1}; NMR (CCl_4) δ 6.25 (m, 2 H), 2.70–0.67 (m, 15 H), with two singlets at 2.55 and 2.49.

Amine 8. This amine can be obtained by direct hydrogenation of **19** in ethanol over PtO_2 (yield 27%): IR (CCl_4) 2820, 2860, 2790, and 1460 cm^{-1}; NMR (CCl_4) δ 0.95 (s, 1 H), 1–1.98 (m, 14 H) (singlet at 1.5), and 2.3–2.6 (m, 5 H) (singlet at 2.38).

Cyclization of 8 by Hofmann–Loeffler–Freytag Reaction. Amine **8** (700 mg) is transformed, following the standard procedure, into the chloroamine **5**. This chloroamine is added *dropwise* to 10 mL of trifluoroacetic acid contained in a quartz tube, which is cooled in an ice water bath. The solution is carefully flushed with nitrogen (0.5 h) and irradiated with a 150-W mercury high-pressure Hanovia lamp. After disappearance of the *N*-chloroamine (iodometric test) (2 h), the acid is distilled under reduced pressure and the residue, dissolved in 10 mL of methanol, treated with potassium carbonate until the solution is alkaline (pH 9–10).

The methanol is stripped off under reduced pressure and the residue taken up with a minimum of water. This aqueous phase is extracted with ether, and the ether layer is washed with brine and dried over magnesium sulfate. After filtration and stripping off the solvent, one gets 500 mg of amine **6** (70%). This amine can be purified by gas chromatography (PEG 4000, OH^-, 1.5 m, 150 °C): mp picrate 264–265 °C; IR (CCl_4) 2930, 2860, 1450, and 1340 cm^{-1}; NMR, see 250-MHz spectrum previously described; high-resolution mass spectrum M^+ found 151.1369 (calcd, 151.1360).

Registry No.—**1**, 55751-48-9; **2**, 55751-50-3; **2** picrate, 62520-73-4; **5**, 62460-66-6; **6**, 62460-67-7; **6** picrate, 62460-68-8; **7**, 59238-80-1; **8**, 62460-69-9; **9**, 6715-18-0; **10** alcohol, 62460-70-2; **10** lactam, 62460-71-3; **11**, 62460-72-4; **13**, 49826-55-3; **14**, 62504-20-5; **15**, 59238-79-8; **17**, 25578-17-0; **18**, 62460-73-5; **19**, 62460-74-6; methylacrylate, 96-33-3; 1,3-cyclohexadiene, 592-57-4.

References and Notes

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