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CHAIR–BOAT INTERCONVERSIONS IN CYCLIC SEVEN-MEMBERED AMIDES AND RELATED STRUCTURES

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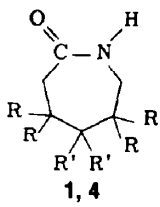
Abstract—The transition state to ring reversal has been examined in a series of 7-membered rings related to caprolactam. The structural changes associated with introduction of Me groups, with alteration of the nature of the C=N double bond, with ring fusion, or with introduction of a second, nonconjugated N atom perturb the transition state to ring reversal. From ^1H and ^{13}C NMR studies, we find that the lactam bond itself favors a different transition state from that present in cycloheptene. With some exceptions, the observed barriers are consistent with TS II, in which ring reversal begins with movement of the C_5 end of the ring, or with TS III, in which ring reversal begins with C_3–C_4 bond torsion. The conclusions are consistent with the structural changes that result from the functional and steric alterations.

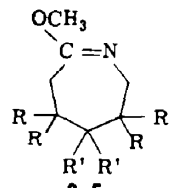
The presence of a double bond within a 7-membered ring considerably alters the conformational situation. In cycloheptane, pseudorotation can occur within both the boat and the chair families, so that a geminal pair of substituents are rapidly interconverted without chair–boat ring flip. In cycloheptene, the chair is a rigid conformation, and there is no pseudorotation. Within the cycloheptene boat family, however, pseudorotation is still rapid. Consequently, geminal interconversion within the chair occurs by a high-barrier sequence of chair–boat flip, boat family pseudorotation, and boat–chair flip, much as in cyclohexane. Provided that the chair is the favored form, conformational stability not unlike that of cyclohexane could be expected. A favored boat, however, would convey much more rapid geminal interconversion.

The chair–boat interconversion can occur by several pathways, which have been studied by NMR[1–3] and molecular mechanics[4–7] methods. Allinger calculated the activation energies for three modes of interconversion, each involving a different initial deformation of the ring and a different transition state. (1) The four carbon fragment that includes the double bond can move into the plane of C_4 and C_6 to produce a transition state with six atoms in the same plane (TS I) (Fig. 1), calculated to be 5.16 kcal/mol above chair cycloheptene.[7] (2) Movement of C_5 into the plane of the other four saturated atoms produces TS II, calculated to be 10.26 kcal/mol above chair cycloheptene.[7] (3) Torsional motion around C_3–C_4 (C_6–C_7) produces a biplanar transition state (TS III), calculated to be 8.87 kcal/mol above chair cycloheptene.[7] Torsion about C_4–C_5 (C_5–C_6) produces a very similar result.

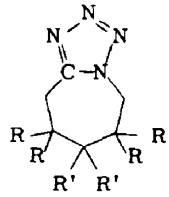
Despite the clarity of these calculations in favoring TS I for cycloheptene, experimental evidence has not been firm. Magnetic resonance experiments have been interpreted in favor of both double bond deformation (TS I) and C_5 deformation (TS II).[1,2] We report herein an approach to cycloheptene conformational analysis that involves altering the electronic nature of the double bond and probing the transition state structure through ring substitution. Our studies on the conformation of hexahydro - 1,4 - diazepinones suggested that substituted lactams would provide a viable vehicle for such a study.[8] Consequently, we have prepared a series of 7-membered rings related to caprolactam. In this series we have varied the mode of Me substitution on the ring in order to produce different degrees of transition state crowding. The caprolactams (**1**, **4**) have a partial double bond that may permit alternative conformational pathways. O-Methylcaprolactim ethers (**2**, **5**) have a nearly full double bond within the ring, approaching that of cycloheptene. Fusion with a tetrazole ring (**3**, **6**) serves in the same capacity as a full double bond to inhibit pseudorotation in the chair family. Hexahydro - 1,4 - diazepinones (**7**–**9**) contain the lactam linkage in which nitrogen substitution can perturb the transition state. For each structure, we have prepared both a simple *gem*-dimethyl compound (**1**–**3**, **7**, **8**) and one with two *gem*-dimethyl groups arranged 1,3 to each other for maximum interaction (**4**–**6**, **9**). We report the measurement of the barriers to chair–



1, 4

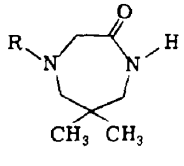


2, 5

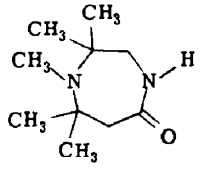


3, 6

1, 2, 3 R = H, R′ = CH_3
4, 5, 6 R = CH_3, R′ = H



7 R = CH_3
8 R = H



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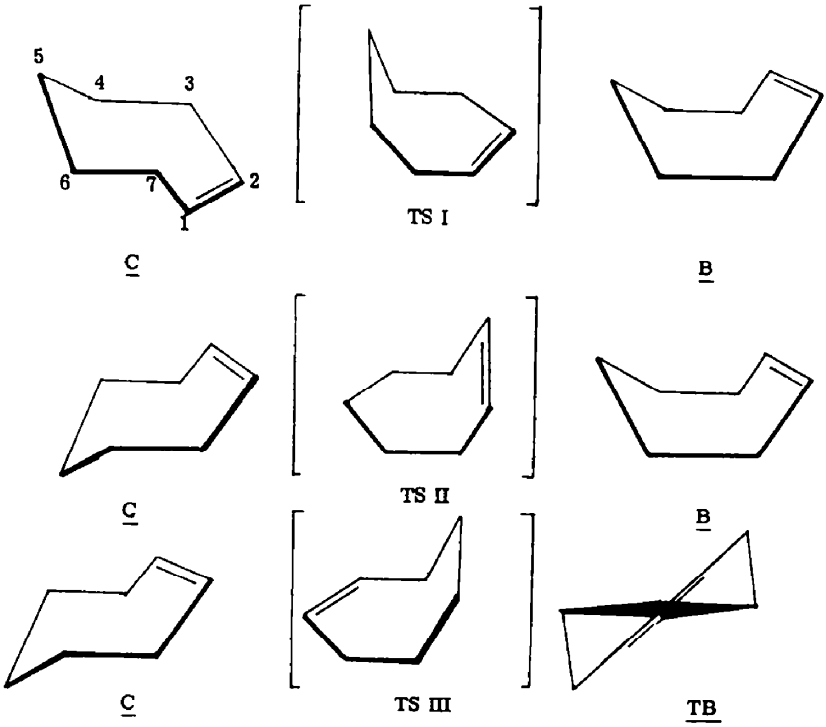


Fig. 1. Three transition states for chair ⇌ boat interconversion in cycloheptene (Ref. 7).

boat interconversion in these systems and discuss the implications of these observations in terms of the transition state structures.

RESULTS

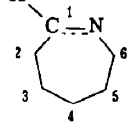
Compounds **1–9** were obtained by standard rearrangement reactions of six-membered rings. 5,5 - Dimethylhexahydroazepin - 2 - one (**1**) was produced by the Beckmann rearrangement of 4,4 - dimethylcyclohexanone, and 5,5 - dimethyl - 2 - methoxytetrahydro - Δ_1 - azepine (**2**) was prepared by the action of dimethyl sulfate on **1**. Treatment of 4,4 - dimethylcyclohexanone with an excess of diazomethane yielded 4,4 - dimethyl - 1,8,9,10 - tetrazabicyclo[5.3.0]deca - 7,9 - diene (**3**). In the tetramethyl series, 4,4,6,6 - tetramethylhexahydroazepin - 2 - one (**4**) and its tetrazole derivative 3,3,5,5 - tetramethyl - 1,8,9,10 - tetrazabicyclo[5.3.0]deca - 7,9 - diene (**6**) were obtained by the Schmidt reaction of 3,3,5,5 - tetramethylcyclohexanone. The 6,6 - dimethylhexahydro - 1,4 - diazepin - 2 - ones (**7**, **8**) were obtained as described previously.[9] 1,2,3,5,5 - Pentamethylhexahydro - 1,4 - diazepin - 5 - one (**9**) was prepared by the Schmidt reaction of 1,2,2,6,6 - pentamethyl - 4 - piperidone.

The ^{13}C spectra were examined as a function of temperature for all systems (**1–9**), and the room temperature chemical shifts may be found in Table 1. Only the geminal Me resonances underwent decoalescence at low temperatures. The coalescence temperatures, the slow exchange chemical shift differences, and the activation free energies are given in Table 2. The ^1H spectra were examined as a function of temperature for some of the systems (**1**, **2**, **4**, **6**, **7** and **9**), and the analogous data from these experiments are also given in Table 2. In the ^1H spectra, decoalescence was observed for only the methylene protons α to the amide bond. The lack of decoalescence for the geminal Me protons was probably the result of relatively small chemical shift separations at slow exchange. The agreement between the $\Delta G^{\ddagger}$ obtained from the ^{13}C and the ^1H spectra is excellent.

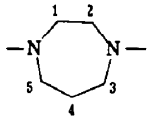
DISCUSSION

All the compounds in the present study resemble cycloheptene in that they have a full or partial double bond within the ring or a similarly constraining ring fusion. The question of conformational family becomes a choice between a rigid chair and a flexible (pseudorotating) boat. The high barriers observed for ring dynamics (8.7–11.4 kcal/mol) are consistent with an interfamily exchange (chair–boat) rather than solely an intrafamily exchange (boat pseudorotation). Con-

Table 1. Carbon-13 chemical shifts (δ in ppm from TMS)



1-6



7-9

Compound	Gem CH_3	C_1	C_2	C_3	C_4	C_5	C_6	CH_3-X
1	28.09	180.74	37.58	31.06	32.33	35.11	41.19	
2	29.24	170.89	41.13	27.84	33.67	36.30	43.98	53.35
3	28.32		39.24	19.38	33.33	37.05	44.73	
4	27.26 30.11	176.94	52.26	49.86	48.78	49.86	52.58	
5	28.27 30.12	169.54	56.84	30.75	42.46	33.21	57.33	52.14
6	27.52 30.17	154.48	56.63	32.28	35.68	34.48	57.64	
7	22.83	62.07	177.58	53.53	33.15	51.87		
8	24.75	63.38	174.93	63.38	48.49	51.95		34.73
9	24.10 26.63	52.12	50.44	159.73	47.63	54.08		31.06

Table 2. Activation parameters for chair–boat interconversion

Compound	T_c, °K		$\Delta\nu$, Hz		$\Delta G^{\ddagger}$, kcal/mol	
	^{13}C	^1H	^{13}C[a]	^1H[b]	^{13}C	^1H
1	237	228	189	48	10.9 ± 0.3	11.1 ± 0.25
2	209	193	188	35	9.6 ± 0.25	9.5 ± 0.3
3	192		221		8.7 ± 0.25	
4	208	208	145	53	9.6 ± 0.25	10.0 ± 0.25
5	209		171		9.6 ± 0.25	
6	243	229	158	38	11.3 ± 0.25	11.3 ± 0.3
7	240	224	89	16	11.4 ± 0.2	11.3 ± 0.3
8	24.		108		11.4 ± 0.25	
9	218	203	240	41	9.9 ± 0.25	9.9 ± 0.25

[a] 20 MHz.
[b] 100 MHz.

sequently, the stable conformation must be the rigid chair, and the observed spectral changes come from chair/boat/twist-boat/chair exchanges, i.e. a chair–chair ring reversal. This conclusion is in agreement with observations in the solid state. X-Ray studies on caprolactam[6,10] and the iodine monochloride complex of pentamethylenetetrazole[11] demonstrated that the chair form is present in the solid.

The fact that the double bond in the caprolactams is only partial suggests that amide torsion may contribute to the conformational dynamics. Amide rotation, however, has a barrier considerably larger (normally around 20 kcal/mol) than those we observe. In the present system, it thus appears that the ring reversal process, with a barrier around 10 kcal/mol, does not require or involve double bond torsion. Similar conclusions were reached in a ^{19}F study of 5,5 - difluorocaprolactam.[1] The observed barriers may be discussed here in terms of the transition states to chair–boat interconversions.

There are at least three modes of chair–boat interconversion[7] (Fig. 1). Replacement of the double bond in cycloheptene by a ring fusion or by an amide bond conveys certain structural alterations. First we will consider how these alterations affect the three transition states. The repulsive C_7H_e–C_1H and C_2H–C_3H_e eclipsing interactions in cycloheptene have been replaced by a possibly repulsive NH–C_7H_e interaction and an attractive CO–C_3H_e interaction in the amides. In aldehydes and ketones, the most favorable arrangement has the aldehydic hydrogen or even the ketonic Me group eclipsed with the CO bond in the same way.[12] Part of the driving force for chair–boat interconversion in cycloheptene via TS I (double bond deformation) is removal of the C_7H_e–C_1H and C_2H–C_3H_e eclipsing interactions. This type of relief is less needed in the caprolactams, since the analogous NH–C_7H_e and CO–C_3H_e interactions are attractive or at least less repulsive (Fig. 2). Thus TS I appears to be less favorable. Formation of TS I also enlarges the bond angles within the ring in the vicinity of the double bond (C_7–N–C_2–C_3). An increase in this angle by the structural modifications of **1–9** would favor TS I, and a decrease would disfavor it. Finally, TS I brings C_4H_a and C_6H_a much closer together. In the 4,4,6,6 - tetramethyl compounds (**4–6, 9**) TS I must be considerably destabilized.

In contrast, TS II (C_s deformation) moves C_4H_a and C_6H_a further apart, while bringing C_3H_a and C_7H_a closer together (Fig. 2). Particularly in the tetramethyl compounds, TS II appears to be more favorable. Formation of TS II also causes a slight reduction in the amide bond angles. This factor may favor TS II for the caprolactams **1** and **2** but may make TS II less likely for the tetrazole **3**, in which the C_6–C_7–N–C_2 angles must be significantly enlarged.

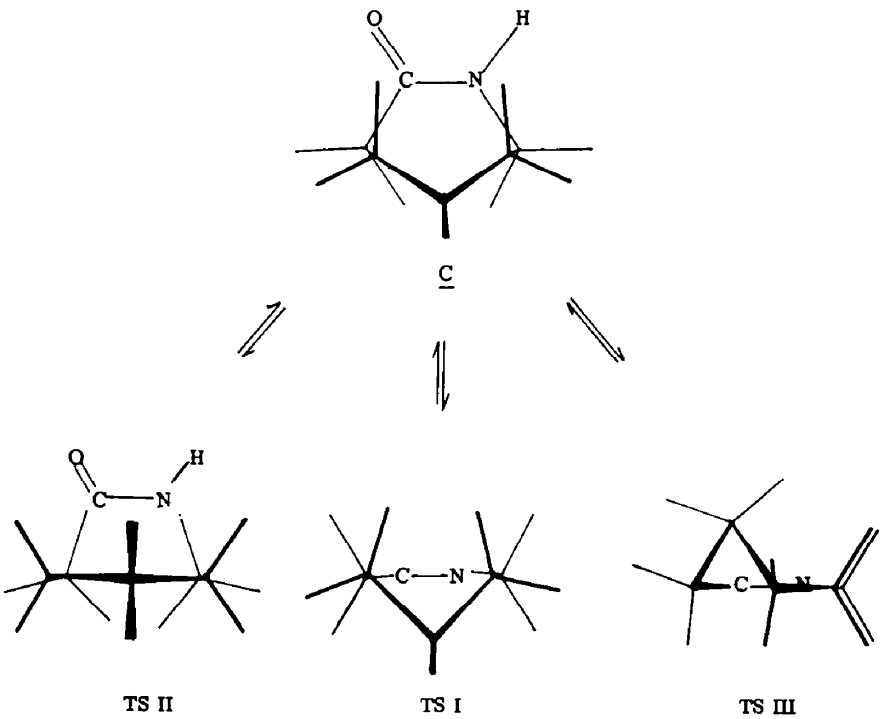


Fig. 2. Frontal projection of the ground state (C), TS I, TS II and TS III for caprolactam.

Transition state TS III can be formed by rotation around the C_6–C_7 bond, bringing about C_6H–C_7H eclipsing (Fig. 2). For the tetramethyl compounds, with two H–CH_3 eclipsed interactions, TS III may not be favorable. Rotation around the C_3–C_4 bond also leads to TS III, but this process can be ruled out because it would disrupt the attractive interaction between C=O or C=N and C_3H.

After this general analysis of the relative merits of the three possible transition states, let us examine each of the systems.

Caprolactams **1** *and* **4**. The lactam moiety C_7–N–C_2–C_3 has one slightly diminished angle (118, 126°) compared to cycloheptene (125°).[7] Such a ring geometry disfavors the formation of TS I, in which these angles must expand. A process forming TS II is favored, since these angles decrease and the attractive CO–NH interaction remains unaltered. The presence of the 5,5-dimethyl group in **1** appears to be very little different from the 5,5-difluoro group studied by Roberts[1] ($\Delta G‡$ = 10.9 and 10.4 kcal/mol, respectively). Further evidence for TS II is found by comparison of the barriers for the 5,5-dimethyl (10.9) and 4,4,6,6 - tetramethyl (9.6 kcal/mol) compounds. If TS I were present for both systems, the barrier for the tetramethyl compound should be considerably larger, since TS I brings the axial groups on C_4 and C_6 closer together. The observation, however, is a 1.3 kcal/mol decrease on going from the dimethyl to the tetramethyl compound. The corresponding decrease in the coalescence temperature is about 30° (Table 2). The lower barrier may be attributed to relief of the ground state Me–Me repulsion on going to TS II. A similar relief is obtained in TS III, which cannot be eliminated as a possibility.

Tetrazole derivatives **3** *and* **6**. The enlargement of the angles around the ring fusion in the ground state probably favors TS I, since this transition state tends to open up these angles even more. Furthermore, if TS II were present in **3**, a decrease in the barrier would have been expected on going to **6**, as in **1** and **4**, because of the Me–Me interaction. In fact, the barrier increases by 2.6 kcal/mol, suggesting a more congested transition state for **3** than for **6**. One possibility is TS I for both systems, but it seems more likely that a change in transition state occurs, for example with TS I for **3** and TS II or TS III for **6**. Such a possibility is shown in Fig. 3. We cannot be more specific with the data at hand.

O-Methylcaprolactim ethers **2** *and* **5**. The free energies of activation were found to be experimentally identical for **2** and **5** (9.6 kcal/mol), as were the coalescence temperatures (209°K). Again, if TS I were favored in both systems, a considerable barrier increase should have been observed for the transition state for **2** and **5**. By a similar argument, the relief of the ground state strain offered by TS II and TS III should have provided a decreased barrier for the tetramethyl compound. Thus the data also eliminate either TS II or TS III as a common transition state for the two systems. Methyl congestion eliminates TS I for **5**, so a possible explanation is TS I for **2** and TS II or TS III for **5**, similar to Fig. 3.

Diazacycloheptanones **7**, **8** *and* **9**. Within this series, introduction of the four Me groups causes a decrease in the barrier, from 11.4 kcal/mol for both **7** and **8** to 9.9 for **9**. The decrease is similar to that observed for the simple caprolactams **1** and **4** and thus also is incompatible with TS I as the transition state. We cannot distinguish unambiguously between TS II and TS III, both of which reduce the axial–axial Me–Me repulsion, but TS II may be preferred. A comparison of the diaza set **7**–**9** with the aza set **1**, **4** shows that introduction of the second N atom imparts a slightly higher barrier. The second N is known to shorten the C–N bond lengths and hence should enhance eclipsing interactions[12] and make the lactam angles harder to open. The TS I requires considerable angle spreading, TS II requires very little, and TS III involves spreading on only one side. Again the conclusion is that TS I is disfavored, and, of the other two possibilities, TS II may be slightly better. Inversion about the nonamide nitrogen remains a rapid process at these temperatures for **7**,[9] **8** and **9**. Solubility problems prevented experiments at lower temperatures. The identity of the barriers for **7** and **8**, despite the differences in substitution at the nonamide nitrogen (Me and H), shows that nitrogen inversion is not involved in the rate-determining step. Replacement of NH by Me normally increases the barrier to inversion.

In summary, perturbation of the chair–boat transition state of cycloheptane by replacement of the double bond with another functionality and by introduction of several Me groups reveals a very complex situation. The tran-

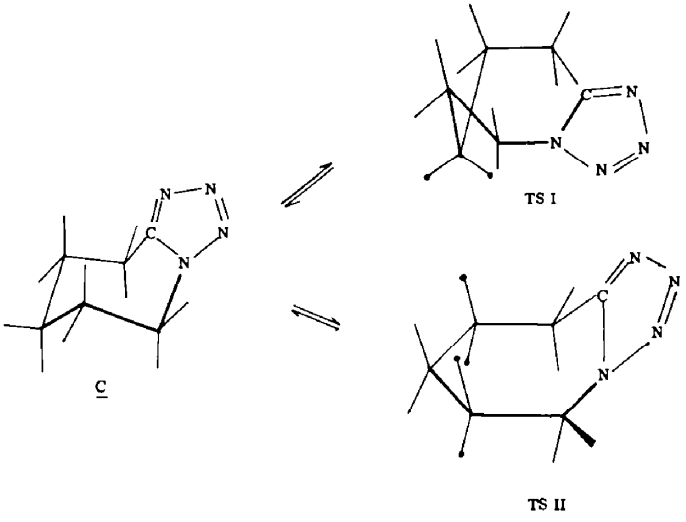


Fig. 3. The probable transition states of **3** (TS I) and **6** (TS II). The filled circles represent methyl groups.

sition state favored for cycloheptene (TS I, double bond deformation) may be present in the bicyclic compound **3** and the ether **2**, because additional Me interactions do not decrease the barrier. For the caprolactams (**1**, **4**) and the diaza systems (**7**, **9**), tetramethyl substitution decreases the barrier, consistent with TS II or TS III. For the bicyclic compounds (**3**, **6**) and the ethers (**2**, **5**), tetramethyl substitution probably changes the transition state. The specific structural alterations of a lactam in comparison with cycloheptene, in the absence of the tetramethyl effects, appear to disfavor the TS I of cycloheptene and favor TS II or TS III. All these systems exist in the rigid chair formation, so that ring reversal takes place through the boat/twist-boat/boat pseudorotation itinerary. Amide bond rotation does not enter into the process for the lactams, nor does inversion of the second nitrogen atom in the diaza systems.

EXPERIMENTAL

The ^1H spectra were recorded at 100 MHz with a Jeol INM4H-100 spectrometer and the ^{13}C spectra at 20 MHz with a Varian CFT-20 spectrometer. The sample temp was measured directly with a thermocouple placed inside an NMR tube containing only solvent. A precision of ±3°C was assured. A mixture of $CH_2Cl_2/CDCl_3$ (3/1) with TMS as an internal standard was used as solvent.

5,5 - *Dimethylhexahydroazepin* - 2 - *one* (**1**). The Beckmann rearrangement of 4,4 - dimethylcyclohexanone oxime[13] was accomplished by heating the compound with conc H_2SO_4 as described for the unmethylated caprolactam,[14] 80% yield, m.p. 90.5–92.5°.

4,4,6,6 - *Tetramethylhexahydroazepin* - 2 - *one* (**4**), 3,3,5,5 - *tetramethyl* - 1,8,9,10 - *tetrazabicyclo*[5.3.0]*deca* - 7,9 - *diene* (**6**), and 1,2,2,7,7 - *pentamethylhexahydrodiazepin* - 5 - *one* (**9**). The appropriate carbonyl compound (0.1 M) 3,3,5,5 - tetramethylcyclohexanone or 1,2,2,5,5 - pentamethyl - 4 - piperidone was dissolved in 150 ml $CHCl_3$ and cooled with dry ice/CH_3OH. Conc H_2SO_4 (50 ml for the cyclohexanone and 80 ml for the piperidone) was added slowly. Sodium azide (0.13 M) was then added in stages, and the mixture was heated to 60° for 6 hr. The contents of the flask was poured over crushed ice, the $CHCl_3$ layer was separated, and the H_2O phase was brought to pH 8–9 at 5°. The ppt of Na_2SO_4 was filtered off, and the filtrate was warmed to 40° and extracted with hot $CHCl_3$ (10 × 50 ml). The combined extracts were dried (Na_2SO_4) and decolorized with charcoal. After the drying agent was filtered off and the solvent was evaporated, the solvent was evaporated, the residue was recrystallized to give **4** or **9** from a mixture of petroleum ether and acetone. In the case of **4**, the insoluble residue from this solvent system was recrystallized from a mixture of acetone and $CHCl_3$ (9/1) to give **6**. The products were **4** (m.p. 146–148°, 50%), **6** (m.p. 199–200°, 20%), and **9** (m.p. 142–144°, 87%).

5,5 - *Dimethyl* - (**2**) and 4,4,6,6 - *tetramethyl* - 2 - *methoxy* - Δ_1 - *azepine* (**5**). To a refluxing mixture of the appropriate caprolactam (**1** or **4**) in 100 ml benzene, Me_2SO_4 (0.02 M) was added slowly. Stirring and heating was continued for 20 hr. The mixture was poured into a 50% Na_2CO_3 aq. The benzene layer was separated, dried (Na_2SO_4), filtered, and evaporated. The residue was distilled under reduced pressure: (**2**), 40% yield, 69–71° (11 mm Hg), n_{20}^D, 1.4623; (**5**), 58% yield, 84–85° (12 mm Hg), n_{20}^D, 1.4610.

4,4 - *Dimethyl* - 1,8,9,10 - *tetrazabicyclo*[5.3.0]*deca* - 7,9 - *diene* (**3**). To a mixture of benzene (100 ml) and conc H_2SO_4 (15 ml) cooled with ice, a soln of 4,4 - dimethylcyclohexanone (3 g, 0.023 M) and hydrazoic acid (from 10.5 g of NaN_3 and 16 ml of H_2SO_4) was added dropwise. The mixture was then poured onto crushed ice, and the benzene layer was removed. The aqueous layer was made basic with KOH and extracted with benzene (3 × 50 ml). The combined benzene layers were dried (Na_2SO_4 and Na_2CO_3), filtered, and concentrated in vacuum. The residue was recrystallized from a mixture of petroleum ether and benzene: 1.9 g (50%), m.p. 166–168°.

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