On the Conformation of Fused Five-Membered Heterocyclic Rings Derived from the Intramolecular Oxime Olefin Cycloaddition Reaction[1]

Alfred Hassner,* Rakesh Maurya, Oded Friedman, and Hugo E. Gottlieb

Department of Chemistry, Bar-Ilan University, Ramat-Gan 52900, Israel

Albert Padwa* and David Austin

Department of Chemistry, Emory University, Atlanta, Georgia 30320

Received March 29, 1993

Thermal intramolecular oxime olefin cycloaddition of α-allylamino aldoximes and ketoximes 4 led stereospecifically to formation of oxadiazabicyclo[3.3.0]octanes 6. The presence of heteroatoms in these bicyclic fused 5-membered rings permits for the first time an evaluation of the conformation of this system by means of NMR. We found that some substituents in 6 restrict the conformational mobility of these five-membered rings to the extent that only one conformer was detected at 20 °C. In other cases an equilibrium between two major conformers was revealed by NMR. Equilibrium measurements indicated a free energy of conversion of 13.2–13.4 kcal/mol, apparently a manifestation of the N-inversion in the isoxazolidine ring. NMR studies also showed that the NH-proton in isoxazolidines 6 prefers an axial orientation. Empirical force field data were adjusted for MM calculations in these bicyclic heterocycles. The MM2 force field with AMBER charge gave the best fit between calculated and experimental coupling constants.

Fused saturated 5-membered rings occur in nature both in carbocyclic (*e.g.*, triquinanes) and heterocyclic (*e.g.*, pyrrolizidine alkaloids) systems and often exhibit interesting pharmacological activity.[2] In contrast to saturated 6-membered rings which usually possess well defined and readily determined conformations (*e.g.*, chair, boat), 5-membered rings are much more flexible, and their conformation is difficult to ascertain.[3] The 1,3-dipolar cycloaddition reaction is among the most powerful tools for 5-membered heterocyclic ring synthesis, since it allows a direct access to cyclic, highly functionalized systems in a regioselective and stereocontrolled manner.[4] The cycloaddition reaction conserves the stereochemistry of the alkene, and a stereocenter on the dipole is often able to influence the relative stereochemistry of the newly formed stereogenic centers in the product. Even greater stereocontrol is possible when both reactants are part of the same molecule, the intramolecular nature often enhancing the stereoselectivity of the cyclization.[5,6] Due to its versatility, the intramolecular dipolar cycloaddition reaction has found wide use in the synthesis of complex natural products.[7-24]

Recently, we described a thermal intramolecular oxime–olefin cycloaddition (IOOC) which afforded fused 5-membered isoxazolidines.[25] These reactions proceed with a remarkable degree of stereoselectivity and were postulated to occur *via* cycloaddition of a reactive NH nitrone species (*e.g.*, 5) to the olefinic double bond.[26] The tricyclic systems, thus prepared (see Scheme I), possessed a certain amount of rigidity, and we used molecular mechanics calculations to correlate calculated J values with empirical proton NMR coupling constants.[26c] Various force field methods and heteroatom parameters were evaluated in order to determine the best fit between the computationally and experimentally determined J values.

We decided to apply the intramolecular oxime olefin cycloaddition to the formation of fused pyrrolidines 6 from

(1) Stereochemistry. 82. For part 81 see: Ghera, E.; Ben-Yaakov, E.; Yecheskel, T.; Hassner, A. *Tetrahedron Lett.* **1992**, 2741.

(2) (a) Comer, F. W.; McCapra, F.; Gureshi, J. H.; Scott, A. I. *Tetrahedron* **1967**, *23*, 4761. (b) Trost, B. M.; Shueg, C. D.; Dininno, F. B., Jr.; McElvain, S. S. *J. Am. Chem. Soc.* **1979**, *101*, 1284. (c) Leonard, N. J. *The Alkaloids*; Academic Press: New York, 1949; Vol. 1, p 107. Robins, D. J. *Prog. Chem. Org. Natl. Prdts* **1982**, *41*, 115.

(3) (a) Fuchs, B. *Top. Stereochem.* **1978**, *10*, 1. (b) Legon, A. C. *Chem. Rev.* **1980**, *80*, 230.

(4) Padwa, A., Ed. 1,3-Dipolar Cycloaddition Chemistry; Wiley-Interscience: New York, 1984; Vols. 1 and 2. Hassner, A. *Heterocycles in Bio-organic Chemistry*; Bergman, J., van der Plas, H. C., Simonyi, M., Eds.; Royal Soc. Chem.: Cambridge, 1991; p 130.

(5) Padwa, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 123. Padwa, A.; Schoffstall, A. M. *Adv. Cycloadd.* JAI Press, Inc.: New York, 1990; Vol. 2, p 1. Rai, K. M. L.; Hassner, A. *Heterocycles* **1990**, *30*, 817.

(6) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1. Terao, Y.; Aono, M.; Achiwa, K. *Heterocycles* **1988**, *27*, 981.

(7) Sammes, P. G.; Street, L. J.; Whitby, R. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 281.

(8) Wender, P. A.; McDonald, F. E. *J. Am. Chem. Soc.* **1990**, *112*, 4956.

(9) Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1985**, *107*, 2569.

(10) Snider, B. B.; Cartaya-Marin, C. P. *J. Org. Chem.* **1984**, *49*, 1688.

(11) Ihara, M.; Takahashki, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1988**, 9.

(12) Chandler, M.; Parsons, P. *J. Chem. Soc., Chem. Commun.* **1984**, 322.

(13) Rousch, W. R.; Walts, A. E. *J. Am. Chem. Soc.* **1984**, *106*, 721. Walts, A. E.; Rousch, W. R. *Tetrahedron* **1985**, *41*, 3463.

(14) Holmes, A. B.; Swithenbank, Williams, S. F. *J. Chem. Soc., Chem. Commun.* **1986**, 265.

(15) Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron* **1985**, *41*, 3455.

(16) Tufariello, J. J.; Meckler, H.; Senaratne, K. P. A. *Tetrahedron* **1985**, *41*, 3447.

(17) Kozikowski, A. P.; Maloney-Huss, K. E. *Tetrahedron Lett.* **1985**, 5759.

(18) Curran, D. P.; Jacobs, P. B.; Elliott, R. L.; Kim, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 5280.

(19) Confalone, P. D.; Ko, S. S. *Tetrahedron Lett.* **1984**, 947.

(20) Smith, R.; Livinghouse, T. *Tetrahedron* **1985**, *41*, 3559.

(21) Jacobi, P. A.; Martinelli, M. J.; Polanc, S. *J. Am. Chem. Soc.* **1984**, *106*, 5594.

(22) Sha, C. K.; Ouyang, S. L.; Hsieh, D. Y.; Chang, R. C.; Chang, C. C. *J. Org. Chem.* **1986**, *51*, 1490.

(23) Pearson, W. H.; Celebuski, J. E.; Poon, Y. F.; Dixon, B. R.; Glans, J. H. *Tetrahedron Lett.* **1986**, 6301.

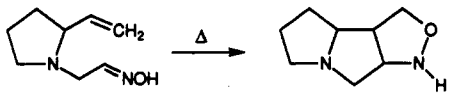
(24) Murthy, K. S. K.; Hassner, A. *Isr. J. Chem.* **1991**, *31*, 237.

(25) Hassner, A.; Maurya, R.; Mesko, E. *Tetrahedron Lett.* **1988**, 5313.

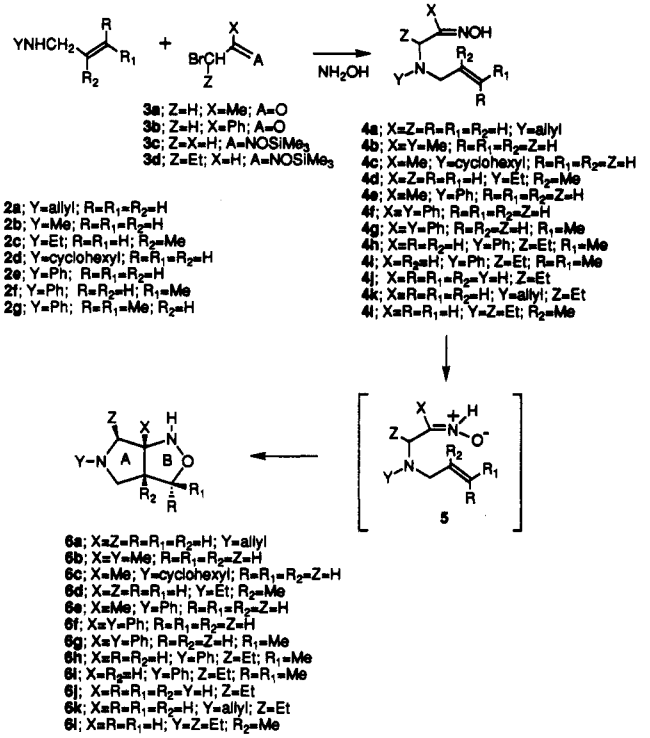
(26) (a) Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89. (b) Hassner, A.; Maurya, R. *Tetrahedron Lett.* **1989**, 5803. (c) Hassner, A.; Maurya, R.; Padwa, A.; Bullock, W. H. *J. Org. Chem.* **1991**, *56*, 2775.

0022-3263/93/1958-4539$04.00/0 © 1993 American Chemical Society

Scheme I

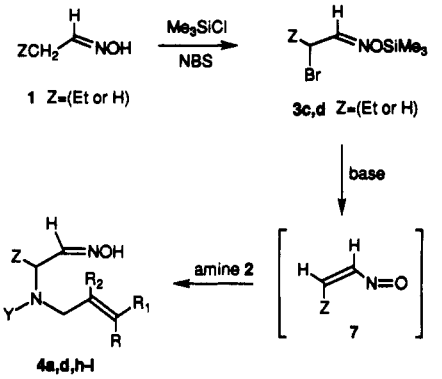


4 in order to evaluate the reaction stereoselectivity and the conformation of the resultant cycloadducts. One of

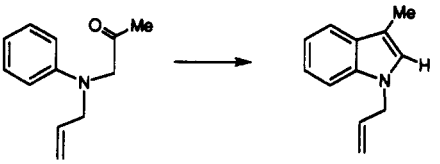


the fused rings contains an isoxazolidine moiety, and it has been shown that unshared orbital interactions on neighboring heteroatoms such as those present in isoxazolidines are responsible for a considerable energy barrier toward ring inversion.[27] The ring system in **6** differs from the all carbon bicyclo[3.3.0]octane in that the otherwise consecutive carbon framework is interrupted by the presence of a nitrogen atom in ring A (pyrrolidine) as well as by the relatively high-energy N–O bond in ring B (isoxazolidine). This could predispose these molecules to a preferred conformation, which may be ascertained by NMR studies, a situation not feasible in the all carbon system. Thus, further insight into the conformational preferences of such fused 5-membered rings may become possible. Furthermore, compounds such as **6** are of interest as precursors to stereoselectively functionalized pyrrolidines, *via* reductive N–O bond cleavage.[28,29]

Synthesis and Stereoselectivity. The unsaturated ketoximes **4b,c,e–g** were readily synthesized by N-alkylation of allylamines **2** with α-bromo ketones **3a,b** at room temperature followed by oximation. When the N-alkylation of **2e** with **3a** was carried out at 120 °C, the sole product was indole **9**, apparently formed by ring closure of **8**. The structure of **9** was determined by CMR and NOE experiments.[30] Since α-bromo aldehydes are difficult to prepare and α-bromo aldoximes are unstable compounds, we used *O*-silyl-protected α-bromo aldoximes **3c,d**



for the preparation of the olefinic aldoximes **4a,d,h–l**.



O-Silylaldoximes **3c,d** are readily obtainable from aldoximes **1** by O-silylation and NBS bromination[31] and serve as vinylnitroso (*i.e.*, **7**) synthons, which on reaction with allylamines **2** led to α-substituted aminoaldoximes **4**. In some cases (**4a,d**), ethyl bromoacetate was aminated with **2a** or **2c** and then reduced to the aldehyde and oximated.

Heating the unsaturated oximes **4** in toluene under an argon atmosphere at 110–180 °C smoothly led to bicyclic compounds **6** in good yields *via* the IOOC reaction and presumably intermediates of type **5** (Table I). In all cases, cycloaddition proceeded to furnish products with the expected *cis* ring junction stereochemistry. Even when three stereocenters were generated as in **6g–l**, a single stereoisomer was isolated, with the side chain always *cis* to the adjacent bridgehead substituent, as determined by NMR (see below). In the case of **6h**, the cycloaddition took place with stereospecific generation of four consecutive stereocenters. Furthermore, the reaction proceeded equally well for aldoximes and ketoximes. The presence of terminal (γ) methyl substituents on the allylamine enhanced the reaction rate (see **6g–i** in Table I), while a methyl substituent on the β-carbon (**6d,l**) retarded the cycloaddition.

Compounds **6a–f** gave very broad ^{1}H- and ^{13}C-NMR lines at room temperature. Cooling of the samples to below −50 °C caused the emergence of two sets of sharp peaks which we have assigned to conformers **10** and **11** on the basis of ^{1}H chemical shifts and coupling constants (*vide infra*). In contrast, **6g–l** exist as essentially one conformer. While their NMR lines are slightly broadened at room temperature, cooling only causes signal sharpening, without the appearance of a noticeable amount of peak doubling. This indicates that while a minor conformer is present (a so-called "*hidden partner*"),[32] the population of the latter is small (<10% under −50 °C). On the basis

(27) Raban, M.; Kost, D. *Tetrahedron* **1984**, *40*, 3345.
(28) Jager, V.; Schwab, W. *Tetrahedron Lett.* **1978**, 3129.
(29) Kozikowski, A. P.; Chen, Y. Y. *J. Org. Chem.* **1981**, *46*, 5248. Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024.
(30) In particular, the Me—C=C^{13} chemical shifts for compound **9** (Me at 8.5, C-3 at 110 ppm) are consistent with the calculated spectra of 1,3-dimethylindole (Me at 9.8, C-3 at 110.1 ppm) rather than with those of 1,2-dimethylindole (Me at 12.2 and C-2 at 138.1 ppm).
(31) Hassner, A.; Murthy, K. S. K. *Tetrahedron Lett.* **1987**, 683.

Table I. Thermolysis of 4a–l at 110 °C in Toluene and NMR Ratio of Conformation of Product 6a–l

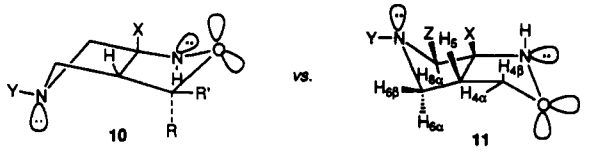
product	reactn time (h)	% yield	ratio 10:11[a]
6a	18	82	1:2
6b	24 (140 °C)	43	1.75:1
6c	56	62	2:1
6d	50	55	1.5:1
6e	24 (180 °C)	43	1.7:1
6f	8	89	6:1
6g	12	81	10 only
6h	14	88	10 only
6i	5	95	10 only
6j	30	50	11 only
6k	10	92	11 only
6l	50	60	11 only

[a] NMR at *ca.* −50 °C.

Table II. Rate Constants and Free Energies for Conformer Interconversion

11b → 10b			11e → 10e		
T (K)	k (s^{-1})	$\Delta G^{\ddagger}$ (kcal/mol)	T (K)	k (s^{-1})	$\Delta G^{\ddagger}$ (kcal/mol)
234.9	4	12.99	246.5	10	13.21
245.4	14	12.98	257.0	22	13.39
255.6	35	13.07	267.6	50	13.53
265.8	73	13.23	278.2	125	13.58
276.0	160	13.33	288.8	470	13.36
286.2	400	13.32	295.6	600	13.54
295.5	1300	13.08			
		avg = 13.2 ± 0.3			avg = 13.4 ± 0.3

of the ^{1}H NMR data (see below) we have determined that **6g–i** exist mainly as **10** while **6j–l** prefer conformation **11**.

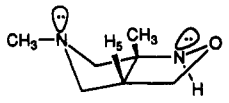


These results show that the presence of a methyl substituent adjacent to the O atom in ring B and *syn* to the ring junction hydrogen (see **6g**) prejudices the molecule in favor of conformer **10**, thus placing the methyl substituent pseudoequatorially (*cf.* **10**, R = Me). Similarly, a single β-substituent in the A-ring (pyrrolidine) at position 8, *syn* to the ring junction hydrogen (**6j–l**), favors conformer **11** (*cf.* Z = Et) in which the A-ring substituent can assume a pseudoequatorial position. The former effect dominates the latter when both rings are substituted (*cf.* **6h**), giving the product with both side chains in a β orientation, but the preferred conformation is **10**, and the ethyl group is forced into a pseudoaxial position. An additional methyl group on C-4 (*cf.* **6i**) does not change these observations.

Conformational Analysis by NMR. Conformations **10** and **11** were established by a detailed analysis of the low-temperature ^{1}H NMR spectra (see Table III). For example, compound **6c** exhibited two sets of peaks with an integral ratio of 2:1. Signal connectivities were confirmed by a COSY experiment. The main diagnostic feature was the absence of a vicinal coupling interaction between a bridgehead hydrogen (H_1 or H_5) and one of the protons on an adjacent methylene. For the major conformer (assigned to **10**), the "*missing*" coupling constant refers to one of the protons on the CH_2N (see $J_{1,8\alpha}$ and $J_{5,6\alpha}$, Table III); conversely, for **11**, the coupling to one of the protons on CH_2O ($J_{5,4\alpha}$) is almost absent. In a five-membered ring, a small value of $^3J_{HH}$ (*i.e.*, a dihedral angle of *ca.* 90°) indicates a *trans* relationship between the protons involved; it also fixes the conformation of the envelope so that the out-of-plane atom (the N or O, respectively) is *anti* to the bridgehead substituents. The other pentacycle must, therefore, have the opposite conformation, with the out-of-plane N or O *syn* to them.

Another notable feature of the spectra is the large chemical shift anisotropy for geminal protons on the ring methylenes. This is due to shielding (hyperconjugation) of the hydrogen which is antiperiplanar to an electron pair on the adjacent heteroatom (N or O). The large $\Delta\delta$ values are relatively independent of substituents and can be relied upon when the absence of bridgehead hydrogens preclude the measurement of $^3J_{HH}$.

Only conformations **10** and **11** can accommodate both these chemical shift and coupling constant derived constraints. Conformation **12** is inconsistent with this data.



12

An inspection of Table III shows that the similarities in δ and J values make the conformational assignment unambiguous even in cases where spectral complexity (*cf.* **6a**) or the small concentration of one conformer (*cf.* **6f**) make the identification of all proton signals difficult. Likewise, for compounds with side chains (**6g–l**), it is easy to determine both the nature of the stereoisomer and the conformation (**10** or **11**) it prefers to adopt. Close inspection of the data in Table III reveals that methyl groups (**6g–i**) in the 4-position introduce small distortions in conformation **10** as shown by small changes in J values, but overall conformer identification is still possible.

We can also establish that the orientation of the NH of the isoxazolidine moiety is always pseudoaxial. This derives from the fact that $^3J_{H\text{-}1,N\text{-}H}$, where measurable, is larger for conformer **10** than **11** (10–12 Hz *vs* 4–5 Hz), well in agreement with the *anti* and *gauche* stereochemical arrangement in the two respective conformers. Furthermore, an NOE experiment in which the angular methyl protons of **10e** and **11e** were irradiated (at low temperature) resulted in a 9% enhancement of the NH signal in the latter conformer but no change in the former (the *anti*-hydrogen in **10e** is too far from the methyl group to generate a detectable NOE).

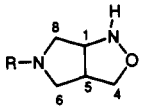
This result is somewhat surprising. The torsional potential function for hydroxylamine and simple acyclic alkylated derivatives has been calculated many groups[33,34] (see, for example, Pople[33a]), and all report that the minimum energy form corresponds to a rotamer in which the dihedral angle ϕ between the bisector of the substituents on nitrogen and the substituent on oxygen is 180°. It is impossible to achieve such an angle in a five-membered ring. Instead, apart from the eclipsed maximum energy

(32) Glazer, R.; Cohen, S.; Donnell, D.; Agranat, I. *J. Pharm. Sci.* **1986**, *75*, 772.

(33) (a) Radom, L.; Hehre, W. J.; Pople, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 2371. (b) Pedersen, L.; Morokuma, K. *J. Chem. Phys.* **1967**, *46*, 3941. (c) Fink, W. H.; Pan, D. C.; Allen, L. C. *J. Chem. Phys.* **1967**, *46*, 895.

(34) (a) Musso, G. F.; Figari, G.; Magnasco, V. *J. Chem. Soc. Faraday Trans. 2* **1983**, *79*, 1283. (b) Ohkuba, K.; Azuma, Y.; Okada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1397. (c) Yabushita, S. Gordon, M. S. *Chem. Phys. Lett.* **1985**, *117*, 321. (d) Han, Y. Z.; Chao, C. D. *Chin. Chem. Lett.* **1991**, *2*, 65. (e) Rastelli, A.; Cocchi, A. *J. Chem. Soc., Farady Trans.* **1991**, *87*, 249.

Table III. Chemical Shift Values and ^{1}H-Coupling Constants for Conformers 10 and 11 of Products 6a–l[a]



δ	10a	10b	10c	10d	10e	10f	10g	10h	10i	11a	11b	11c	11d	11e	11f	11j	11k	11l
1	3.79	–	–	3.28	–	–	–	3.94	3.99	4.13	–	–	3.56	–	–	3.62	3.65	3.08
2(NH)	*ca* 5.1	5.35	5.29	5.29	5.15	5.40	5.58	5.08	*ca* 5.1	5.53	4.78	4.81	5.64	4.98	5.47	5.26	5.32	5.55
4α	3.29	3.43	3.41	3.47	3.47	3.55	3.95	3.72	–	3.94	4.02	4.00	3.99	4.03	4.13	4.04	3.88	3.95
4β	4.42	4.52	4.52	3.99	4.61	4.54	–	–	–	3.44	3.62	3.62	3.21	3.87	x	3.49	3.35	3.17
5	x	2.63	2.51	–	2.86	3.35	2.94	2.84	2.88	x	2.69	2.67	–	2.86	x	3.20	3.00	–
6α	x	2.83	2.92	3.04	3.53	3.66	3.75	3.33	3.44	x	2.14	2.10	x	3.19	x	2.67	1.78	2.03
6β	x	2.31	2.27	1.81	3.15	3.40	3.45	3.38	3.31	x	3.26	3.47	x	3.78	x	3.46	3.32	3.13
8α	x	2.93	3.04	2.91	3.65	3.82	3.82	3.70	3.72	x	2.32	2.25	x	3.24	x	2.70	1.87	1.97
8β	x	2.03	1.98	2.15	2.84	3.14	3.20	–	–	x	2.89	3.14	x	3.42	x	–	–	–
I (Hz)																		
1,2	x	–	–	12	–	–	–	10	x	5	–	–	4	–	–	5	5	5
1,5	x	–	–	–	–	–	–	8	8	x	–	–	–	–	–	8	8.5	–
1,8α	x	–	–	<1	–	–	–	<1	<1	x	–	–	8.5	–	–	8	8	7.5
1,8β	x	–	–	5	–	–	–	–	–	x	–	–	8.5	–	–	–	–	–
8α,8β	x	10	10	11	11	11	11	–	–	x	10	9.5	x	9.5	x	–	–	–
4α,4β	8	8	8.5	8.5	8.5	8	–	–	–	8.5	9	9	8.5	9	9	9	9	8.5
4α,5	8	8	8	–	7.5	7	6.5	6.5	–	<1	<1	<1	–	2	<1	<1	<1	–
4β,5	8	8	8.5	–	8.5	8	–	–	–	x	6	6	–	7.5	x	6	6	–
5,6α	x	<1	<1	–	1	<1	1.5	2.5	3.5	x	8	8	–	8	x	9	9	–
5,6β	x	7	7	–	8	7	7.5	7	8	x	8	8	–	8	x	9	9	–
6α,6β	x	9	9.5	9.5	10	9	10	10	10.5	x	8	8	x	10	x	9	9	9

[a] x: unknown (could not be determined from spectrum). –: not present (substituent ≠ H: δ_H, J_{HH}).

rotamer ($\phi = 60°$), two likely staggered conformations may be considered: (a) the electron pair on N *gauche* to both electron pairs on the O atom ($\phi = 0°$) and (b) the N-electron pair *gauche* to one of the O-atom electron pairs and *anti* to the other ($\phi = 120°$). Although the calculations of Pople and others seem to predict that (b) would be more stable by some 3 kcal/mol, our results show that (a) predominates instead. This agrees with calculations performed on the parent isoxazolidine[35] which assign minimum energy to an axial NH. The only experimental evidence we found in the literature for this conformation comes from the photoelectron spectra of isoxazolidine and some N-alkylated derivatives, obtained by Rademacher and Freckmann.[35b] These workers have found that the parent compound is a 3:1 mixture of conformers with axial and equatorial NH bonds, respectively. However, N-alkylated derivatives shift the equilibrium in favor of the equatorial NR form. They also examined some six-membered tetrahydrooxazines and found them all to have exclusively equatorial NR or NH bonds. Thus, all the available data seem to indicate that pseudoaxial NH's, while unexpected, are indeed characteristic of isoxazolidines.

Conformer Interconversion. As was mentioned above, NMR spectra taken at low temperatures showed two sets of signals for some of the bicyclic isoxazolidines. For two of these (**6b** and **6e**), the rate of interconversion between the conformers was determined by full line shape analyses of the angular methyl proton signals. The values obtained were 13.2 and 13.4 kcal/mol in the –40° to 20 °C temperature range (see Table II). Any pathway for the transformation of conformer **10** to **11** must involve the inversion of the two nitrogen atoms and the "*flipping*" of the envelopes of the two five-membered rings, a total of four discrete steps. The measured energies refer to the rate-determining step, *i.e.*, the step with the highest energy barrier within the lowest energy of the possible overall pathways. This step is almost certainly the inversion of the isoxazolidine nitrogen atom.

The dynamic behavior of hydroxylamines was extensively reviewed by Raban and Kost.[27] For simple acyclic compounds, it is not clear if the NMR measurements indicate a nitrogen inversion or a rotation along the N–O bond. Probably, these two processes have similar energy barriers and the rate-determining step depends on the specific molecule under study. However, for small-ring cyclic N–O compounds, it is assumed that the torsional process (including a ring flip) is a low-energy one and that nitrogen inversion is rate-determining. For an N-substituted bicyclic isoxazolidine obtained by a cycloaddition reaction similar to the one presented in this paper, Raban and co-workers[36] measured a free energy of activation of 13.9 kcal/mol at –21 °C, in good agreement with the results in Table II.

Molecular Mechanics Calculations. Molecular mechanics (MM) calculations represent a reliable, fast, and efficient way of determining molecular properties.[37] There are several force fields for which extensive applications have been reported and which are currently in use worldwide.[38,39] One of the goals of our research was to evaluate the applicability of the MM approach to heterocycles such as **6a–l**. The MM2 force field can calculate structural features for a variety of organic functional groups within experimental error. The original MM2 force field, however, has a significant number of documented inadequacies including the way it treated hydrogen bonds.[40] This has led to the development of several alternative

(35) (a) Leroy, G.; Nguyen, M. T.; Sana, M. *Tetrahedron* **1978**, *34*, 2459. (b) Rademacher, P.; Freckmann, B. *Tetrahedron Lett.* **1978**, 841.

(36) Raban, M.; Jones, F. B., Jr.; Carlson, E. H. *Banucci*, E.; LeBel, N. A. *J. Org. Chem.* **1990**, *35*, 1496.

(37) For a review, see: Burkert, U.; Allinger, N. L. *Molecular Mechanics*: American Chemical Society: Washington, D.C., 1982.

(38) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. Allinger, N. L.; Chang, S. H. M.; Glaser, D. H.; Hönig, H. *Isr. J. Chem.* **1980**, *20*, 51.

(39) Weinger, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput. Chem.* **1986**, *7*, 230. Jorgenson, W. L.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1988**, *110*, 1657.

(40) Lipkowitz, K.; Allinger, N. *QCPE* **1987**, *7*, 19.

packages such as AMBER,[41] ECEPP,[42] CVFF,[43] or CHARMM[44] which are now widely used in force field calculations, especially for proteins and peptides. While it is true that MM calculations have been applied to molecules that contain heteroatoms, these computations have generally involved relatively simple heterocycles.

Before considering the conformations these heterocycles can adopt, we point out that the calculations we have performed are based on empirical force fields, and accordingly, the results derived herein can be only as good as the force field itself. Checking the validity of a force field by comparison of calculated energies and geometries with experimental data or high-quality quantum chemical *ab initio* calculations for heterocyclic systems is difficult for several reasons. First, experimental structural information on heterocycles is only available for the condensed phase. Secondly, complex heterocyclic systems are characterized by a large number of bonded and nonbonded interactions which all contribute significantly to the stabilization or destabilization of the molecule. Therefore, the potential energy surface will show a significant number of local minima. If an energy minimization is performed by starting from the experimentally observed structure, the system will adopt the conformation of the nearest local minimum, which is not necessarily the global minimum. Consequently, the deviation between calculated and experimental structures could be difficult to interpret because good agreement may be incidental and/or result from cancellation of errors. Moreover, experimental information on relative stabilities of different heterocyclic conformations is sparse. In principle, high-quality *ab initio* calculations can be used to provide this information. However, due to the very high computational requirements both in cpu time and intermediate storage, such calculations are not feasible in most laboratories.

At first glance, it would seem appropriate to examine the component energies, *e.g.*, stretch, bend, torsion, *etc.* terms, and determine which force field is most appropriate. This however, should not be done. Component energies are not important; rather, they reflect what the author of the force field deemed important in order to reproduce the databank of experimental information. We have used several different empirical force fields for MM calculations with the hope of obtaining some precise information on the dynamic properties of these bicyclic isoxazolidines. The first is the standard, full MM2 calculation using the Still–Steliou Model 2.96 program.[38] Global minima were found by making use of multiconformer generation in Model (TTY, Conf, Statistical, Coordinate) followed by Batch minimization using Bakmdl.[45] The particular parameters used were those of the NOH (no hydrogen) field developed by Still and implemented by Steliou in the program Model. Conformational analysis was also carried out using the AMBER force field found in Model as well as the MM2 force field using AMBER charges (option 2). Finally, we employed a method which involved using Kollman's AMBER force field and MNDO ESP derived charges.[46] For MM calculations using heterocycles of type **6**, it is critically important to model the electrostatic interactions between the heteroatoms as accurately as possible. Since it is a difficult task to assign charges based on any type of experimental data, these charges must be determined by some theoretical technique. A technique which has been recently used to extract atomic charges was described by Kollman and Merz.[46] These authors demonstrated that semiempirical methods gave electrostatic potential (ESP) derived atomic point charges that are in good agreement with *ab initio* ESP charges. Thus, it is possible to obtain 6-31G* quality point charges by using MNDO semiempirical methods,[47] which require much less computer time than the corresponding 6-31G* calculation. The ESP charges obtained by this method were imported back into Model 2.96, and structures within 3 kcal/mol of the lowest (global) energy conformer were retained for study. A Boltzmann distribution of the various conformers for each cycloadduct at 25 °C was then established. The calculations indicate that there are several low-energy conformations for these bicyclic isoxazolidines which are very dependent on the substituent groups.

Table IV. Calculation of JAB for Cycloadduct 6 Based on Model's MM2 (With Charge) Force Field

structure	J_{AB}	calcd (Hz)	found (Hz)	structure	J_{AB}	calcd (Hz)	found (Hz)
10a	4α,5	9.2	8.0		4β,5	5.7	X
	4β,5	9.0	8.0		1,5	9.9	8.5
	1,5	10.2	8.0		1,8α	7.7	8.0
	1,8α	0.9	<1.0	**11k**	4α,5	1.3	<1.0
10h	4α,5	8.0	8.0		4β,5	5.7	6.0
	5,6α	1.2	2.5		5,6α	10.1	9.0
	5,6β	6.8	7.0		5,6β	8.0	9.0
11a	4α,5	1.3	1.0				

The lowest energy conformers obtained using Model's MM2 force field with AMBER charge (option 2) were found to be most consistent with the NMR data and the observed conformation distribution. Vicinal coupling constants were calculated using standard equations[48] and weighted by the Boltzmann populations of the conformers based on steric energies. As shown in Table IV, the correlation is good; the calculated vicinal coupling constants are very close to the experimentally measured values when this force field is used. For example, the calculations using the MM2 (with charge) force field reveal a 0.31 kcal/mol difference between conformers **10a** (minor) and **11a** (major) which corresponds to an equilibrium ratio of 32% **10a** to 68% **11a** (see Figure 1). This is in excellent agreement with the experimental findings (**10a**:**11a** = 33:66). The calculations also show that the lowest energy conformer of cycloadducts **6b** and **6d** corresponds to **10b** (60%) and **10d** (58%). Compounds **6h** and **6l** were found to exist predominantly (90%) as conformer **10**, whereas structures **6j** and **6k** clearly favor conformer **11** (>90%) in which the ethyl substituent is found in the pseudoequatorial position.

(41) Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Ghio, C.; Alagona, G.; Profeta, S.; Weiner, P. *J. Am. Chem. Soc.* **1984**, *106*, 765.
(42) Momany, F. A.; McGuire, R. F.; Burgess, A. W.; Scheraga, H. A. *J. Phys. Chem.* **1975**, *79*, 2361.
(43) Stern, P. S.; Chorev, M.; Goodman, M.; Hagler, A. T. *Biopolymers* **1983**, *22*, 1885.
(44) Brooks, B. R.; Bruccoleri, R. E.; Olafson, B. D.; States, D. J.; Swaminathan, S.; Karplus, M. *J. Comput. Chem.* **1983**, *4*, 187.
(45) The authors gratefully acknowledge Professor Kosta Steliou of the University of Montreal for providing us with Model 2.96. Minimizations were carried out with Bakmdl on an IBM RS/6000 computer. We also thank Professor Mark Midland, University of California—Riverside, for the UNIX version of Bakmdl.
(46) Besler, B. H.; Merz, K. M.; Kollman, P. A. *J. Comput. Chem.* **1990**, *11*, 431.
(47) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899; **1977**, *99*, 4907.
(48) Haasnoot, C. A. G.; de Leeue, F. A.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

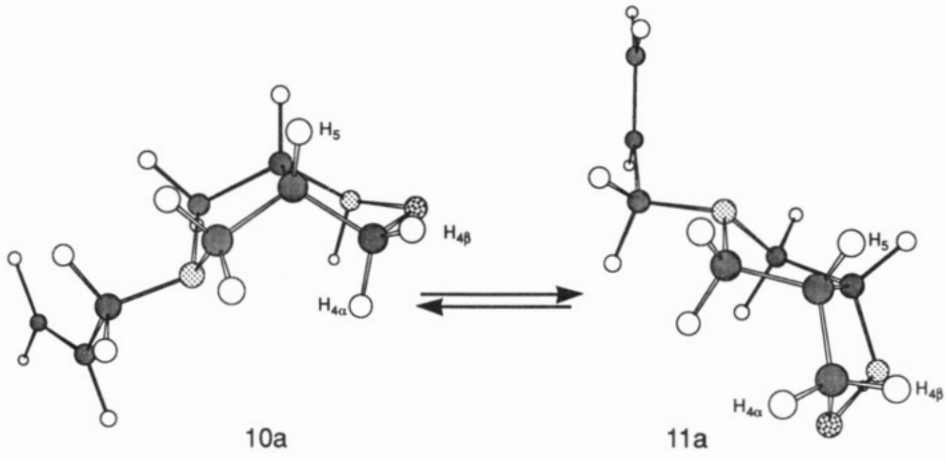
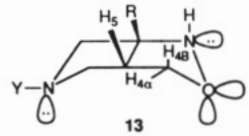


Figure 1. Molecular mechanics calculation of conformer distribution derived from the IOCC reaction of unsaturated oxime **4a**.

The other force fields do not respond as well to these types of compounds as judged by the MM-derived coupling constants and conformational distribution. Both the MM2 and Kollman's ESP derived force fields indicate that the preferred orientation of cycloadducts **6a–f** corresponds to the *syn* conformer **13**. The NMR data, however, clearly



13

rule out this possibility. AMBER, on the other hand, does not correctly predict the relative ratio of conformers, although it does well with the geometries. In many of the other cases examined, the MM2-, AMBER-, and ESP-derived force fields showed no regular trends. Only the MM2 (with charge) force field seemed to be able to best account for the conformational population and geometries.

In conclusion, our results indicate that the molecular mechanics treatment of bicyclic isoxazolidines of type **6** is significantly dependent on the type of the force field used. The conformational preference calculated by Model's MM2 (with charge) force field nicely fits the experimental findings. This hybrid force field provides an adequate combination of molecular interactions which are related to both steric and charge repulsion from the heteroatoms present in the isoxazolidine and pyrrolidine rings.

Experimental Section

***N,N*-Diallyl-1-amino-2-acetaldoxime (4a).** To a solution of diallylamine (485 mg, 5 mmol) in benzene (20 mL) at 0 °C was added dropwise a solution of ethyl bromoacetate (1.64 g, 10 mmol) in benzene (5 mL). The mixture was stirred at rt for 2 h, washed with water (3 × 3 mL), and dried ($MgSO_4$). Evaporation of the solvent and chromatography (SiO_2, petroleum ether) gave ethyl (*N,N*-diallylamino)acetate (1.46 g, 80%) as an oil: ^{1}H-NMR ($CDCl_3$) δ 5.86 (ddt, J = 17, 10, and 6 Hz, 1H), 5.20 (ddd, J = 17, 3, and 1.6 Hz, 1H), 5.15 (d, J = 10 Hz, 1H), 4.16 (q, J = 7 Hz, 2H), 3.31 (s, 2H), 3.24 (bd, J = 6 Hz, 4H), and 1.27 (t, J = 7 Hz, 3H).

The above ester (1 g, 5.45 mmol) was reduced by DIBAL (6 mL of 1.0 M solution in hexane) at −78 °C in toluene for 1 h, and the resulting aldehyde was oximated *in situ* as shown for **4b** to give 400 mg (47%) of oxime **4a** (*E:Z* = 4.3:1): ^{1}H-NMR ($CDCl_3$) δ (*E*-isomer), 7.48 (t, J = 6 Hz, 1H), 5.86 (m, 2H), 5.20 (dm, J = 10 Hz, 2H), 5.19 (dm, J = 10 Hz, 2H), 3.24 (d, J = 6 Hz, 2H), and 3.15 (dt, J = 6 and 1 Hz, 4H); ^{1}H-NMR ($CDCl_3$) δ (*Z*-isomer), 6.91 (t, J = 4 Hz, 1H), 5.86 (m, 2H), 5.20 (dm, J = 17 Hz, 2H), 5.19 (dm, J = 10 Hz, 2H), 3.43 (d, J = 4 Hz, 1H), and 3.15 (dt, J = 6 and 1 Hz, 4H).

7-Allyl-3-oxa-2,7-diazabicyclo[3.3.0]octane (6a). A solution of *N,N*-diallyl-1-amino-2-acetaldoxime (100 mg, 0.65 mmol) in toluene (40 mL) was refluxed for 18 h. Evaporation of the solvent and chromatography (SiO_2, $CHCl_3$:MeOH = 95:5) gave **6a** (82 mg, 82%) as an oil: ^{1}H-NMR ($CDCl_3$) δ 5.87 (ddt, J = 17, 10, and 6 Hz, 1H), 5.18 (ddd, J = 17, 3, and 1 Hz, 1H), and 5.10 (ddt, J = 10, 2, and 1.5 Hz, 1H); ^{13}C-NMR (CD_2Cl_2:$CDCl_3$ = 6:1, −95 °C) conformer **11a** δ 134.8 (d), 116.3 (t), 74.9 (t), 63.2 (d), 59.1 (t), 58.7 (t), 57.7 (t), and 46.4 (d); ^{13}C-NMR (CD_2Cl_2:$CDCl_3$ = 6:1, −95 °C) conformer **10a** δ 134.8 (d), 116.3 (t), 76.7 (t), 64.5 (d), 56.9 (t), 55.8 (t), 54.1 (t), and 46.4 (d).

***N*-Allyl-*N*-methyl-1-amino-2-propanone Oxime (4b).** A solution of bromoacetone, 89 mg (0.649 mmol), in 1 mL of dichloromethane was injected slowly to a stirred solution of *N*-methylallylamine (219 mg, 3.08 mmol) in 3 mL of dichloromethane. After 10 min at room temperature, the solution was washed with three 1-mL portions of water, and the organic layer was dried over magnesium sulfate. Evaporation of the solvent gave 78 mg (0.61 mmol) of *N*-allyl-*N*-methyl-1-amino-2-propanone as an oil (95%). No further purification was needed: ^{1}H-NMR ($CDCl_3$) δ 5.82 (dtd, J = 17, 13, and 10 Hz, 1H), 5.23–5.13 (m, 2H), 2.14 (s, 3H), 2.28 (s, 3H), 3.06 (dt, J = 6.5 and 1 Hz, 2H), and 3.19 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 207.4 (s), 135.0 (d), 118.1 (t), 66.6 (t), 60.8 (t), 42.8 (q), and 27.5 (q); MS *m/e* (CI, I − butane) ($C_7H_{13}NO$ MW 127) 128 (M + H, 100), 113 (1.9), 98 (0.7), and 97 (5.5).

To a stirred solution of 99.7 mg (0.785 mmol) of the above amino ketone was added 60 mg (0.863 mmol) of hydroxylamine hydrochloride, 34.5 mg (0.86 mmol) of sodium hydroxide, and 2 mL of water. After 3 h the solvent was evaporated almost to dryness, ether was added, the water was separated, and the organic layer was washed with 3 mL of brine and dried over magnesium sulfate. Evaporation of the solvent and purification by chromatography (SiO_2, NH_4OH:MeOH:$CHCl_3$ = 1:10:70) gave 79 mg (0.556 mmol) of oxime (*E:Z* = 2:1) **4b** (71%) as an oil: ^{1}H-NMR ($CDCl_3$) δ *E*-isomer 5.86 (ddt, J = 17, 10, and 6.5 Hz, 1H), 5.25–5.11 (m, 2H), 3.01 (bs, 2H), 3.02 (t, J = 7.5 Hz, 2H), 2.19 (bs, 3H), and 1.93 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ (*E*-isomer) 156.7 (s), 135.2 (d), 117.9 (t), 60.6 (t), 60.1 (t), 42.1 (q), and 12.9 (q). ^{1}H-NMR ($CDCl_3$) δ (*Z*-isomer) 5.86 (ddt, J = 17, 10, and 6.5 Hz, 1H), 5.25–5.11 (m, 2H), 3.3 (bs, 2H), 3.02 (t, J = 7.5 Hz, 2H), 2.25 (bs, 3H), and 1.92 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ (*Z*-isomer) 155.4 (s), 134.5 (d), 118.5 (t), 60.8 (t), 55.1 (t), 42.4 (q), and 19.5 (q); MS m/e (CI,

I - butane) ($C_7H_{14}N_2O$ MW 142), 193 (MH^+, 100), 128 (MH^+, 0.19), 125 (19), 116 (0.15), 102 (5.5), and 84 (35).

1,7-Dimethyl-3-oxa-2,7-diazabicyclo[3.3.0]octane (6b). A solution of oxime **4b**, 125 mg (0.88 mmol), in toluene was heated in a sealed tube at 190 °C for 24 h. The solution was evaporated, and the brown viscous oil was chromatographed (SiO_2, $CHCl_3$/5% MeOH) to give 34 mg (0.24 mmol) (27%) of **6b** as an oil: ^{1}H-NMR ($CDCl_3$, −45 °C) conformer **10b** δ 2.33 (s, 3H), and 1.33 (s, 3H); ^{1}H-NMR ($CDCl_3$, −45 °C) conformer **11b** δ 2.33 (s, 3H) and 1.48 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ (25 °C) 78.4 (t), 73.2 (s), 63.3–67.6 (vbm), 58.8–63.3 (vbm), 54.3 (d), 41.4 (q), and 23.4 (q); MS m/e (EI) ($C_7H_{14}N_2O$ MW 142) (M^+, 10), 111 (23), 97 (83), 96 (23), 82 (1.4), and 70 (100).

***N*-Allyl-*N*-cyclohexyl-1-amino-2-propanone oxime (4c)** was prepared from bromoacetone and *N*-allylcyclohexylamine as shown for **4b** to give *N*-allyl-*N*-cyclohexyl-1-amino-2-propanone (86%) as an oil: ^{1}H-NMR ($CDCl_3$) δ 5.76 (ddt, J = 17, 10, and 6 Hz, 1H), 5.09 (ddd, J = 17, 4, and 1.5 Hz, 1H), 5.00 (ddt, J = 10, 2, and 2 Hz, 1H), 3.13 (bs, 2H), 3.08 (dt, J = 6, and 1 Hz, 2H), 2.41 (m, 1H), 2.09 (s, 3H), 1.72 (m, 4H), 1.53 (m, 1H), and 1.10 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 210.7 (s), 136.7 (d), 117 (t), 60.9 (d), 60.6 (t), 54.9 (t), 29.2 (t), 27.2 (q), 26.1 (t), and 25.9 (t); MS *m/e* (CI, I - butane) ($C_{12}H_{21}NO$ MW 195) 196 (MH^+, 100), 155 (0.43), 153 (5), and 96 (0.14).

Oximation of *N*-allyl-*N*-cyclohexyl-1-amino-2-propanone carried out as shown for **4b** gave **4c** (*E*:*Z* = 4:1) (95%) as an oil: ^{1}H-NMR ($CDCl_3$) δ (*E*-isomer) 5.70 (ddt, J = 17, 10, and 6 Hz, 1H), 5.06 (ddd, J = 17, 3, and 1.5 Hz, 1H), 4.98 (ddt, J = 10, 2, and 1.5 Hz, 1H), 3.03 (s, 2H), 3.00 (dt, J = 6, and 1 Hz, 2H), 2.42 (m, 1H), 1.82 (s, 3H), 17.0 (m, 4H), and 1.13 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ (*E*-isomer) 158.5 (s), 137.4 (d), 116.2 (t), 59 (d), 53.6 (t), 53.2 (t), 28.9 (t), 26.4 (t), and 26.1 (t); ^{1}H-NMR ($CDCl_3$) δ (*Z*-isomer) 5.78 (ddt, J = 17, 10, and 6 Hz, 1H), 5.12 (ddd, J = 17, 3, and 1 Hz, 1H), 5.07 (ddt, J = 17, 3, and 1.5 Hz, 1H), 3.34 (s, 2H), 3.06 (dt, J = 6, and 1 Hz, 2H), 2.42 (m, 1H), 1.80 (s, 3H), 1.53 (m, 4H), and 1.03 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ (*Z*-isomer) 155.7 (s), 139.5 (d), 118 (d), 60.1 (d), 54 (t), 50 (t), 28.4 (t), 24.7 (t), and 25.9 (t); MS *m/e* (CI, I - butane) ($C_{12}H_{22}N_2O$ MW 210), 211 (MH^+, 100), 194 (42), 193 (33), 180 (0.44), 170 (1.16), 153 (64), and 152 (45). Anal. Calcd for $C_{12}H_{22}N_2O$: C, 68.53; H, 10.54. Found: C, 68.36; H, 10.37.

1-Methyl-7-cyclohexyl-3-oxa-2,7-diazabicyclo[3.3.0]-octane (6c) was obtained from **4c** as shown for **6a**, reaction time 56 h (62%), as an oil: ^{1}H-NMR ($CDCl_3$) δ 2.52 (m, 1H), 1.78 (m, 4H), 1.6 (bs, 1H), and 1.13 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 79 (bt), 71.7 (s), 61.2 (bd), 58.8 (m), 55.5 (m), 52.7 (d), 31.1 (t), 25.8 (t), 24.4 (t), and 23.3 (q); MS *m/e* (CI, I - butane) ($C_{12}H_{22}N_2O$ MW 210), 211 (MH^+, 100), 196 (0.6), 180 (3), 179 (68), 166 (0.86), 165 (5.8), 128 (1.6), 97 (10), and 96 (0.85). Anal. Calcd for $C_{12}H_{22}N_2O$: C, 68.53; H, 10.54. Found: C, 68.73; H, 10.62.

***N*-(2-Methyl-2-propenyl)-*N*-ethyl-1-amino-2-acetaldoxime (4d)** was prepared as shown for **4a** using *N*-ethylmethallylamine to obtain first ethyl (*N*-allyl-*N*-methylamino)acetate (80%): ^{1}H-NMR ($CDCl_3$) δ 4.87 (d, J = 14 Hz, 2H), 4.15 (q, J = 7 Hz, 2H), 3.28 (s, 2H), 3.11 (bs, 2H), 2.65 (q, J = 6.5 Hz, 2H), 1.75 (bs, 3H), 1.26 (t, J = 7 Hz, 3H), and 1.04 (t, J = 7 Hz, 3H). Reduction of the ester and oximation as shown for **4a** gave **4d** (*E*:*Z* = 1.4:1) (50%) as an oil: ^{1}H-NMR ($CDCl_3$) δ (*E*-isomer) 9.2 (bs, 1H), 7.46 (t, J = 6 Hz, 1H), 4.89 (bs, 2H), 3.17 (d, J = 6 Hz, 1H), 2.98 (bs, 2H), 2.53 (qd, J = 7 and 2.2 Hz, 2H), 1.74 (s, 3H), and 1.03 (t, J = 7 Hz, 3H); ^{1}H-NMR ($CDCl_3$) δ (*Z*-isomer) 8.60 (bs, 1H), 6.88 (t, J = 4 Hz, 1H), 4.85 (bs, 2H), 3.37 (d, J = 4 Hz, 1H), 2.98 (bs, 2H), 2.53 (qd, J = 7 and 2.2 Hz, 2H), 1.76 (s, 3H), and 1.07 (t, J = 7 Hz, 3H).

7-Ethyl-5-methyl-3-oxa-2,7-diazabicyclo[3.3.0]octane (6d) was prepared from **4d** as shown for **6a**, reaction time 50 h (50%), as an oil: ^{1}H-NMR ($CDCl_3$) δ 2.46 (q, J = 7 Hz, 2H), 1.28 (s, 3H), and 1.08 (t, J = 7 Hz, 3H); ^{13}C-NMR ($CDCl_2$:$CDCl_3$ = 6:1) δ (**10d**) 82.9 (t), 71.3 (d), 62.5 (t), 54.2 (t), 54.0 (s), 48.2 (t), 22.8 (q), and 12.9 (q); ^{13}C-NMR ($CDCl_2$:$CDCl_3$ = 6:1) δ (**11d**) 81.0 (t), 69.7 (d), 64.8 (t), 60.0 (t), 48.9 (t), 21.44 (q), and 12.3 (q).

***N*-Allyl-*N*-phenyl-1-amino-2-propanone Oxime (4e).** A solution of *N*-allylaniline, 225 mg (1.96 mmol), in 5 mL of dichloromethane was stirred for 3 days at room temperature, with 82.5 mg (0.6 mmol) of bromoacetone. The solution was washed with three 1-mL portions of water, and the organic layer was dried over magnesium sulfate. Evaporation and purification by chromatography (SiO_2, petroleum ether:ethyl acetate = 1:1) afforded 79 mg (0.42 mmol) (70%) of *N*-allyl-*N*-phenyl-1-amino-2-propanone as an oil: ^{1}H-NMR ($CDCl_3$) δ 7.13 (m, 2H), 6.66 (m, 1H), 6.52 (m, 2H), 5.80 (ddt, J_1 = 16.5, 11, and 5 Hz, 1H), 5.12 (ddd, J = 17.5, 3.5, and 1.5 Hz, 1H), 5.11 (ddd, J = 10.5, 3.5, and 1.5 Hz, 1H), 3.94 (dt, J = 5, and 1.5 Hz, 2H), 3.92 (bs, 2H), and 2.08 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 208.3 (s), 198.2 (s), 133.5 (d), 129.3 (s), 117.5 (s), 116.9 (t), 112.4 (s), 60.9 (t), 54.4 (t), and 27.0 (q); MS *m/e* (EI) ($C_{12}H_{15}NO$ MW 189) 189 (M^+, 11), 146 (M^+, 100), 119 (0.13), 105 (20), and 91 (1.8).

The above ketone (25 mg, 0.132 mmol) was oximated as described for **4b** to give 22.8 mg (0.11 mmol) of **4e** (*E*:*Z*, 2:1) as a clear oil (84%): ^{1}H-NMR ($CDCl_3$) δ (*E*-isomer), 7.14 (m, 2H), 6.65 (m, 2H), 6.55 (m, 1H), 5.75 (ddt, J = 10, 7, and 5 Hz, 1H), 5.10 (m, 1H), 5.07 (m, 1H), 3.91 (bs, 2H), 3.86 (dt, J = 5, 2, and 1.5 Hz, 2H), and 1.81 (bs, 3H); ^{13}C-NMR ($CDCl_3$) δ (*E*-isomer), 156.5 (s), 148.6 (s), 133.5 (d), 129.1 (s), 117.4 (d) 116.8 (t), 113.1 (d), 54.3 (t), 53.4 (t), and 11.7 (q). ^{1}H-NMR ($CDCl_3$) δ (*Z*-isomer) 7.13 (m, 2H), 6.66 (m, 2H), 6.55 (m, 1H), 5.80 (ddt, J = 10, 7, and 5 Hz, 1H), 5.13 (m, 1H), 5.08 (m, 1H), 4.20 (bs, 2H), 3.90 (dt, J = 5 and 2 Hz), and 1.73 (bs, 3H); ^{13}C-NMR ($CDCl_3$) δ (*Z*-isomer) 156.6 (s), 148.1 (s), 133.2 (d), 129.3 (d), 117.0 (d), 116.8 (d), 112.0 (d), 54.3 (t), 48.0 (t), and 17.2 (q); MS *m/e* (EI) ($C_{12}H_{15}NO$ MW 204) 204 (M^+, 48), 187 (57), 146 (100), 105 (33.5), 91 (8.8), and 77 (56).

7-Phenyl-5-methyl-3-oxa-2,7-diazabicyclo[3.3.0]octane (6e). A solution of the phenyl oxime **6b**, 16 mg (0.08 mmol), in 10 mL of toluene was heated in a sealed tube at 180 °C for 24 h. The solution was evaporated, and the brown viscous oil was chromatographed (SiO_2 petroleum ether:ethyl acetate = 1:2) to give 7 mg (0.034 mmol) of **6e** (43%) as an oil: ^{1}H-NMR ($CDCl_3$) δ 7.18 (m, 2H), 6.73 (m, 1H), 6.61 (m, 2H), and 1.39 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ (25°C) 148.5 (s), 129.2 (d), 118.2 (d), 118.0 (d), 79.4 (t), 72.4 (s), 57.9 (t), 53.1 (d), and 23.11 (bs); MS *m/e* (EI) ($C_{12}H_{15}N_2O$ MW 204) 206 (M^+ + 2, 0.21), 205 (M^+ + 1, 8.9), 204 (M^+, 64), 173 (15), 159 (12), 132 (5.4), 119 (7.3), 105 (100), 91 (49), and 77 (90).

***N*-Allyl-*N*-phenyl-1-amino-2-acetophenone (4f).** A solution of bromoacetone (820 mg, 4.12 mmol) and *N*-allylaniline (1.64 g, 12.36 mmol) in acetonitrile (100 mL) was stirred at room temperature for 30 h. Evaporation of the solvent and chromatography (SiO_2, petroleum ether:Et_2O = 85:15) gave *N*-allyl-*N*-phenyl-1-amino-2-acetophenone (823 mg, 80%) as an oil: ^{1}H-NMR ($CDCl_3$) δ 8.10 (m, 2H), 6.61 (m, 1H), 7.50 (m, 2H), 7.17 (m, 2H), 6.71 (m, 1H), 6.62 (m, 2H), 5.93 (ddt, J = 17, 10, and 5 Hz, 1H), 5.25 (ddd, J = 17, 3, and 1 Hz, 1H), 5.19 (ddd, J = 10, 3, and 1 Hz, 1H), 4.75 (s, 2H), and 4.06 (dt, J = 5 and 1.5 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 196.4 (s), 148.6 (s), 135.6 (s), 134.2 (d), 133.5 (d), 129.1 (d), 128.8 (d), 127.7 (d); 117.9 (d), 116.4 (dd), 112.5 (d), 56.5 (t), and 54.4 (t); MS *m/e* (CI, methane) ($C_{17}H_{17}NO$ MW 251), 292 ($MC_3H_5^+$, 2.6) 280 ($MC_2H_5^+$, 14.3), 252 (MH^+, 100), 234 (7.4), 211 (1.3), and 146 (18.25).

The above ketone was oximated to **4f** as shown for **4b** (*E*:*Z* = 1:1) (81%) as an oil: ^{1}H-NMR ($CDCl_3$) δ (*E*-isomer) 7.20–7.49 (m, 7H), 6.74–6.87 (m, 3H), 5.82 (ddt, J = 17, 11, and 5 Hz, 1H), 5.19 (assigned by COSY, ddd, J = 11, 3, and 1.5 Hz, 1H), 5.18 (ddd, J = 17, 3, and 1.5 Hz, 1H), 4.39 (s, 2H), and 3.93 (dt, J = 5 and 1.5 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ (*E*-isomer) 155.5 (s), 148.4 (s), 133.6 (d), 132.3 (s), 129.0 (s), 128.3 (d), 127.7 (d), 117.2 (d), 116.5 (dd), 113 (d), 54.4 (t), and 53.4 (t). ^{1}H-NMR ($CDCl_3$) δ (*Z*-isomer) 7.20–7.49 (m, 7H), 6.74–6.84 (m, 3H), 5.76 (ddt, J = 17, 11, and 5 Hz, 1H), 5.18 (ddd, J = 11, 3, and 1.5 Hz, 1H), 5.13 (ddd, J = 17, 3, and 1.5 Hz, 1H), 4.66 (s, 2H), and 3.81 (dt, J = 5 and 1.5 Hz, 2H); ^{13}C-NMR ($CDCl_3$) (*Z*-isomer) δ 158.6 (s), 148.5 (s), 134.8 (s), 133.4 (d), 129.1 (d), 128.2 (d), 127.4 (d), 117.5 (d), 116.8 (dd), 113.5 (d), 53.8 (t), and 46.01 (t); MS *m/e* (CI, methane) ($C_{17}H_{18}N_2O$ MW 266), 307 ($MC_3H_5^+$, 2.10), 295 ($MC_2H_5^+$, 5), 267 (MH^+, 100), 250 (2.5), 249 (11), 239 (0.85), 208 (1.12), 147 (5.9), 146 (59), 133 (2.5), and 134 (2.5).

1,7-Diphenyl-3-oxa-2,7-diazabicyclo[3.3.0]octane (6f) was prepared from **4f** as shown for **6a**, reaction time 8 h (89%), as an oil: ^{1}H-NMR ($CDCl_3$) δ 7.60 (m, 2H), 7.38 (m, 2H), 7.27 (m, 3H), 6.83 (t, J = 7.5 Hz, 1H), and 6.72 (d, J = 9 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 148.2 (s), 142.4 (s), 129.1 (d), 128.5 (d), 127.3 (d), 125.8 (d), 118.4 (d), 114.2 (d), 79.7 (dd), 77.9 (s), 59.4 (bt), 54.6 (t), and

54.5 (d); MS *m/e* (EI) ($C_{17}H_{18}N_2O$ MW 266) 266 (M^+, 38), 236 (44), 235 (56), 221 (8), 144 (76), 132 (100), and 105 (65).

***N*-(2-*trans*-Butenyl)-*N*-phenyl-1-amino-2-acetophenone Oxime (4g).** Bromoacetophenone and (2-*trans*-butenyl)-*N*-phenylamine were reacted as shown for **4b** at room temperature overnight to afford *N*-(2-*trans*-butenyl)-*N*-phenyl-1-amino-2-acetophenone (80%) as an oil: ^{1}H-NMR ($CDCl_3$) δ 7.99 (m, 2H), 7.59 (m, 1H), 7.48 (m, 2H), 7.17 (m, 2H), 6.69 (m, 1H), 6.63 (m, 2H), 5.60 (m, 2H), 4.72 (s, 2H), 3.98 (dt, J = 2 and 0.5 Hz, 2H), 1.69 (dm, J = 4 Hz, 3H). Oximation of the above ketone as shown for **4b** gave *N*-(2-*trans*-butenyl)-*N*-phenyl-1-amino-2-acetophenoxime (64%) as an oil: ^{1}H-NMR ($CDCl_3$) δ 9.20 (bs, 1H), 7.41 (m, 2H), 7.29 (m, 3H), 7.19 (m, 2H), 6.73 (m, 3H), 5.50 (ddt, J = 15.5, 6.5, and 1.5 Hz, 1H), 5.33 (dtd, J = 15, 5.5, and 1.5 Hz, 1H), 4.58 (s, 2H), 3.68 (dq, J = 5.5 and 1.5 Hz, 2H), 1.60 (dq, J = 6.5 and 1.5 Hz, 3H).

1,7-Diphenyl-4-methyl-3-oxa-2,7-diazobicyclo[3.3.0]-octane (6g) was obtained from **4g** as shown for **6a**, reaction time 12 h (81%), as an oil: ^{1}H-NMR ($CDCl_3$) δ 7.59 (m, 2H), 7.36 (m, 2H), 7.25 (m, 2H), 6.73 (m, 2H), 6.63 (m, 1H), and 1.33 (d, 6.5 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 148.4 (s), 143.4 (s), 129.2 (d), 128.4 (d), 127 (d), 125.9 (d), 118.8 (d), 114.5 (d), 88.7 (d), 78.5 (s), 62.1 (d), 59.8 (t), 53.7 (t), and 18.2 (q).

***N*-Phenyl-*N*-(2-butenyl)-2-aminobutanaldoxime (4h).** To a solution of *N*-phenyl-*N*-2-butenylamine (1.03 g, 7 mmol) and TBAF (1 mL, 1.08 M solution in THF, 1 mmol) in chloroform (1 mL) at 0 °C under argon was added dropwise a solution of α-bromo *O*-(tri-methylsilyl) aldoxime[31] (238 mg, 1 mmol) in chloroform (15 mL). The reaction mixture was stirred at room temperature for 1 h and then transferred to a separatory funnel with the aid of chloroform (50 mL) and washed with brine (3 × 5 mL). The organic layer was dried ($MgSO_4$), concentrated under reduced pressure, and chromatographed (SiO_2, petroleum ether: Et_2O = 90:10) to give **4h** (155 mg, 84%) as an oil: ^{1}H-NMR ($CDCl_3$) δ 8.38 (bs, 1H), 7.42 (d, J = 5.5 Hz, 1H), 7.20 (m, 2H), 6.82 (m, 2H), 6.73 (m, 1H), 5.62 (ddt, J = 15.5, 6.5, and 1.5 Hz, 1H), 5.45 (dtd, J = 15, 5.5, and 1.5 Hz, 1H), 4.29 (dt, J = 7 and 6 Hz, 1H), 3.80 (m, 2H), 1.83 (dq, J = 7.6 and 7 Hz, 2H), 1.66 (dd, J = 5.6 and 1.2 Hz, 3H), and 0.96 (t, J = 7 Hz, 3H).

4-Methyl-7-phenyl-8-ethyl-3-oxa-2,7-diazabicyclo[3.3.0]-octane (6h) was prepared from **4h** as shown for **6a**, reaction time 14 h (88%), as an oil: ^{1}H-NMR ($CDCl_3$) δ 7.23 (m, 2H), 6.73 (m, 1H), 6.62 (m, 2H), 1.68 (tdd, J = 15, 8, and 3 Hz, 1H), 1.39 (d, J = 5.6 Hz, 3H), 1.33 (ddd, J = 14, 7, and 1 Hz, 1H), and 0.94 (t, J = 7.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 146.4 (s), 129.2 (d), 117.1 (d), 113.9 (d), 87.4 (d), 70.5 (d), 61.9 (d), 53.4 (d), 50.2 (t), 21.0 (t), 18.3 (q), and 10.4 (q).

***N*-Phenyl-*N*-(3-methyl-2-butenyl)-2-aminobutanaldoxime (4i)** was prepared from *N*-phenyl-*N*-(3-methyl-2-butene)-amine and α-bromo *O*-(trimethylsilyl)butyraldoxime as shown for **4h** (65%): ^{1}H-NMR ($CDCl_3$) δ 8.93 (bs, 1H), 7.41 (d, J = 5 Hz, 1H), 7.19 (m, 2H), 6.79 (m, 2H), 6.72 (m, 1H), 5.13 (m, 1H), 4.28 (dt, J = 7 and 6 Hz, 1H), 3.18 (bd, J = 5.6 Hz, 2H), 1.82 and 1.79 (ABQ split into qu, J = 7.5 Hz, 2H), 1.68 (s, 6H), and 0.95 (t, 7.5 Hz, 3H).

4,4-Dimethyl-7-phenyl-8-ethyl-3-oxa-2,7-diazabicyclo[3.3.0]-octane (6i) was obtained as an oil from **4i** as shown for **6a**, reaction time 5 h (95%). This cyclization also proceeded at room temperature (100%) after 12 h: ^{1}H-NMR ($CDCl_3$) δ 7.22 (m, 2H), 6.71 (m, 1H), 6.61 (m, 2H), 1.35 (m, 2H), 1.34 (s, 3H), 1.27 (s, 3H), and 0.93 (t, J = 8 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 146.3 (s), 129.2 (d), 116.7 (d), 113.5 (d), 85.4 (s), 70.7 (d), 63.4 (d), 54.4 (d), 48.3 (t), 27.5 (q), 22.1 (t), 21.8 (q), and 10.1 (q).

***N*-Allyl-2-aminobutanaldoxime (4j)** was prepared as an oil from allylamine and α-bromo *O*-(trimethylsilyl)butyraldoxime as shown for **4h** (80%): ^{1}H-NMR ($CDCl_3$) δ 7.24 (d, J = 7.5 Hz, 1H), 5.89 (ddt, J = 17, 10, and 6 Hz, 1H), 5.18 (ddd, J = 17, 3, and 1.5 Hz, 1H), 5.10 (ddd, J = 10, 2, and 1 Hz, 1H), 3.25 (m, 3H), 1.67 (ddd, J = 15, 14, and 7 Hz, 1H), 1.58 (ddd, J = 15, 14, and 7 Hz, 1H), and 0.92 (t, J = 7 Hz, 3H).

8-Ethyl-3-oxa-2,7-diazabicyclo[3.3.0]octane (6j) was prepared from **4j** as shown for **6a**, reaction time 30 h (50%): ^{1}H-NMR ($CDCl_3$) δ 1.75 (td, J = 15 and 7 Hz, 1H), 1.58 (td, J = 14 and 7 Hz, 1H), and 1.04 (t, J = 7 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 76.7 (t), 71.7 (d), 66.2 (d), 51.7 (t), 49.0 (d), 2.66 (t), and 11.34 (q); MS *m/e* (CI, methane) ($C_7H_{14}N_2O$ MW 142), 183 (MCH_5^+, 2.2), 171 ($MC_2H_5^+$, 3.6), 143 (MH^+, 100), 142 (2), and 114 (2.4).

***N,N*-Diallyl-2-aminobutanaldoxime (4k)** was obtained as an oil from diallylamine and α-bromo-*O*-(trimethylsilyl)butyraldoxime as shown for **4h** (81%): ^{1}H-NMR ($CDCl_3$) δ 8.85 (bs, 1H), 7.4 (d, J = 7.5 Hz, 1H), 5.84 (dddd, J = 17, 10, 7, and 5 Hz, 2H), 5.21 (ddd, J = 17, 4, and 2 Hz, 1H), 5.15 (dm, J = 10 Hz, 2H), 3.33 (ddm, J = 13 and 5.5 Hz, 2H), 3.29 (m, 1H), and 3.08 (dd, J = 14.5 and 7.5 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 151.0 (d), 136.1 (d), 117.2 (t), 60.3 (d), 52.9 (t), 23.1 (t), and 10.8 (q); MS *m/e* (CI, I − butane) ($C_{10}H_{18}N_2O$ MW 182), 239 ($MC_4H_9^+$, 2.5), 22.5 ($MC_3H_7^+$, 8.2), 183 (MH^+, 100), 166 (2.6), 165 (19.8), 153 (15.1), and 138 (59). Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.89; H, 9.96. Found: C, 63.74; H, 9.94.

7-Allyl-8-methyl-3-oxa-2,7-diazabicyclo[3.3.0]octane (6k) was prepared as an oil from **4k** as shown for **6a**, reaction time 10 h (92%): ^{1}H-NMR ($CDCl_3$) δ 5.85 (m 1H), 5.17 (bd, J = 17 Hz, 1H), 5.08 (bd, J = 10 Hz, 1H), 1.41 (m, 2H), and 0.95 (t, J = 8.5 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 135.1 (d), 117.1 (t), 75.9 (t), 70.5 (d), 69.8 (d), 58.7 (t), 55.6 (t), 45.9 (d), 23.5 (t), and 9.3 (q); MS *m/e* (EI) ($C_{10}H_{18}N_2O$ MW 182), 183 (MH^+, 9.7), 182 (M^+, 3.8), 167 (0.85), 155 (0.8), 153 (31.5), 123 (100), 109 (94), 96 (13.2), 82 (16), and 68 (20). Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.89; H, 9.96. Found: C, 66.17; H, 9.70.

***N*-Ethyl-*N*-1,2-dimethyl-2-propenyl-2-aminobutanaldoxime (4l)** was prepared as an oil from *N*-ethyl-*N*-(2-methyl-2-propenyl)amine and α-bromo-*O*-(trimethylsilyl)butyraldoxime as shown for **4h** (78%): ^{1}H-NMR ($CDCl_3$) δ 8.84 (bs, 1H), 7.37 (d, 1H), 4.90 (s, 1H), 4.82 (s, 1H), 3.20 (dt, J = 7 and 7 Hz, 1H), 3.12 (d, J = 14 Hz, 1H), 2.92 (d, J = 14 Hz, 1H), 2.62 (dq, J = 7 and 7 Hz, 1H), 2.41 (dq, J = 7 and 7 Hz, 1H), 1.72 (s, 3H), 1.61 (m, 2H), 1.01 (t, J = 7 Hz, 3H), and 0.92 (t, J = 7 Hz, 3H).

5-Methyl-7,8-diethyl-3-oxa-2,7-diazabicyclo[3.3.0]-octane (6l) was obtained as an oil from **4l** as shown for **6a**, reaction time 50 h (60%): ^{1}H-NMR ($CDCl_3$) δ 2.90 (m, 1H), 1.95 (m, 1H), 1.84 (m, 1H), 1.37 (m, 1H), 1.30 (s, 3H), 1.07 (t, J = 7 Hz, 3H), and 0.95 (t, J = 7 Hz, 3H); ^{13}C-NMR (CD_2Cl_2:$CDCl_3$ = 2:1) δ 81.3 (t), 76.7 (d), 72 (d), 64.0 (t), 52.4 (s), 46.8 (t), 23.0 (t), 22.0 (q), and 12.3 (q).

1-Allyl-3-methylindole (9). A solution of allylaniline (450 mg, 3.38 mmol) and bromoacetone (165 mg, 1.2 mmol) in CH_2Cl_2 (20 mL) was heated at 80 °C for 24 h in a sealed tube. The reaction mixture was washed with water (3 × 2 mL) and dried ($MgSO_4$). Evaporation of the solvent and chromatography (SiO_2, petroleum ether:Et_2O = 95:5) afforded 1-allyl-3-methylindole (150 mg, 73%): ^{1}H-NMR ($CDCl_3$) δ 7.48 (ddd, J = 8, 1.5, and 1 Hz, 1H), 7.17 (dt, J = 8 and 1 Hz, 1H), 7.1 (ddd, J = 8, 7, and 1 Hz, 1H), 7.01 (ddd, J = 8, 8, and 1 Hz, 1H), 6.75 (bd, J = 1 Hz, 1H), 5.86 (ddt, J = 17, 10, and 5.5 Hz, 1H), 5.06 (dd, J = 10.3 and 1.5 Hz, 1H), 4.97 (ddd, J = 17.3 and 1.5 Hz, 1H), 4.54 (dt, J = 5.5 and 1.5 Hz, 2H), and 2.23 (d, J = 1 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 135.4 (s), 132.8 (d), 127.8 (d), 124.4 (d), 120 (d), 117.9 (d), 117.6 (d), 115.9 (t), 109.5 (s), 108.3 (d), 47.5 (t), and 8.42 (q); MS *m/e* (EI) ($C_{12}H_{13}N$ MW 171) 173 (M^+ + 2, 4), 172 (M^+ + 1,14), 171 (M^+, 100), 170 (53), 156 (32), 144 (26), 131 (5.4), 130 (49), 116 (2), 115 (7), and 104 (5).

Acknowledgment. This research was supported by grant No. 90-00227 from the United States–Israel Binational Science Foundation, Jerusalem, Israel. A.P. wishes to acknowledge support by the National Institutes of Health (CA-26751).

Supplementary Material Available: Reduced-temperature ^{1}H NMR spectra of **6a–l** and **9** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.