mass spectrum, m/e 241 and 239 (M^+).

5,7-Dimethyl derivative (**7**): mp 170–171 °C; IR (KBr) 3050, 2970, 1620, 1565, 1482, 1435, 1410, 1380, 1255, 1157, 1147, 1050, 1008, 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74 (br s, H-6), 8.12 (br s, H-8), 2.68 (br s, Me-7), 2.71 (br s, Me-5); mass spectrum, m/e 239 and 237 (M^+).

3-Azidobenzo-*as*-triazine N^1-Oxides 11–13. To solutions of 2 mmol of **8–10** in 50 mL of acetone was added 2.2 mmol of sodium azide dissolved in a minimum volume of water, and the resulting solutions were heated at reflux for 3 h. The reaction mixtures were then diluted with water and extracted with methylene chloride. The organic extracts were dried over magnesium sulfate and, after being filtered, concentrated to 5–7 mL. On addition of hexane, products **11–13**, in 55%, 70%, and 68% yields, respectively, were obtained.

7-Methyl derivative (**11**): mp 118–119 °C; mass spectrum, m/e 202 (M^+). Anal. Calcd for $C_8H_6N_6O$: C, 47.53; H, 2.99; N, 41.57. Found: C, 47.31; H, 3.22; N, 41.30.

7-Methoxy derivative (**12**): mp 139–141 °C; mass spectrum, m/e 218 (M^+). Anal. Calcd for $C_8H_6N_6O_2$: C, 44.04; H, 2.77; N, 38.52. Found: C, 44.00; H, 2.57; N, 38.31.

5,7-Dimethyl derivative (**13**): mp 157–158 °C; mass spectrum, m/e 216 (M^+). Anal. Calcd for $C_9H_8N_6O$: C, 50.00; H, 3.73; N, 38.87. Found: C, 50.28; H, 3.98; N, 38.60.

3-Azidobenzo-*as*-triazines 2–4. The general procedure was identical with that described for the corresponding N^1-oxido derivatives but started from **5–7**. Compounds **2–4** were obtained in 43%, 89%, and 47% yields, respectively.

7-Methyl derivative (**2**): mp 90–92 °C; mass spectrum, m/e 186 (M^+). Anal. Calcd for $C_8H_6N_6$: C, 51.61; H, 3.26; N, 45.14. Found: C, 51.84; H, 3.01; N, 44.88.

7-Methoxy derivative (**3**): mp 146–148 °C; mass spectrum, m/e 202 (M^+). Anal. Calcd for $C_8H_6N_6O$: C, 47.52; H, 3.00; N, 41.56. Found: C, 47.20; H, 3.24; N, 41.29.

5,7-Dimethyl derivative (**4**): mp 111–113 °C; mass spectrum, m/e 200 (M^+). Anal. Calcd for $C_9H_8N_6$: C, 53.99; H, 4.03; N, 41.98. Found: C, 53.78; H, 4.31; N, 41.85.

Registry No. 2a, 82581-98-4; **2b**, 82581-99-5; **2c**, 82582-00-1; **3a**, 82582-01-2; **3b**, 82582-02-3; **3c**, 82582-03-4; **4a**, 82582-04-5; **4b**, 82582-05-6; **4c**, 82582-06-7; **5**, 54448-63-4; **6**, 82582-07-8; **7**, 82582-08-9; **8**, 82582-09-0; **9**, 82582-10-3; **10**, 82582-11-4; **11a**, 82582-12-5; **11b**, 82582-13-6; **12a**, 82582-14-7; **12b**, 82582-15-8; **13a**, 82582-16-9; **13b**, 82582-17-0; 7-methyl-3-aminobenzo-*as*-triazine 1-oxide, 27281-74-9; 7-methoxy-3-aminobenzo-*as*-triazine 1-oxide, 27238-35-3; 5,7-dimethyl-3-aminobenzo-*as*-triazine 1-oxide, 82582-18-1.

Heterocyclic Deformations from Molecular Enlargement

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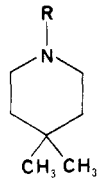
The ease of distortion of saturated nitrogen heterocycles has been examined by progressively increasing the bulk of the substituent at nitrogen. The heterocycles included the pharmacophoric piperidine and morpholine six-membered rings, as well as the five-membered oxazolidine ring. Response to increased bulk of substitution was intended to be a crude model for distortions within the drug–receptor complex. Substitution at nitrogen included methyl, (1-adamantyl)methyl, and 6-substituted β-cyclodextrin within a tetrahedral series, and acetyl and (1-adamantyl)carbonyl within a trigonal series. With methyl and acetyl serving as standards for the undistorted rings, we have found that the NCH_2CH_2X dihedral angle within all three heterocycles is decreased only by about 1° on introduction of the adamantyl groups. In agreement with this flattening distortion, the barrier to ring reversal of the piperidine is decreased by 1.4 kcal/mol on replacement of *N*-methyl by *N*-adamantylmethyl. The β-cyclodextrin ring imposes a much more severe distortion, as this same dihedral angle in the piperidine and morpholine rings decreases 5–6°. The barrier to rotation about the amide bond decreases 5–6 kcal/mol in all three heterocycles on going from acetyl to adamantylcarbonyl. These studies show that the response of these heterocycles to increased steric bulk of N substitution is a flatter and hence more flexible ring.

When a drug or hormone complexes with its biochemical receptor, it adopts an appropriate conformation. This conformation may be the same as that of the ground state, a distorted variety of the ground state, or a new, stable conformation. For many cyclic molecules, full rotations about single bonds are not possible, so that the conformational alternatives comprise either rearrangement of substituent positions or distortions of the ground-state conformation. These distortions may consist of partial rotations about single bonds (torsional modifications) or alterations of bond angles (valence-angle deformations).

In order to examine the ability of ring compounds to distort on complexation with a larger molecular entity, we have prepared a series of N-substituted heterocycles, which would be termed partially flexible in the Williams classification.[2] Piperidine and morpholine rings are particularly common in drugs, so we have selected **1** and **2** as



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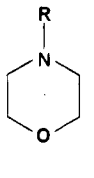

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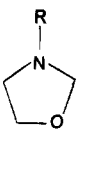

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subjects for this study. Whereas the six-membered ring is relatively rigid and subject only to the high-energy process of ring reversal (aside from the deformations mentioned above), the five-membered ring is quite flexible and subject to the low-energy process of pseudorotation. Thus the oxazolidine **3** may respond in a different fashion from the piperidine and the morpholine compounds. The *gem*-dimethyl group was placed in the piperidine ring in order to simplify the ^1H spectrum.

Our objective was to examine rings **1–3** in order to assess their sensitivities to distortion on progressive enlargement of the group R attached at nitrogen. The results would give some insight into the events that occur on formation

(1) This work was supported by the National Institutes of Health (Grant No. GM26124).

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Table I. Ring Torsional Angles

system	substituent	J_{trans}, Hz	J_{cis}, Hz	ΔJ_{gem}, Hz	R[a]	ψ[b]
1	CH_3	7.7	3.6	1.7	2.15	58
	$AdCH_2$[c]	7.45	3.65	1.3	2.05	57
	β-CD[d]	7.1	4.6	1.5	1.55	53
	CH_3CO	7.65	3.9	<0.5	1.95	56.5
	AdCO[e]	7.7	3.8	<0.5	2.05	57
2	CH_3	6.55	2.8	<0.5	2.35	59
	$AdCH_2$[c]	6.45	2.7	<0.5	2.35	59
	β-CD[d]	5.65	3.6	<0.5	1.55	53
	CH_3CO[f]	5.9	3.7	2.45	1.6	53
		6.0	3.35	2.25	1.8	55
	AdCO[e]	5.7	3.7	0.2	1.5	53
3	CH_3	7.4	6.2	3.65	1.2	48[g]
	$AdCH_2$[c]	7.15	6.3	3.8	1.15	47.5[g]
	CH_3CO	7.0	6.05	1.0	1.15	47.5[g]
	AdCO[e]	6.75	6.15	1.15	1.1	46.5[g]

[a] $R = J_{trans}/J_{cis}$. [b] $\psi = \cos^{-1}[3/(2 + R)]^{1/2}$. [c] Adamantylmethyl. [d] β-Cyclodextrin, with the heterocycle attached through nitrogen to a 6-carbon on one sugar ring. [e] Adamantylcarbonyl. [f] Measurements were made below the coalescence temperature for amide bond rotation, so that the two sides of the ring are nonequivalent. [g] See ref 7.

of the drug–receptor complex. *N*-Methyl (R = CH_3) and *N*-acetyl (R = $CH_3(C{=}O)$) were used to represent the uncomplexed small molecule, in which the nitrogen atom could be sp^3 or sp^2, respectively. A tenfold increase in the bulk of the substituent was achieved by the use of *N*-adamantylmethyl [R = (1-adamantyl)methyl] and *N*-adamantylcarbonyl [R = (1-adamantyl)carbonyl]. Another tenfold increase in size was achieved by the use of β-cyclodextrin. A single heterocycle can be introduced onto the narrower end of the β-cyclodextrin cavity by tosylation of the 6-position and displacement of tosylate by the heteroatom nitrogen (R = 6-substituted β-cyclodextrin, in which one 6-hydroxy group has been replaced by the heterocycle).

The heterocycles 1–3 were chosen for the wide variety of conformational probes they offer. (1) Each molecule has a CH_2CH_2 group. The N–C–C–X (X = O or CMe_2) dihedral angle ψ (4) can be measured by the *R* value me-

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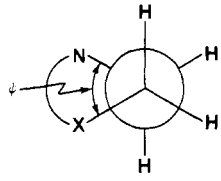
X: O, CMe_2



thod.[3] This angle ψ indicates how flattened or puckered the ring is, so that distortions caused by the R group can be monitored. (2) Amide bond rotation (around the N–CO bond) can be measured in the acetyl and adamantylcarbonyl systems. The sensitivity to bulk of this parameter has already been established.[4] (3) In the six-membered rings, the barrier to ring reversal can be measured. This barrier is known to be highly sensitive to ring distortions. Thus replacement of one CH_2 group by a carbonyl group reduces the barrier from 10.5 kcal/mol in cyclohexane to 4.1 kcal/mol in cyclohexanone.[5] The flatter ring of cyclohexanone is closer to the transition state to ring reversal. Using these probes, we report herein the conformational deformations in piperidine, morpholine, and oxazolidine rings by substituents on nitrogen that range from methyl to β-cyclodextrin.

Table II. Barriers to Amide Bond Rotation and Ring Reversal

system	substituent	T_c, K	$\Delta G^{\ddagger}$ (amide), kcal/mol	$\Delta G^{\ddagger}$ (ring rev), kcal/mol
1	CH_3	262		12.1
	$AdCH_2$[a]	234		10.7
	CH_3CO	355	17.2	
	AdCO[b]	239	12.0	
2	CH_3CO	353	16.9	
	AdCO[b]	231	10.8	
3	CH_3CO	348	17.4	
	AdCO[b]	265	12.7	

[a] Adamantylmethyl. [b] Adamantylcarbonyl.

Results

The *R* value method involves analysis of the AA'BB' spectrum of the CH_2CH_2 fragments within molecules 1–3.[3] The spectra are fully determined by two vicinal couplings, J_{trans} and J_{cis}, and by the difference between the geminal couplings, ΔJ_{gem}. The ratio *R* of the vicinal couplings gives the NCCX dihedral angle (see, 4) from the formula $\psi = \cos^{-1}[3/(2 + R)]^{1/2}$. These quantities are given in Table I for the 14 systems under study. A value of *R* close to 2.0 implies that the ring is nearly undistorted and that ψ is 56–58°. Larger values indicate puckering ($\psi > 58°$) and smaller values flattening ($\psi < 56°$).

The barrier to amide bond rotation was measured for 1–3 with R = acetyl and adamantylcarbonyl by standard coalescence methods. The figures are given in Table II. Ring reversal cannot be measured in the five-membered-ring oxazolidine nor in the amide systems. The barriers for ring reversal in the methyl and adamantylmethyl compounds in the piperidine series are also given in Table II.

Discussion

The dihedral angle that is supplied by the *R* value analysis is illustrated in structure 4. The average error for the method is about 1°.[3,5,7] These results refer to the structure in solution. The change from methyl to adamantylmethyl is very small. Possibly 1° of flattening is seen. The same is the case for the change from acetyl to adamantylcarbonyl. (Alkyl should not be compared to alkylcarbonyl, because of the change in hybridization at nitrogen.) In these six cases, slight flattening is indicated in four, very slight puckering in one, and no effect in one. Certainly only minor distortions are caused in the piperidine, morpholine, and oxazolidine rings on introduction of adamantyl in place of methyl at nitrogen in either the amine or the amide. On the other hand, considerable flattening is indicated upon introduction of the β-cyclodextrin group at nitrogen. The difference between methyl and β-cyclodextrin is 5° for the piperidine and 6° for the morpholine compound. A substituent of this bulk has a major distorting effect on the heterocycle ring.

Amide bond rotation barriers appear to be more sensitive to introduction of steric bulk. The barrier drops from 17.2 to 12.0 kcal/mol for the piperidines, from 16.9

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(7) Because of a systematic error in rings below six members, the *R* value method overestimates ψ in five-membered rings by about 15°. Thus the values in Table I for the oxazolidines are too high. Their relative values, however, are quite reliable. See: Lambert, J. B.; Papay, J. J.; Khan, S. A.; Kappauf, K. A.; Magyar, E. S. *J. Am. Chem. Soc.* **1974**, *96*, 6112–6118.

to 10.8 kcal/mol for the morpholines, and from 17.4 to 12.7 kcal/mol for the oxazolidines on going from acetyl to adamantylcarbonyl. The smallest decrease in the barrier is found for the oxazolidines. The smaller CNC bond angle in this five-membered ring may diminish interactions of the adamantyl group with the ring. The general lowering of the barrier to rotation for N—(C=O)X ↔ $^{+}$N=(C—O^{-})X with an increase in the bulk of X probably indicates steric resistance to planarity of the amide bond. Larger bond angles and hence relaxed steric interactions are permitted by greater deviations from planarity. Deviations from planarity require increased single bond character in the amide bond and hence result in a lower barrier.

Finally, the comparison of ring-reversal barriers for the 1-methyl- and 1-[(1-adamantyl)methyl]piperidines (12.1 and 10.7 kcal/mol, respectively) is particularly significant. The above R value analysis indicated a flattening of only 1° between these two systems. This small flattening, however, is translated into a decrease in the ring-reversal barrier of more than 1 kcal/mol. The 28 °C difference in the coalescence temperatures makes the barrier differences indisputable. A ring that is flattened reverses more easily because it is closer to the transition state.[5] Ring reversal cannot be measured in the amides and in the five-membered rings.

Our data indicate higher mobility and flexibility of the heterocycle rings upon attachment at nitrogen to larger molecular pieces. Even the relatively small change from methyl to adamantyl flattens the ring by about a degree and lowers the barrier to ring reversal by more than 1 kcal/mol. Complexation with β-cyclodextrin produces a much larger flattening, up to 6°. Steric bulk also lowers the barrier to amide rotation, as has previously been appreciated.[4] These results suggest that piperidine and morpholine rings in drugs may become flatter, more flexible, and more easily distorted upon complexation with their receptor.

Experimental Section

Proton spectra were recorded on a Perkin-Elmer R-20B, a Varian CFT-20, or a Nicolet NT-360.[8] The IR spectra were recorded on a Perkin-Elmer 283. The coupling constants were calculated by spectral simulation with SIMEQ, a program supplied by Varian for use on the Varian CFT-20.

3,3-Dimethylglutarimide was prepared by modifications of the preparation of the 2,3-dimethylsuccinimides by Burns et al.[9]

4,4-Dimethylpiperidine was prepared from 3,3-dimethylglutarimide by the method of Bishop et al.[10]

1,3-Oxazolidine was prepared by the condensation of 2-aminoethanol with paraformaldehyde.

General Procedure for the Preparation of Amides.[11] To a 2.0 M solution of the acid chloride in benzene at 0 °C was added dropwise a 1/1 mixture of the amine and triethylamine. After the addition was complete, the mixture was allowed to come to room temperature. The mixture was then suction filtered, and the solid was washed thoroughly with benzene. The filtrate was collected, and the benzene was removed under reduced pressure.

4-Acetylmorpholine and 1-acetyl-4,4-dimethylpiperidine were purified on a silica gel column with acetone or ether as the mobile phase.

3-Acetyl-1,3-oxazolidine was further purified by distillation at 79–81 °C (0.5 mm): 2.75 g (50%); ^{1}H NMR ($CDCl_3$; two sets of signals were present because of slow amide bond rotation) δ 4.87, 4.78 (s, 2, OCH_2N), 3.98 (m, 2, CH_2O), 3.50 (m, 2, CH_2N), 1.95, 1.91 (s, 3, CH_3CO); IR 1645 (s), 1430 (s) cm^{-1}. Anal. Calcd for $C_5H_9NO_2$: C, 52.2; H, 7.88; N, 12.2. Found: C, 51.7; H, 7.86; N, 11.8.

4-[(1-Adamantyl)carbonyl]morpholine was recrystallized from ethanol/H_2O as beige crystals: 10.53 g (77%); mp 118–120 °C; ^{1}H NMR ($CDCl_3$) δ 3.64 (br m, 8, OCH_2CH_2N), 1.69 (br m, 9, adamantyl), 1.69 (d, 6, adamantyl); IR ($CHCl_3$) 2911 (m), 2858 (m), 1633 (s) cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.45; H, 9.33; N, 5.67.

1-[(1-Adamantyl)carbonyl]-4,4-dimethylpiperidine was recrystallized from ethanol/H_2O as slightly yellow crystals: 10.01 g (57%); ^{1}H NMR ($CDCl_3$) δ 3.56 (m, 4, CH_2N), 1.95 (br m, 9, adamantyl), 1.72 (d, 6, adamantyl), 1.31 (m, 4, $CH_2C(CH_3)_2$), 0.99 (s, 6, $(CH_3)_2C$); IR 2907 (m), 2850 (m), 1623 (s), 1408 (s), 1250 (s), 1171 (s) cm^{-1}. Anal. Calcd for $C_{18}H_{29}NO$: C, 78.49; H, 10.61; N, 5.08. Found: C, 78.31; H, 10.56; N, 4.93.

3-[(1-Adamantyl)carbonyl]-1,3-oxazolidine was recrystallized from ethanol/H_2O as white crystals: 4.69 g (36%), mp 98–100 °C; ^{1}H NMR ($CDCl_3$) δ 4.95 (s, 2, OCH_2N), 3.75 (m, 4, OCH_2CH_2N), 1.91 (br m, 9, adamantyl), 1.71 (d, 6, adamantyl); IR ($CHCl_3$) 2908 (m), 1604 (s), 1410 (s), 1115 (s) cm^{-1}. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.52; H, 9.05; N, 5.36.

4-Methylmorpholine was prepared by the reductive condensation of formaldehyde with morpholine.[12]

1,4,4-Trimethylpiperidine was prepared from 4,4-dimethylpiperidine by the same procedure for 4-methylmorpholine.

3-Methyl-1,3-oxazolidine was prepared by condensation of 2-(methylamino)ethanol with paraformaldehyde.[13]

4-[(1-Adamantyl)methyl]morpholine.[14] To 0.38 g (0.01 mol) of $LiAlH_4$ in 10 mL of diethyl ether at 0 °C was added dropwise a solution of 2.5 g (0.01 mol) of 4-[(1-adamantyl)carbonyl]-morpholine in 50 mL of ether. After the addition was complete, the mixture was heated at reflux overnight. The mixture was then cooled at 0 °C, and H_2O was carefully added until all of the hydride had reacted (~3 mL). The solid was filtered off and washed several times with ether. The ether layers were combined and dried, and the ether was removed under reduced pressure to give a residue of white crystals: 2.33 g (99%); mp 62–63 °C; ^{1}H NMR ($CDCl_3$) δ 3.70 (m, 4, CH_2O), 2.49 (m, 4, ring CH_2N), 1.95 (s, 5, CH_2N and adamantyl), 1.7–1.4 (m, 12, adamantyl); IR ($HCCl_3$) 2905 (m), 1455 (s), 1150 (s) cm^{-1}. Anal. Calcd for $C_{15}H_{25}NO$: C, 76.55; H, 10.71; N, 5.95. Found: C, 75.80; H, 10.75; N, 5.67.

1-[(1-Adamantyl)methyl]-4,4-dimethylpiperidine[14] was prepared by the same method used for the morpholine. This procedure gave white crystals: 2.40 g (92%); mp 109–111.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.43 (m, 4, ring CH_2N), 1.94 (s, 5, CH_2N and adamantyl), 1.68 (d, 6, adamantyl), 1.52 (d, 6, adamantyl), 0.95 (m, 4, $CH_2C(CH_3)_2$), 0.89 (s, 6, $(CH_3)_2C$); IR ($HCCl_3$) 2905 (m), 2850 (m), 1450 (m), 1110 (m) cm^{-1}. Anal. Calcd for $C_{18}H_{31}N$: C, 82.69; H, 11.95; N, 5.36. Found: C, 82.10; H, 11.87; N, 5.15.

3-[(1-Adamantyl)methyl]-1,3-oxazolidine. To 10 mL of 2-aminoethanol and 23 mL of triethylamine at 0 °C was added a solution of 5.5 g of 1-adamantylcarbonyl chloride in 50 mL of benzene. The mixture was filtered and the solid was washed with benzene. The filtrate was then dried and the solvent removed under reduced pressure to give 2-[[(1-adamantyl)carbonyl]-amino]ethanol: 5.19 g (91%); ^{1}H NMR ($CDCl_3$) δ 3.45 (m, 4, NCH_2CH_2O), 1.98–1.61 (m, 15, adamantyl); IR ($HCCl_3$) 3460 (s), 1640 (s), 1510 (s), 1450 (s) cm^{-1}.

This amide was reduced, by the same procedure as for reduction of the (1-adamantyl)carbonyl amides of morpholine and 4,4-dimethylpiperidine, to give 2-[[1-(adamantyl)methyl]amino]ethanol: 3.0 g (62%); ^{1}H NMR ($CDCl_3$) δ 3.4 (m, 2, CH_2O), 2.7 (m, 2, CH_2CH_2N), 2.15 (s, 2, CH_2N), 1.9–1.4 (m, 15, adamantyl); IR ($HCCl_3$) 2903 (m), 2845 (m), 1450 (s) cm^{-1}.

To a solution of 1.5 g (7.2 mmol) of 2-[[(1-adamantyl)-methyl]amino]ethanol in 50 mL of benzene was added 0.216 g

(8) The NT-360 is located at the Purdue Biochemical Magnetic Resonance Laboratory, which is supported by NIH Grant No. RR01077 from the Division of Research Resources.

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(7.2 mmol) of paraformaldehyde. The solution was refluxed, and the H_2O formed was removed via a Dean-Stark trap. After 4 h, the benzene was removed under reduced pressure. The residue was separated on a silica gel column with diethyl ether as the mobile phase. The 3-[(1-adamantyl)methyl]-1,3-oxazolidine (R_f 0.8) was obtained as a liquid: 2.84 g (89%); ^1H NMR ($CDCl_3$) δ 4.10 (s, 2, OCH_2N), 3.60 (m, 2, CH_2O), 2.85 (m, 2, CH_2N), 2.1 (s, 2, CH_2N), 1.9 (m, 3, CH of adamantyl), 1.6 (d, 6, CH_2 of adamantyl), 1.46 (d, 6, CH_2 of adamantyl); IR ($HCCl_3$) 2905 (m), 2850 (m), 1450 (m), 1005 (m) cm^{-1}. Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.68; H, 10.58; N, 6.16.

6-Tosyl-β-cyclodextrin.[15] To 2.5 g (2.2 mmol) of freshly dried β-cyclodextrin (heated at 100 °C under vacuum) was added approximately 600 mL of freshly distilled pyridine (from BaO). This mixture was stirred until the β-cyclodextrin was completely dissolved, and 10 g of toluenesulfonyl chloride was added. The reaction mixture was stirred at room temperature for 40 min, and 20 mL of H_2O was added. The pyridine was then removed under reduced pressure. The resulting syrup was shaken with 100 mL of acetone, and the acetone was decanted off. This procedure was repeated in order to remove all the toluenesulfonic acid. The solid remaining in the flask was recrystallized from an ethyl acetate/2-propanol/water (10/13/7) solvent system to give a white powder: 0.83 g (27%); mp 157.5-158.5 °C; ^1H NMR (Me_2SO-d_6) δ 7.8 (d, CH=CSO_3), 7.3 (d, CH=CCH_3), 4.4-3.5 (br m, cyclodextrin), 2.40 (s, CH_3). Anal. Calcd for $C_{49}H_{76}SO_{37}$: C, 45.54; H, 5.16. Found: C, 44.55; H, 5.12.

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6-Morpholino-β-cyclodextrin. To 100 mg of 6-tosyl-β-cyclodextrin was added 2 g of morpholine. This mixture was heated for 48 h at 75 °C. The solution was then diluted to 10 mL with acetone and placed on a silica gel column with acetone as the mobile phase (R_f 0.9). The fraction containing the substituted β-cyclodextrin was separated, and the solvent was removed under reduced pressure. To the resulting syrup was added 1 mL of H_2O, and the mixture was then freeze-dried to give a white powder: 0.026 g (25%); mp 254-256 °C dec; ^1H NMR (Me_2SO-d_6) δ 4.88 (br m, HC(O)O), 3.83-3.08 (br m, cyclodextrin), 3.52 (m, ring CH_2O), 2.69 (m, ring CH_2N).

6-(4,4-Dimethylpiperidino)-β-cyclodextrin. To 100 mg of 6-tosyl-β-cyclodextrin was added 2 g of 4,4-dimethylpiperidine. This mixture was heated for 48 h at 75 °C. The solution was cooled, diluted to 10 mL with acetone, and eluted on a column of silica gel with acetone as the mobile phase (R_f 0.9). The fraction containing the substituted β-cyclodextrin was collected, and the acetone was removed under reduced pressure. The resulting syrup was dissolved in H_2O, and the solution was freeze-dried to give a white powder: 65 mg; mp 151 °C dec; ^1H NMR δ 4.88 (br m, HC(O)O), 3.83-3.08 (br m, cyclodextrin), 2.88 (m, ring CH_2N), 2.44 (t, CH_2N), 1.38 (m, $CH_2C(CH_3)_2$), 0.97 (s, $(CH_3)_2C$).

Registry No. 1 (R = CH_3), 1003-84-5; 1 (R = $AdCH_2$), 82679-29-6; 1 (R = β-CD), 82679-30-9; 1 (R = CH_3CO), 82679-31-0; 1 (R = AdCO), 82679-32-1; 2 (R = CH_3), 109-02-4; 2 (R = $AdCH_2$), 22508-54-9; 2 (R = β-CD), 82679-33-2; 2 (R = CH_3CO), 1696-20-4; 2 (R = AdCO), 22508-50-5; 3 (R = CH_3), 27970-32-7; 3 (R = $AdCH_2$), 82679-34-3; 3 (R = CH_3CO), 3672-60-4; 3 (R = AdCO), 82679-35-4; 6-tosyl-β-cyclodextrin, 67217-55-4; 2-aminoethanol, 141-43-5; 1-adamantylcarbonyl chloride, 2094-72-6; 2-[[(1-adamantyl)-carbonyl]amino]ethanol, 78743-65-4; 2-[[(1-adamantyl)methyl]-amino]ethanol, 65738-69-4.

Synthesis of the Benzotricyclooctane Ring System. Intramolecular [2 + 2] Cycloaddition of Indene Derivatives

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The photosensitized triplet reactions of several 1-allyl-substituted indenes have been studied. The triplet-sensitized irradiations gave benzotricyclo[3.3.0.$0^{2,7}$]octanes in good yield by means of a novel intramolecular [2 + 2] cycloaddition. The effect of substituents on the regioselectivity of the sensitized rearrangement was studied in some detail. With the simple 1-allyl-substituted isomer, 1,5-cyclization of the excited state is the preferred path. This mode of cyclization is favored on the basis of strain, radical stability, and entropy factors. We have found, however, that the normal closure predicted by the rule of five does not occur in the photosensitized irradiation of the 1-prenyl-substituted isomer. With this system, intramolecular [2 + 2] cycloaddition gives rise to the benzotricyclo[3.2.1.$0^{3,8}$]octane system. The diradical produced from the sensitized 1,4-cyclization path is long lived enough to allow internal disproportionation to compete with radical coupling. The facility with which the intramolecular [2 + 2] indene photocycloadditions occur makes this type of approach particularly attractive for the synthesis of some unusual polycyclic ring compounds.

In recent years organic chemists have become increasingly aware of the power of photochemical [2 + 2] cycloadditions for the construction of complex polycyclic molecules.[1-4] In particular, the photocycloaddition reactions of α,β-unsaturated carbonyl compounds has been the subject of intensive study.[5] More recently, a number of approaches to the synthesis of a variety of tricyclic ring systems have used an intramolecular variant of this reaction.[6-16] Strained polycyclics containing bicyclo[2.1.0]pentane and bicyclo[2.2.0]hexane units have also been prepared by this method.[17-20] These compounds play an important role in the understanding of many aspects of organic chemistry.[20-25] For this reason, synthetic efforts using the photochemical [2 + 2] cycloaddition reaction

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