3,7,9-Triheterabicyclo[3.3.2]decan-10-ones: An Unusual Family of Heterocycles Obtained from 3,7-Diheterabicyclo[3.3.1]nonan-9-ones

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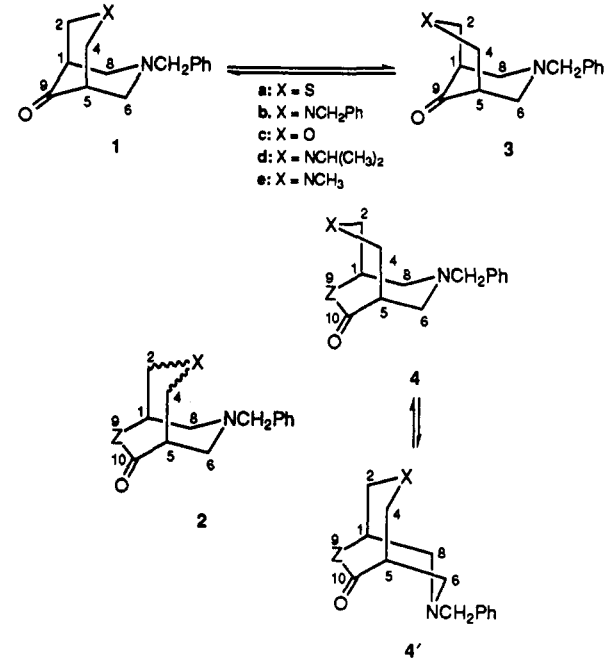
A series of new 3,7,9-triheterabicyclo[3.3.2]decan-10-ones is reported for the first time. Members of the family of 3,7-diheterabicyclo[3.3.1]nonan-9-ones served as precursors of the title compounds. Spectral evidence suggests the 3,7,9-triheterabicyclo[3.3.2]decan-10-ones exist in a chair–boat (CB) ⇄ boat–chair (BC) equilibrium in solution. It is speculated that steric hindrance around the carbonyl group and possibly the variance in conformation BC versus CC of the individual 3,7-diheterabicyclo-[3.3.1]nonan-9-one precursors in solution may influence the ease of oxygen and nitrogen insertion in the ring enlargement to give the title molecules. Confirmation that three members of the bicyclo-[3.3.2]decan-10-ones exist in BC forms in the solid state was achieved via single crystal X-ray diffraction analysis for 7-benzyl-3-thia-7,9-diazabicyclo[3.3.2]decan-10-one (**4a**), 3,7-dibenzyl-3,7,9-triazabicyclo-[3.3.2]decan-10-one (**4c**), and 3,7-dibenzyl-9-oxa-3,7-diazabicyclo[3.3.2]decan-10-one (**4d**).

Carbocyclic bicyclo[3.3.2]decane systems are known[1] with the major conformer considered to be a boat–boat (BB) form for the eight-membered ring in the majority of cases examined which is also believed to be true for the bicyclo[3.3.1]nonanes.[2] The synthesis and chemistry of bridgehead alkenes in related bicyclo[3.3.2]decene systems have been reviewed.[3] Although the corresponding 3,7-diheterabicyclo[3.3.1]nonanes have been investigated primarily within the past two decades,[4] very little work has been published on the 3,7-dihetera- or 3,7,9-triheterabicyclo[3.3.2]decanes and derivatives. To be sure, a search of the literature is exceedingly difficult without direct reference to specific compounds, but it appears that no comprehensive review has been published for the latter two heterocyclic families.

We report herein useful synthetic approaches to certain 3,7,9-triheterabicyclo[3.3.2]decan-10-one systems. 3,7-Diheterabicyclo[3.3.1]nonan-9-ones **1** (CC) ⇄ **3** (BC) are quite well known[4,5] and served as precursors for the title compounds represented by conformer **2** (the wiggly bonds are meant to imply the conformation is undefined). However, some 3,7-diheterabicyclo[3.3.1]nonan-9-ones are also thought to exist primarily in the boat–chair (BC) (represented by **3**) form both in solution and in the solid state.[4,5] The question arises as to whether the CC or BC form would predominate in 3,7,9-triheterabicyclo[3.3.2]-decan-10-ones and relatives.[6] For the purposes of dis-



a: X = S, Z = NH
b: X = SO_2, Z = O
c: X = NCH_2Ph, Z = NH
d: X = NCH_2Ph, Z = O
e: X = O, Z = NH
f: X = O, $HClO_4$, Z = O
g: X = $^+N(H)CH(CH_3)_2$, ClO_4^-, Z = NH
h: X = $^+N(H)CH(CH_3)_2$, ClO_4^-, Z = O
i: X = NCH_3, Z = NH
j: X = $^+N(H)CH_3$, ClO_4^-, Z = O

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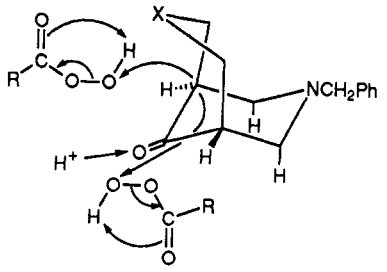
cussion of this work, we have assumed the equilibrium **4** ⇄ **4'** is present in solution for all examples with primarily the BC ⇄ CB forms present.

Treatment of **1a** ⇄ **3a** (X = S)[7] with sodium azide/sulfuric acid in chloroform led to **4a** (76%) as a crystalline product.[8,9] Oxygen insertion via a Baeyer–Villiger approach with **1a** ⇄ **3a** and peracetic acid/H_2SO_4 in boiling chloroform surprisingly (we had expected the sulfoxide under our conditions) yielded sulfone **4b** resulting from sulfur oxidation concomitant with ring expansion. With *m*-$ClC_6H_4CO_3H$ (MCPBA) and **1a** ⇄ **3a**, only a complex, intractable mixture was obtained. In a similar manner, **1b** ⇄ **3b**[10] (X = NCH_2Ph) was converted to lactam **4c** and lactone **4d**, respectively, except the oxidizing agent for the latter conversion was MCPBA rather than peracetic acid/H_2SO_4 which gave only a very complex mixture from **1c** ⇄ **3c**.[11]

Nitrogen insertion into ketone **1c** ⇄ **3c** (X = O)[12] proceeded smoothly to lactam **4e**, but lactonization of **1c** ⇄ **3c** with MCPBA gave an oil (75%) which had to be converted to the hydroperchlorate **4f** (33.4%). Purification of salt **4f** was facile via recrystallization, with the overall yield from **1c** ⇄ **3c** being 25%. In a like manner, ketones **1d** ⇄ **3d** [X = $NCH(CH_3)_2$] and **1e** ⇄ **3e** (X = NCH_3) reacted with peracetic acid, but isolation of a solid product was achieved only as the hydroperchlorate lactones **4h** (55.4% from crude amine) and **4j** (81.9% from crude amine), respectively. Conversion of ketones **1d** ⇄ **3d** (X = $NCH(CH_3)_2$) and **1e** ⇄ **3e** (X = NCH_3)[13] to the respective lactams **4g** (hydroperchlorate lactam, 60.0% from crude intermediate amine) and **4i** (84.9%) under the conditions cited above with sodium azide/H_2SO_4 in chloroform was effective.

It seems reasonable that rate and regioselectivity of oxygen insertion into ketones **1a** ⇄ **3a** (X = S), **1b** ⇄ **3b** (X = NCH_2Ph) and **1c** ⇄ **3c** (X = O) may well be dependent upon the suspected high contribution of a BC conformer **3**[13,14] (**3a** has been confirmed as a BC conformer in the solid state[5] and **1b** is considered a flattened CC conformer in solution[13]). In view of the accepted mechanism[11] of attack by a peracid on the carbon atom of a carbonyl group in a ketone, a heteroatom (with or without a substituent) at the 3-position in a boat arrangement of a ring could hinder approach of the oxidizing agent. Moreover, with sulfur at this position immediate and direct oxidation to a sulfoxide or a sulfone would not be unreasonable. The axial hydrogens in the piperidinone ring could also retard attack from the "bottom side" as illustrated. These observations are in agreement with the modest yields of **4b** (12.1%), for example, which has the large sulfur atom as X. With the ketones **1d** ⇄ **3d** [X = $NCH(CH_3)_2$] and **1e** ⇄ **3e** [X = NCH_3] possibly the



presence of the *N*-isopropyl and *N*-benzyl groups, respectively, may screen the carbonyl group to hinder attack by any nucleophile at least from one face of the carbonyl group.[10,13] It appears that in 3-alkyl-7-benzyl-3,7-diazabicyclo[3.3.1]nonan-9-ones with alkyl groups larger than methyl may result in generation of a CC ⇄ BC equilibrium or at least a flattened CC form for the system in solution. In any event, the yields were modest of the immediate *precursors* (21.3 and 11.3%, respectively) of expected lactones hydroperchlorates **4h** (55.4% from precursor amine) and **4j** (81.9% from precursor amine) although the procedures were simple to perform. The system with two *N*-benzyl groups may exist exclusively in solution as **1b** (X = NCH_2Ph) since lactone **4d** was obtained in good yield (66.1%). As illustrated, the heteroatom may hinder a "top" approach and the axial protons may restrict the "bottom" approach of the peracid in systems with a high population of BC or CB form. Since mixtures were obtained in all oxidations, multiple side reactions may also occur concurrent with the new ring-forming operation. Although space-filling molecular models imply that hindrance to attack on the carbonyl group is less in a CC form, no theoretical calculations have appeared to support this conjecture, but such theoretical studies are in progress in our laboratory.

Nitrogen insertion progressed much more favorably with members of **1** → **4**, the lowest yield being realized with **4g**

(6) (a) Some disagreements have developed concerning the presence of either a CC or BC form in selected carbocyclic members of this family. See: Russell, G. A.; Keske, R. G. *J. Am. Chem. Soc.* **1970**, *92*, 4460–4461. (b) Doyle, M.; Hafter, R.; Parker, W. *Tetrahedron Lett.* **1971**, 3985–3986.

(7) Solid ketone **3a** is known to be a BC form; see data in ref 5a.

(8) (a) A few partially related examples were uncovered, such as 3-benzyl-3-azabicyclo[3.3.1]nonan-9-one (a BC form was postulated), and behaved similarly to give the corresponding lactam, although very few properties of the latter were disclosed. See Groves, J. T.; Olson, J. R. *Inorg. Chem.* **1985**, *24*, 2715–2717. For a peripherally related case with pseudopelletierine in a Schmidt reaction; see (b) Paquette, L. A.; Wise, L. D. J. *Am. Chem. Soc.*, **1965**, *87*, 1561–1566. See also: (c) Plostnieks, J. *J. Org. Chem.* **1966**, *31*, 634–636. For a review of nitrogen insertion reactions with bridged bicyclic ketones, see (d) Krow, G. R. *Tetrahedron* **1983**, *37*, 1283–1307.

(9) A recent example of lactam formation in the family of a bicyclo[3.3.1]nonan-9-one involved treatment of the oxime of 3-(phenylsulfonyl)-bicyclo[3.3.1]nonan-9-one (a BC form was postulated) with polyphosphate ester (PPE) at reflux to give 3-(phenylsulfonyl)-9-azabicyclo[3.3.2]decan-9-one; see Padwa, A.; Kline, D. N.; Murphree, S. S.; Yeske, P. E. *J. Org. Chem.* **1992**, *57*, 298–306.

(10) Ketone **3b** has been tentatively designated as a BC form since the 3-benzyl-7-methyl-3,7-diazabicyclo[3.3.1]nonan-9-one is a BC in the solid state: see Smith-Verdier, P.; Florcenio, F.; Garcia-Blanco, S. *Acta Crystallogr.* **1983**, *39C*, 101–103.

(11) (a) Compare with: Starcher, P. S.; Phillips, B. *J. Am. Chem. Soc.* **1958**, *80*, 4079–4082. (b) For a review on oxygen insertion in bridged bicyclic ketones, see: Krow, G. R. *Tetrahedron* **1981**, *37*, 2697–2724. No example was recorded in this review nor was any found wherein a heteroatom (such as N, P, etc.) vulnerable to oxidation was present in a 3,7-diheterabicyclo[3.3.1]nonan-9-one system being subjected to oxygen insertion conditions. The parent compound bicyclo[3.3.1]nonan-9-one and a few simple relatives are known to undergo such oxygen insertion: see (c) Cope, A. C.; Gale, D. M. *J. Am. Chem. Soc.* **1963**, *85*, 3743–3747. (d) Appleton, R. A.; Baggaley, K. H.; Egan, S. C.; Davies, J. M.; Graham, S. H.; Lewis, D. O. *J. Chem. Soc. (C)* **1968**, 2032–2309. (e) Hellman, H. M.; Jerrussi, R. A.; Lancaster, J. *J. Org. Chem.* **1967**, *32*, 2148–2151.

(12) (a) Ketone **1c** was originally considered a flattened CC conformer in view of certain spectral evidence: see Arjunan, P.; Berlin, K. D.; Barnes, C. L.; van der Helm, D. *J. Org. Chem.* **1981**, *46*, 3196–3204. However, there is some question on this matter from recent ^{17}O NMR studies which suggest an equilibrium in solution involving **1c** (CC) ⇄ **3c** (BC); see (b) Mulekar, S. V.; Berlin, K. D. *J. Org. Chem.* **1989**, *54*, 4758–4767.

(13) (a) Some have argued that 3-alkyl-7-methyl-3,7-diazabicyclo[3.3.1]-nonan-9-ones adopt flattened CC forms in solution: see Arias, M. S.; Galvez, E.; Del Castillo, J. C.; Vaquero, J. J. *Mol. Struct.* **1987**, *156*, 239–246. High contributions from a BC form have not been eliminated, however. (b) Preliminary studies revealed that ketone **1d** exhibited certain proton NMR data over a temperature range which suggested a possible **1d** (BC) ⇄ **3d** (CC) equilibrium: see Zisman, S. A., Ph.D. Dissertation, Oklahoma State University, 1989.

(14) No overall assessment has been published regarding the parameters which govern the ratio of CC/BC conformers of ketones **1** ⇄ **3** in solution. General discussions on the subject are found in refs 4 and 5.

(hydroperchlorate). Recent studies[15] support the generation of iminodiazonium ions from the reaction of a ketone with hydrazoic acid in an acid-catalyzed media. Since hydrazoic acid is small, relative to the peracids described previously in the oxidative insertion processes, steric factors may be less important in formation of the lactams. An interesting contrast in comparison is that involving the preparation of **4a** from **1a** ⇄ **3a** (X = S) versus **4g** from **1d** ⇄ **3d** [X = $NCH(CH_3)_2$], the amine *precursor* of **4g** being isolated in low yield (39.0%) compared to that (76.1%) for **4a**. The known[5] high population of the **3a** (BC) conformer may retard formation of lactone **4b**, but one might tentatively conclude that the longer C–S bonds could allow a more facile approach of the smaller hydrazoic acid to the carbon of the C=O group compared to that by a peracid. Conceivably, the major conformer for **1d** ⇄ **3d** may also be a **3d** (BC) with the isopropyl group attached to N in a boat form and located at the "bow" of the boat-like ring with the C=O group at the 9-position.

In the above arguments, a BC ⇄ CC equilibrium is probable for all examples **1** ⇄ **3**. This is especially important when one considers the acid media involved in all reactions and which likely produces quaternary nitrogen atoms that could induce formation of BC or CB conformers. The presence of such protonated tertiary nitrogen atoms might well offer greater hindrance around the carbonyl group for attack by nucleophiles. Interestingly, attempted salt formation with perchloric acid and **1a** ⇄ **3a** (X = S) in an ethanol/water (1:1) solution resulted in the simultaneous formation of the *N*-protonated derivative containing a 9,9-diol system.[16] Thus, *N*-protonation occurred but the flattening effect on the bicyclic system was altered with conversion of the C(9)=O group to a $C(9)(OH)_2$ function presumably in a CC form.

When a large excess (5 equiv) of *m*-$ClC_6H_4CO_3H$ was employed with **1d** ⇄ **3d**, only a complex mixture formed. With 1.5 equiv of *m*-$ClC_6H_4CO_3H$ and **1d** ⇄ **3d**, a large amount of starting material was recovered. Only when 4 equiv of peracetic acid were utilized with **1d** ⇄ **3d** was a satisfactory yield of **4h** realized. No explanation for these observations is obvious.

Transannular *endo*-H(3),H(7) distances have been suggested to decrease in going from the bicyclo[3.3.1]nonane system to the bicyclo[3.3.2]decane system on the basis of Dreiding models.[17,18] Stretching frequencies [$\nu_{(C-H)}$] for *endo*-H(3),H(7) in bicyclo[3.3.1]nonane led to an estimate[19] of the H(3)···H(7) distance as 170 pm which agrees to some degree with the X-ray data.[20] In contrast, calculations from $\nu_{(C-H)}$ values for bicyclo[3.3.2]decane inferred a distance for H(3)···H(7) of about 200 (±20) pm.[1] Consequently, the latter suggests *greater* flexibility in a two-atom bridged system compared to a one-atom bridged system. One other point bearing on the arguments is that which includes a double bond in the system. For example, in bicyclo[3.3.2]dec-9-ene, there may exist restricted flexibility in a CC conformer with a resultant increased *endo*-H(3)···H(7) interaction and possibly leading to a preferred BC conformation.[1] Since the ^{13}C NMR resonances for C(10) in lactones **4b,d,f,h,j** and lactams **4a,c,e,g,i** appear to have comparable shifts in the range of 169.6–178.6 ppm,[21 a,b] a tentative conclusion might be that all have the same type of conformer and may be heavily populated with BC forms. However, since the lactams may also possess double bond character in the N(9)–C(10) bond {as in bicyclo[3.3.2]dec-9-ene}, relief of nonbonded interactions involving heteroatoms at the 3- and 7-positions could result in a population with BC or a flattened or twist–twist CC form in solution.

In order to investigate the BC ⇄ CB of a 3,7,9-triheterabicyclo[3.3.2]decan-9-one system in solution, a temperature study of the proton NMR spectrum was initiated with lactone **4d** ⇄ **4d'** (X = NCH_2Ph) over the range of −75 °C to +80 °C. A complicated multiplet from 2.7–2.9 ppm was revealed on a solution of **4d** ⇄ **4d'** in acetone-d_6 at room temperature (Figures 1–3). At −75 °C, this multiplet collapsed to a pair of doublets for the axial (2.73 ppm) and equatorial (2.85 ppm) protons at what appeared to be magnetically equivalent positions of C(2,4,6,8). At +80 °C in toluene-d_7, the same signals were shifted to 2.37–2.5 ppm but remained complex as observed at room temperature in acetone-d_6. The implication is that one form exists at −75 °C, but that a dynamic, fluxional system occurs with **4d** ⇄ **4d'** at room temperature. Although it is tempting to speculate these systems have only a BC (or CB) form at low temperatures, the nature of the substituted heteroatom may well dictate the form of the major conformer.

Slow crystallization of **4a** (from dichloromethane/hexane) as well as **4c** and **4d** (from ethanol/hexane) permitted isolation of crystals suitable for X-ray diffraction analysis.[21c] Stereoplots of **4a**, **4c**, and **4d** are shown in Figure 4, parts a, b, and c, respectively. The bicyclo[3.3.2]-decane system has the boat–chair (BC) conformation in all three compounds in the solid state. *These are the first X-ray structure determinations of the free bicyclo[3.3.2]-decan-10-one systems.* There are, however, two crystal structures of the basic structural unit in which the 9- and 10-atoms are part of an aromatic system.[22,23] Nevertheless, in these two latter structures, the bicyclo[3.3.2]decane unit also assumes a BC conformation. These observations are consistent with the predictions of Doyle, Hafter, and Parker[24] for the preferred BC conformer of the bicyclo-

(15) Bach, R. D.; Wolber, G. J. *J. Org. Chem.* **1982**, *47*, 239–245.
(16) Bailey, B. R., III; Berlin, K. D.; Holt, E. M. *Phosphorus Sulfur* **1984**, *20*, 131–137.
(17) Leonard, N. J.; Coll, J. C. *J. Am. Chem. Soc.* **1970**, *92*, 6685–6686.
(18) See ref 1c.
(19) (a) Martin, J. Ph.D. Thesis, University of Glasgow, 1964. (b) Eglinton, G.; Martin, J.; Parker, W. *J. Chem. Soc.* **1965**, 1243–1251. (c) Brown, W. A. C.; Eglinton, G.; Martin, J.; Parker, W. *Proc. Chem. Soc.* **1964**, 57–58. (d) Brown, W. A. C.; Martin, J.; Sim, G. A. *J. Chem. Soc. (C)* **1965**, 1844–1857.
(20) Reference 19c contains the X-ray data for a bicyclo[3.3.1]nonane from which the *endo*-H(3)···H(7) distance of 1.8 Å along with a C(3)···C(7) distance of 3.06 Å was extracted. Reference 2a contains X-ray data for a 3-azabicyclo[3.3.1]nonane system which reveal a C(7)···N(3) distance of 3.02 Å.
(21) (a) For a summary of such shifts, see Levy, G. C.; Lichter, R. L.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance Spectroscopy*, 2nd ed.; Wiley-Interscience: New York, 1980. The ^{13}C NMR shift for the carbonyl carbon in the seven-membered caprolactam is 178.6 ppm (chapter 5, page 151 in the above reference). (b) The value for caprolactone is 165.3 ppm as found in Strothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic Press: New York, 1972; Chapter 8, page 300. Of course, these simple monocyclic systems may adopt several conformations in solution and therefore the ^{13}C chemical shifts for the carbon atom of the C=O group are likely an average and may not be entirely satisfactory models for members of **4**. (c) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
(22) Hafter, R.; Murray-Rust, J.; Murray-Rust, P.; Parker, W. *J. Chem. Soc., Chem. Commun.* **1972**, 1127.
(23) Murray-Rust, J.; Murray-Rust, P. *Acta Crystallogr.* **1975**, *B31*, 310–311.
(24) Doyle, M.; Hafter, R.; Parker, W. *Tetrahedron Lett.* **1971**, 3985–3986.

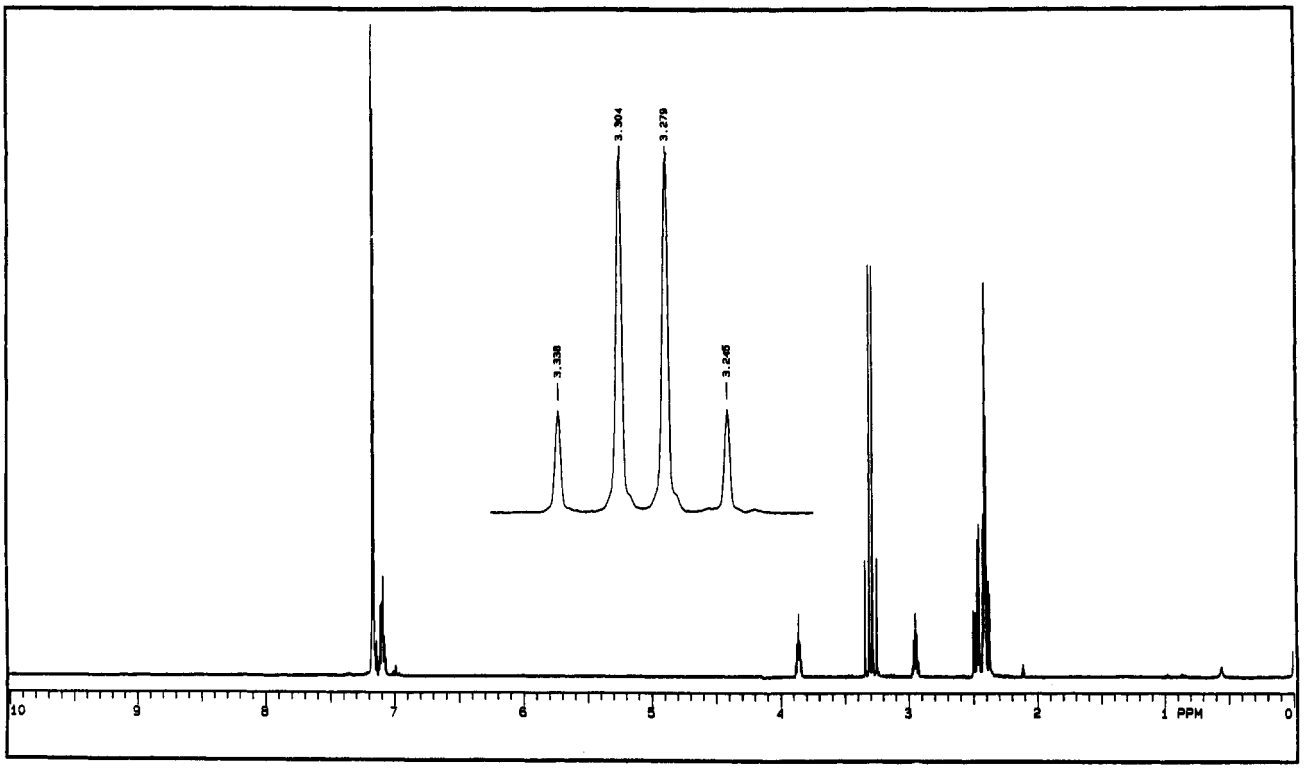


Figure 1. Proton NMR spectrum of **4d** in toluene-d_8 at +80 °C.

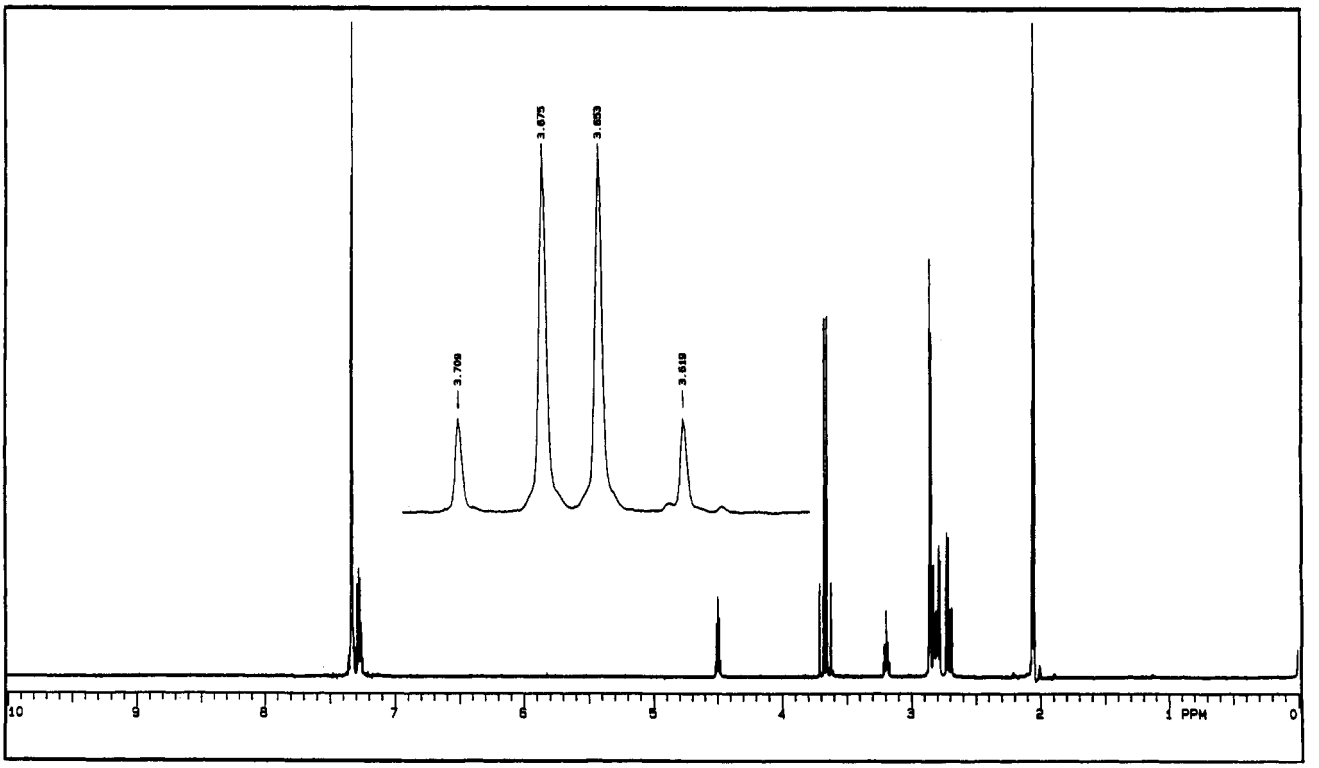


Figure 2. Proton NMR spectrum of **4d** in acetone-d_6 at room temperature.

[3.3.2]decane system when the 1–5–9–10 portion of the molecule is planar as it is in **4a,c,d**.

The X(3)···N(7) nonbonded distances in our three compounds are similar to those observed in the analogous bicyclo[3.3.1]nonane system. For example, the S(3)···N(7) distance in **4a** is 3.74 Å which is shorter than in **3a** which is 3.85 Å.[5] In **4c** and **4d** the comparable distances are 3.43 and 3.45 Å, respectively, while in the analogous bicyclo[3.3.1]nonan-9-one[10] counterpart the distance is 3.47 Å. In the bicyclo[3.3.2]decane system the CC form leads to an unacceptable (X)3···(N)7 nonbonded distance of the order of 2.5 Å, and is, therefore, not an expected conformation for such compounds either in the solid state or solution. Of course, this does not eliminate highly flattened CC forms being present, particularly in solution.

A further inspection of the conformation of **4a,c,d** shows that the free electron pair in the N-containing seven-membered rings is axial in both the chair and boat ring

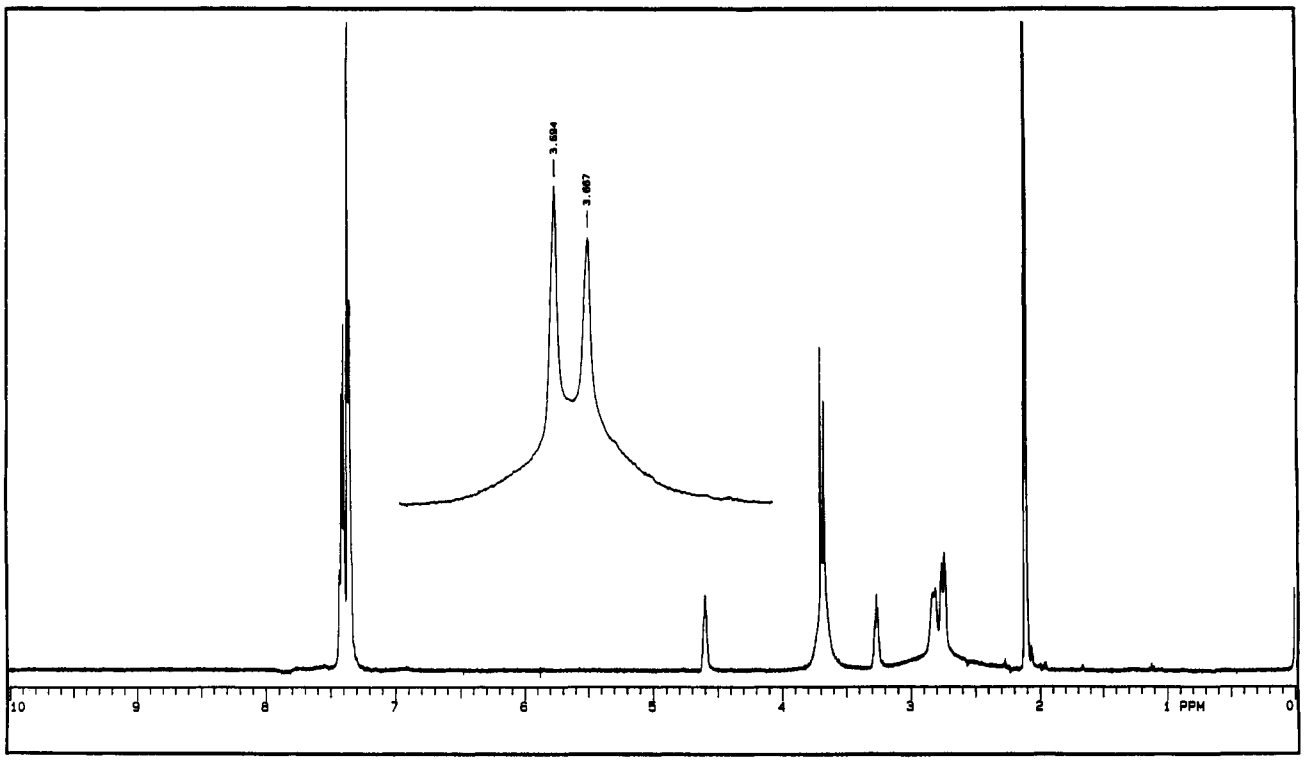
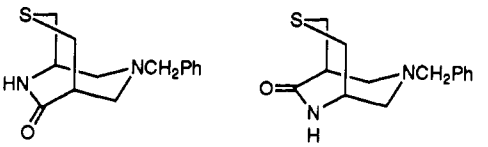


Figure 3. Proton NMR spectrum of **4d** in acetone-d_6 at −75 °C.

conformations. Thus, for such a ring to undergo ring reversal from a boat to a chair conformation, or vice versa, the normal activation energy for this process is further increased by a required inversion of the substituted pyramidal nitrogen atom to return the subtituent to an equatorial position. Conceivably, the total activation energy for the BC ⇄ CB interconversion in both **4c** and **4d** becomes sufficiently large that in these formally achiral compounds the equilibrium between the two conformations will be slow which in turn can cause disorder as observed in the crystal structure determinations. It is noteworthy that in the 3,7-diazabicyclo[3.3.1]nonan-9-one system the free electron pair is axial in both the chair and boat N-containing heterocyclic rings.[10]

Lactam **4a** can be compared to ketone **3a** in that both structures contain sulfur in a boat conformer while there is also an N-containing chair conformer present. The disorder observed in the structure determination of **4a** cannot be caused by a BC ⇄ CB equilibrium. There is no intuitively obvious reason, however, for a nonregiospecific insertion[25] reaction involving **3a** and NaN_3 under the acidic conditions employed. However, there could very well be a preferred direction of attack (by HN_3 or *m*-$ClC_6H_4CO_3H$) from the less hindered face of the carbonyl group in **3** if there is a boat form present in which one heteroatom in the boat screens one face of the carbonyl group. Nevertheless, conversion of the intermediate resulting from attack by either reagent on the carbonyl group in members of **3** should give equal amounts of both enantiomers. Interestingly, achiral **1a** ⇄ **3a** leads to chiral **4a** ⇄ **4a′** while achiral **1c** ⇄ **3c** leads to **4c** ⇄ **4c′** or **4d** ⇄ **4d′**. The inversion barrier to ring reversal through a CC form in **4c** → **4c′** and **4d** → **4d′** must be large, and thus **4c**, **4c′**, **4d**, and **4d′** are chiral. Conceivably, the presence of impurities might induce an unusual crystalline process and lead to a 3:1 proportion observed for the enantiomeric systems shown below, both with the S-heterocyclic ring in



the boat form and the N-ring in the chair form, and which cocrystallize. Cocrystallization of nonequivalent amounts of stereoisomers in the solid state is somewhat rare, but it has been observed in certain heterocyclic systems.[26]

The angles between the various three- and four-membered planes in **4a,c,d** and the bicyclo[3.3.1]nonan-9-one analogs are shown in Figure 5. It is obvious that plane 1 leans away to a smaller extent from the ring in the boat conformation (plane 5) in the decane system than in the nonane system. This is caused by the fact that the 1···4 interaction of the six-membered ring in the nonane system does not exist in the decane system because the ring is seven- rather than the six-membered.

In summary, we have been able to obtain several members in the series of the title compounds by convenient and simple routes. Spectral and X-ray diffraction analyses strongly imply the systems are all boat–chair (BC) forms in the solid state and *in solution*. These bicyclic systems are potentially excellent synthons for the preparation of highly functionalized eight-membered heterocycles via simple hydrolysis of the lactam and lactone groups. Such eight-membered ring systems have considerable potential for the development of supramolecular chemistry and molecular recognition as caged compounds since the "N-

(25) The subject has been reviewed; see: Hudlicky, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington, D. C., 1990; pp 186–195 and refs therein.

(26) Fink, R.; van der Helm, D.; Berlin, K. D. *Phosphorus Sulfur*, 1980, *8*, 325–330.

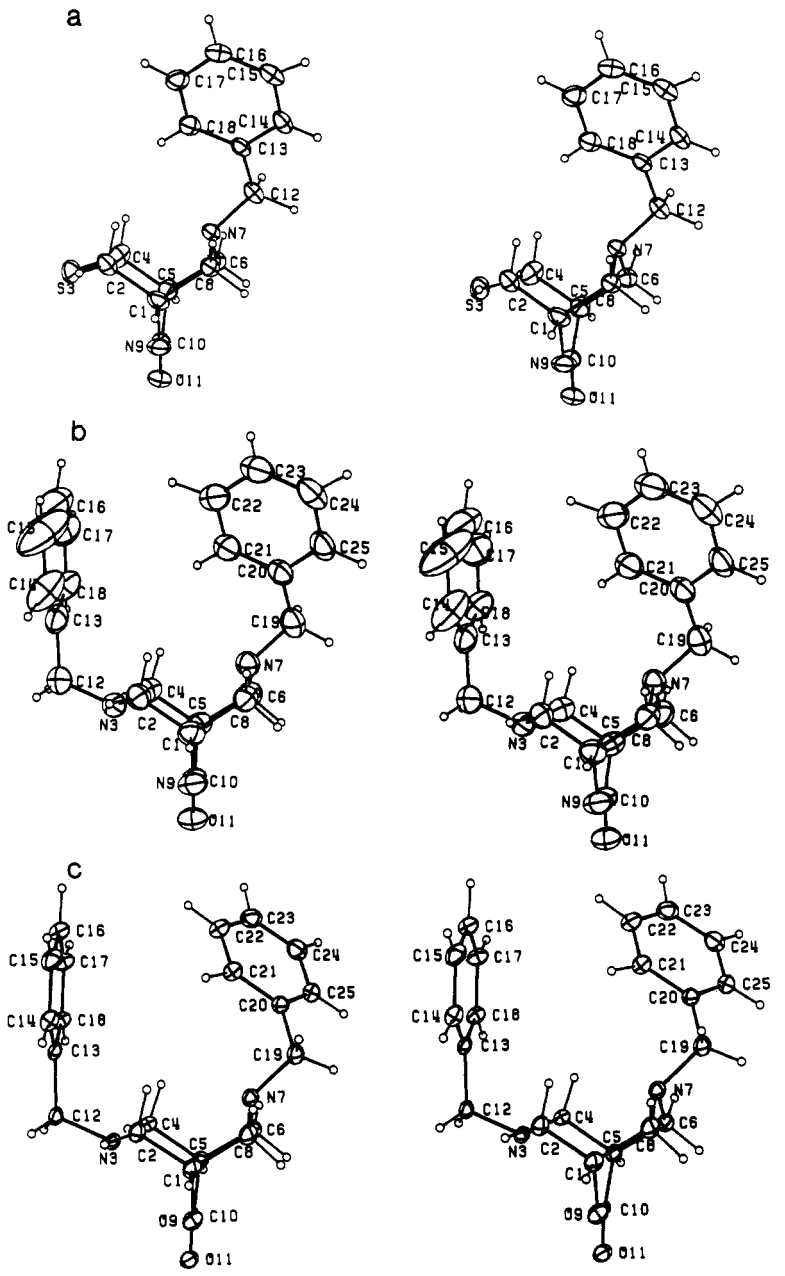


Figure 4. Stereo ORTEP plots of **4a** (a), **4c** (b) and **4d** (c). Ellipsoids are drawn at the 30% probability level, except for the H atoms.

arms" and the carboxyl group can have a variety of substituents.[27]

Experimental Section

General. Melting points are uncorrected. IR spectra were recorded as KBr pellets or as films. ^1H and ^{13}C NMR spectra were observed at 299.94 and 75.43 MHz, respectively. A few spectra for ^1H were observed at 399.99 MHz and for ^{13}C at 100.6 MHz. Mass spectral data were recorded on a VG analytical instrument Model ZAB-2SE. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

Syntheses were executed under an atmosphere of N_2 with magnetic stirring. The following reagents were used without further purification: glacial acetic acid, hydrochloric acid (37%), *m*-chloroperbenzoic acid (85%), paraformaldehyde, peracetic acid (32%), perchloric acid (60%), sodium azide, sodium carbonate, sodium hydroxide (97%), sodium sulfate, and sulfuric acid. The following compounds required distillation prior to use: benzylamine (bp 57–59 °C/4.25 mmHg), *N*-benzyl-4-piperidinone (bp 120–122 °C/1.0 mmHg), and *N*-isopropyl-4-piperidinone (bp 38–41 °C/0.05 mmHg), and *N*-methyl-4-piperidinone (bp 112–115 °C/2.0 mmHg). 4-Thianone (mp 63–64 °C) was prepared from known methods[5,28] and sublimed (55 °C/1.0 mmHg) before use. Reagent grade solvents were used without further purification and chromatographic separations were performed on a Chromatotron (plate, 4-mm thick) using silica gel 60 PF-254 with $CaSO_4$. While no problems were encountered in the use of NaN_3/H_2SO_4 in $HCCl_3$, caution should be exercised in handling such mixtures.

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one (1a ⇄ 3a). The following procedure is markedly improved over that reported for **1a** ⇄ **3a**.[5,28] A mixture of benzylamine (7.38 g, 68.9 mmol), HCl (37%, 3.4 g, 34.5 mmol), glacial acetic acid (6.2 g, 103.3 mmol), and paraformaldehyde (16.5 g, 551.2 mmol) was stirred under N_2 at rt for 15 min. In one portion, 4-thianone (8.0 g, 68.9 mmol) was added to the mixture which was then brought to reflux under N_2 for 8 h. The fluorescent, pink solution was allowed to cool to rt and then concentrated to give a reddish oil. This oil was dissolved in H_2O (100 mL), and the solution was extracted (ether, 2 × 100 mL). The aqueous layer was chilled (~5 °C, ice–water bath) and then made basic (pH ~ 12) with NaOH

(27) Newkome, G. R. Eight-Membered and Larger Rings. In *Progress in Heterocyclic Chemistry*; Suschitzky, H., Scriven, E. F. V., Eds., Pergamon Press: Oxford, UK, 1991; Vol. 3, Chapt. 8.

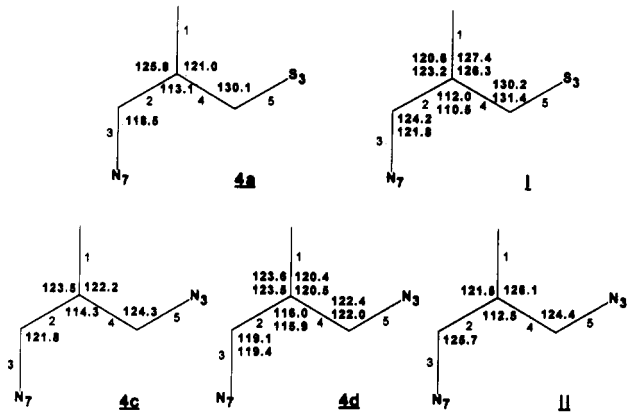


Figure 5. Angles between planes in **4a**, **4c**, **4d** (molecules A and B) and nonane analogues **I** (molecules A and B) (ref 5) and **II** (ref 10). The planes are as follows: plane 1 C(1), C(5), N(9)/O(9), C10); plane 2 C(1), C(5), C(6), C(8); plane 3 C(6), N(7), C(8); plane 4 C(1), C(2), C(4), C(5); plane 5 C(2), N(3)/S(3), C(4).

pellets to form a cloudy yellow solution. This solution was extracted with ether (3 × 100 mL), dried (Na_2SO_4), filtered, and concentrated to give a reddish oil. The oil was then dissolved in Skelly B (2 × 200 mL), followed by decantation of the supernatant, and then concentrated to give a light yellow solid. Sublimation (110 °C/0.1 mmHg) of the solid gave 8.22 g (48%) of ketone **3a** as a white solid: mp 90.0–91.0 °C (lit.[5] mp 91–93 °C). Spectral data for **1a** ⇄ **3a** are included to aid structural evaluation via comparison with similar data for the lactones and lactams: IR (KBr) cm^{-1} 3090, 3060, 3030 (Ar–H), 2960, 2920, 2800, 1725, 1600, 1495, 740, 700; ^1H NMR ($DCCl_3$) δ 2.78 (m, 2 H), 2.82 (m, 2 H), 3.15 (m, 4 H), 3.25 (m, 2 H), 3.58 (s, 2 H), 7.38–7.25 (m, 5 H); ^{13}C NMR ($DCCl_3$) δ 34.79, 47.26, 58.49, 61.42, 127.31, 128.24, 128.69, 137.93 213.21; mass spectral data calculated for $C_{14}H_{17}NOS$ *m/z* (M^+) 247.1031, found 247.1042.

3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9-one (1b ⇄ 3b). The following procedure gave much better results than previously reported.[29] A mixture of benzylamine (10.7 g, 100 mmol), HCl (37%, 4.9 g, 50 mmol), glacial acetic acid (6.0 g, 100 mmol), and paraformaldehyde (6.3 g, 210 mmol) in CH_3OH (100 mL) was brought to a gentle reflux with stirring under N_2 over 15 min. A solution of *N*-benzyl-4-piperidinone (18.93 g, 100 mmol) and glacial acetic acid (6.0 g, 100 mmol) in CH_3OH (100 mL) was then added dropwise over 1 h, and this was followed by a period of reflux of 18 h. After the first 10 h of reflux, the mixture was treated with another portion of paraformaldehyde (6.3 g, 210 mmol). After 18 h at reflux, this orange reaction mixture was concentrated to a viscous oil and then dissolved in H_2O. Combined extracts (ether, 2 × 100 mL) of the acidic aqueous layer were discarded. Basification of the chilled (10 °C, via ice–water bath) water layer to pH ~ 12 was effected by the addition of 10% NaOH. The combined extracts (CH_2Cl_2, 3 × 100 mL) were dried (Na_2SO_4), filtered, and concentrated to give a viscous red oil. This oil was dissolved in Skelly B (2 × 250 mL), and the supernatant extracts were concentrated. The resulting the deep orange oil was distilled (200–210 °C/ 10^{-5} mmHg) to give a light yellow oil that solidified upon standing at −10 °C. Crystallization was effected by dissolving the oil in hot pentane and chilling (−10 °C) the solution to give 22.3 g (69%) of **1b** (or **3b**): mp 80.0–81.0 °C (lit.[29] mp 70–71 °C). Since the mp is widely different from that reported and since no spectral data have been recorded for **1b** ⇄ **3b**, the following data are included: ^1H NMR ($DCCl_3$) δ 2.52–2.59 (m, 2 H), 2.78–2.84 (m, 4 H), 3.02–3.08 (m, 4 H), 3.56 (s, 4 H), 7.23–7.36 (m, 10 H); ^{13}C NMR ($DCCl_3$) δ 46.8, 58.2, 61.4, 127.2, 128.1, 129.2, 138.2, 214.8.

7-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (1c ⇄ 3c). The procedure for the preparation of ketone **1a** ⇄ **3a** was used to obtain **1c** ⇄ **3c**. The reagents were tetrahydropyran-4-one (3.0 g, 29.9 mmol), benzylamine (3.2 g, 29.9 mmol), HCl (37%, 1.4 g, 14.9 mmol), glacial acetic acid (2.7 g, 44.9 mmol), and paraformaldehyde (7.2 g, 239.6 mmol). After the usual workup, the yellowish oil was distilled (130–140 °C/1.5 mmHg) to give 3.56 g (51.4%) of a clear oil which solidified upon standing; mp 37–38 °C (lit.[12,30] bp 118–120 °C/1.0 mmHg). This is the first report of **1c** (or **3c**) being isolated as a solid. ^1H NMR ($DCCl_3$) δ 2.51 (s, 2 H), 2.90–2.96 (m, 2 H), 3.13 (m, 2 H), 3.56 (s, 2 H), 3.86 (m, 2 H), 4.19 (d, 2 H), 7.31–7.33 (m, 5 H); ^{13}C NMR ($DCCl_3$) δ 49.62, 57.77, 61.34, 73.68, 127.18, 128.33, 128.65, 138.02, 212.04.

7-Benzyl-3-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (1d ⇄ 3d). The procedure used for the preparation of ketone **1b** ⇄ **3b** was followed and gave much better results than that reported.[31] The reagents used were benzylamine (10.7 g, 100 mmol), *N*-isopropyl-4-piperidinone (14.1 g, 100 mmol), HCl (37%, 4.9 g, 50 mmol), glacial acetic acid (12.0 g, 200 mmol), and paraformaldehyde (6.3 g, 210 mmol) in deoxygenated (N_2 bubbled through for 2 h) MeOH (100 mL). Upon completion of the usual workup, the orange oil was distilled (140–170 °C/10^{-5} mmHg) to give a yellow oil which was seeded and chilled (−10 °C) for 24 h. The white solid obtained weighed 20.02 g (74%): mp 47.0–48.0 °C (lit.[31,32] mp 46.0–47.5 °C). Recrystallization (hot pentane) gave an analytical sample of **1d** (or **3d**): mp 49–50 °C; IR (KBr) cm^{-1} 3095, 3070, 3035, 2975, 2900, 2820, 1745, 740, 700; ^1H NMR ($DCCl_3$) δ 1.02 (d, 6 H, *J* = 6.5), 2.58 (s, 2 H), 2.87 (m, 5 H), 3.03 (m, 4 H), 3.53 (s, 2 H), 7.30 (m, 5 H); ^{13}C NMR ($DCCl_3$) δ 18.25, 46.93, 53.41, 53.71, 58.07, 61.25 , 127.09, 128.25, 128.69, 138.67, 215.20. Anal. Calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28. Found: C, 75.18; H, 8.61; N, 10.24.

7-Benzyl-3-methyl-3,7-diazabicyclo[3.3.1]nonan-9-one (1e ⇄ 3e). The same procedure was followed as for the synthesis of ketone **1b** ⇄ **3b**. The reagents were benzylamine (16.0 g, 150 mmol), HCl (37%, 7.4 g, 75.0 mmol), glacial acetic acid (18.0 g, 300 mmol), *N*-methyl-4-piperidinone (16.8 g, 150 mmol), and paraformaldehyde (9.4 g, 315 mmol). After the usual workup, the viscous reddish oil was distilled (145–160 °C/10^{-5} mm Hg) to give a clear oil (28.32 g, 72.8%) which solidified to **1e** (or **3e**) upon standing at −10 °C; mp 61–62 °C (lit.[5] mp 60–61 °C; the previously reported yield was 45%). ^1H NMR ($DCCl_3$) δ 2.29 (s, 3 H), 2.56 (m, 2 H), 2.71 (m, 2 H), 2.86 (m, 2 H), 3.03 (m, 4 H), 3.55 (s, 2 H), 7.26–7.33 (m, 5 H); ^{13}C NMR ($DCCl_3$) δ 44.98, 46.56, 59.39, 60.49, 61.11, 127.17, 128.29, 128.72, 138.45, 214.66.

7-Benzyl-3-thia-7,9-diazabicyclo[3.3.2]decan-10-one (4a). To ketone **1a** ⇄ **3a** (2.0 g, 8.0 mmol) in $HCCl_3$ (40 mL) at 0–5 °C (20 min) was added dropwise concd H_2SO_4 (7.9 g, 80.8 mmol) which was followed by sodium azide (1.05 g, 16.17 mmol) being added in three equal portions (over 30 min). After the reaction mixture had warmed to rt, it was heated at reflux (8 h). After cooling to rt, the reaction mixture was poured into ice–water (50 g in 15 mL of water), and the resulting mixture was neutralized (Na_2CO_3). The pH of this mixture was adjusted to 13 with 10% NaOH. Extraction ($HCCl_3$; 4 × 30 mL) of this mixture gave an organic layer which was dried (Na_2SO_4), filtered, and concentrated to give a light brown solid. Recrystallization (hot MeOH/decolorizing charcoal) afforded 1.6 g (76%) of an off-white solid **4a**: mp 226–227 °C. IR (KBr) cm^{-1} 3195, 3056, 2958, 2926, 2798, 1656, 735, 705; ^1H NMR ($DCCl_3$) δ 2.45–2.88 (m, 6 H), 2.93 (m, 1 H), 3.17 (m, 2 H,), 3.56 (s, 2 H), 3.64 (m, 1 H), 6.72 (m, 1 H), 7.28–7.36 (m, 5 H); ^{13}C NMR ($DCCl_3$) δ 24.32, 31.43. 47.94, 48.62, 54.90, 61.12, 63.44, 127.49, 128.50, 129.02, 138.33, 176.99. Anal. Calcd for $C_{14}H_{18}N_2SO$: C, 64.09, H, 6.91, N, 10.68. Found: C, 64.33, H, 6.88, N, 10.85. Mass spectral data calculated for $C_{14}H_{18}N_2SO$ *m/z* (M^+) 262.1139, found 262.1137.

7-Benzyl-9-oxa-3-thia-7-azabicyclo[3.3.2]decan-10-one 3,3-

(28) Johnson, P. Y.; Bechtold, G. A. *J. Org. Chem.* **1970**, *35*, 584–592. See also ref 5a and Bailey, B. R., III. Ph.D. Dissertation, Oklahoma State University, 1983.

(29) (a) Binnig, F.; Raschak, M.; Trieber, J. H. U.S. Patent 3,962,449, 1976; *Chem. Abstr.* **1976**, *84*, 150675x. (b) Binnig, F.; Friedrich, L.; Hofmann, H. P.; Krieskott, H.; Mueller, C.; Raschack, M. U.S. Patent 4,183,935, 1980; *Chem. Abstr.* **1979**, 90, 121569h. (c) Binnig, F.; Mueller, C. D.; Raschack, M.; von Philipsborn, G. U.S. Patent 4,556,662, 1985; *Chem. Abstr.* **1983**, *98*, 16738f.

(30) See ref 12 and Arjunan, P. Ph.D. Dissertation, Oklahoma State University, 1980.

(31) Zisman, S. A.; Berlin, K. D.; Scherlag, B. J. *Org. Prep. Proc. Int.* **1990**, 22, 255–264. See also ref 13b.

Dioxide (4b). A standard system containing ketone **1a** ⇄ **3a** (1.0 g, 4.0 mmol) in $HCCl_3$ (40 mL) was cooled (5 °C), and to this solution was added concd H_2SO_4 (5.9 g, 60.6 mmol) followed by dropwise addition of peracetic acid (32%, 4.8 g, 20.2 mmol) over a 10-min period. After the addition, the mixture was allowed to warm to rt and was then heated at reflux (18 h). After cooling to room temperature, H_2O was added and the heterogeneous solution was transferred into ice–water (50 g). Neutralization (solid Na_2CO_3, ~3.0 g) followed with further adjustment of the pH (~12) with 10% NaOH. The layers were separated, and the aqueous layer was again extracted ($HCCl_3$, 3 × 30 mL). The combined organic layers were washed with H_2O (75 mL) and saturated NaCl (75 mL) and then dried ($NaSO_4$) and finally filtered. Evaporation of the solvent left a light red solid which was washed with ether. The solid was dissolved in a minimum of hot EtOAc and decolorized to give 0.143 g (12%) of a white solid **4b**; mp 234–235 °C; IR (KBr) cm^{-1} 3451, 3056, 3021, 2982, 2931, 2838 (C-H), 1742, 1317, 1204, 730, 700 ; ^1H NMR ($DCCl_3$–DMSO-d_6) δ 2.75–3.04 (m, 3 H), 3.28 (m, 2 H), 3.51–3.77 (m, 7 H), 4.84 [m, 1 H, H(1)], 7.29–7.41 (m, 5 H); ^{13}C NMR ($DCCl_3$–DMSO-d_6) δ 40.49, 49.92, 52.02, 52.86, 58.64, 60.56, 68.69, 126.22, 127.11, 127.55, 135.94, 169.69; mass spectral data calcd for $C_{14}H_{17}NO_4S$ *m/z* (M^+) 295.0878, found 295.0880. Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.94; H, 5.80. Found: C, 57.34; H, 6.13.

3,7-Dibenzyl-3,7,9-triazabicyclo[3.3.2]decan-10-one (4c). The same approach used to prepare **4a** was employed with ketone **1b** ⇄ **3b** (2.0 g, 6.24 mmol), concd H_2SO_4 (3.7 g, 37.4 mmol), and sodium azide (0.81 g, 12.48 mmol) in $HCCl_3$ (40 mL). After the prescribed workup, concentration of the solvent gave off-white solid **4c** [2.06 g, 99%; recrystallized from hexane/ethyl acetate (1:1)]: mp 169–171 °C; IR (in $HCCl_3$) cm^{-1} 3200, 1665; ^1H NMR ($DCCl_3$) δ 2.67 (m, 4 H), 2.73 (m, 4 H), 2.86 (m, 1 H), 3.41 (m, 1 H,), 3.62 (s, 4 H), 6.51 (m, 1 H), 7.20 (m, 10 H); ^{13}C NMR ($DCCl_3$) δ 46.1, 48.1, 51.9, 56.6, 62.6 , 127.0, 128.2, 128.7, 138.4, 178.6; mass spectral data calcd for $C_{21}H_{25}N_3O$ *m/z* (M^+) 335.1997, found 335.1992. Anal. Calcd for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.51. Found: C, 74.95; H, 7.65.

3,7-Dibenzyl-9-oxa-3,7-diazabicyclo[3.3.2]decan-10-one (4d). A solution of 3,7-dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**1b** ⇄ **3b**, 0.50 g, 1.56 mmol) in $HCCl_3$ (40 mL) was chilled (5 °C), and concd sulfuric acid (2.3 g, 23.4 mmol) was added dropwise (15 min). To this solution was added solid *m*-$ClC_6H_4CO_3H$ (0.67 g, 3.90 mmol) in three equal portions (0.22 g) over 20 min. The resulting mixture was allowed to come to rt and then was boiled (18 h). After cooling to rt, the new solution was diluted (ice–water, 50 g) and neutralized (Na_2CO_3). The two layers were separated, and the aqueous layer was extracted ($HCCl_3$, 3 × 30 mL). The combined organic layers were washed with H_2O (70 mL) and saturated NaCl (70 mL) and then dried (Na_2SO_4). After filtration and concentration, a light yellow solid was obtained. Purification was achieved by allowing a hot ethanol solution of crude **4d** to stand in a diffusion chamber with a flask containing *n*-pentane which led to white solid **4d** (0.34 g, 66.1%): mp 121–122 °C; IR (film) cm^{-1} 1728; ^1H NMR ($DCCl_3$) δ 2.77 (d, J = 5.6, 4 H), 2.82 (d, J = 3.2, 2 H), 2.88 (d, J = 5.6, 1 H), 2.93 (d, J = 5.2, 1 H), 3.27 (m, 1 H), 3.62, 3.69 (m, 4 H), 4.47 (m, 1 H), 7.30 (m, 10 H); ^{13}C NMR ($DCCl_3$) δ 46.6, 51.6, 56.1, 62.4, 72.9, 127.3, 128.4, 128.7, 138.0, 175.2; mass spectral data calcd for $C_{21}H_{24}N_2O_2$ *m/z* (M^+) 336.1837, found 336.1839. Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19. Found: C, 75.03; H, 7.35.

7-Benzyl-3-oxa-7,9-diazabicyclo[3.3.2]decan-10-one (4e). The procedure for preparing lactam **4a** was used with ketone **1c** ⇄ **3c** (0.50 g, 2.16 mmol), NaN_3 (0.28 g, 4.32 mmol), and concd H_2SO_4 (3.18 g, 32.40 mmol). The workup gave a white solid which was recrystallized [EtOAc/hexane (1:1)] to give 0.213 g (41%) of white **4e**: mp 120–121 °C; IR (KBr) cm^{-1} 3200, 3091, 3051, 2958, 2927, 2824, 1656, 731, 707; ^1H NMR ($DCCl_3$) δ 2.69–2.84 (m, 5 H), 3.37 (m, 1 H), 3.66 (s, 2 H), 3.73–3.93 (m, 4 H), 6.81 (m, 1 H), 7.26–7.33 (m, 5 H); ^{13}C NMR ($DCCl_3$) δ 48.01, 49.37, 51.46, 56.10, 62.65, 65.75, 69.83, 127.22, 128.37, 128.72, 138.32, 177.69. Anal. Calcd for $C_{14}H_{18}N_2O_2 \cdot 0.1H_2O$: C, 67.77; H, 7.39. Found: C, 67.74; H, 7.33.

7-Benzyl-3,9-dioxa-7-azabicyclo[3.3.2]decan-10-one Hydroperchlorite (4f). The procedure used for the preparation of lactone **4d** was followed using ketone **1c** ⇄ **3c** (0.50 g, 2.16 mmol), *m*-$ClC_6H_4CO_3H$ (85%, 1.1 g, 5.4 mmol), and concd H_2SO_4 (3.18 g, 32.40 mmol) with $HCCl_3$ (60 mL). Following the workup, evaporation left a light yellow oil (0.40 g, 75.0%) which was redissolved (ether/MeOH, 1:1), and the new solution was cooled (ice–water bath). To this solution was added dropwise $HClO_4$ (60%, 0.34 g, 2.02 mmol) over 5 min. The white precipitate was filtered and recrystallized (EtOH, 95%) to obtain 0.188 g (25.3% from **1c** ⇄ **3c** and 33.4% from the intermediate yellow oil) of off-white platelettes **4f**: mp 220-221 °C; IR (KBr) cm^{-1} 3152, 3023, 2954, 2874, 1749, 1087 , 735, 705; ^1H NMR (DMSO-d_6) δ 3.29 (bs, 1 H), 3.57–4.16 (m, 8 H), 4.34 (bs, 2 H), 4.69 (bs, 1 H), 7.50–7.59 (m, 5 H), 9.42 (bs, 1 H); ^{13}C NMR (DMSO-d_6) δ 44.76, 50.86, 55.52, 61.45, 66.29, 70.75, 72.28, 128.94, 129.78, 131.38, 172.32. Anal. Calcd for $C_{14}H_{18}ClNO_7$; C, 48.78; H, 5.26. Found; C, 48.41; H, 5.59.

7-Benzyl-3-isopropyl-3,7,9-triazabicyclo[3.3.2]decan-10-one Hydroperchlorate (4g). The same procedure used to prepare lactam **4a** was followed using ketone **1d** ⇄ **3d** (2.00 g, 7.34 mmol), concd H_2SO_4 (10.8 g, 110.1 mmol), and NaN_3 (1.2 g, 18.4 mmol) in $HCCl_3$ (70 mL), but the period of heating was 18 h. Upon completion of the workup, concentration left a yellow oil which was washed with ether (2 × 75 mL). The washes were concentrated to give 820 mg (39%) of a yellow oil. This oil was dissolved in ether (25 mL) and cooled (ice bath, 5 °C) whereupon $HClO_4$ (60%, 0.60 g, 3.57 mmol) was added dropwise over 5 min. The white precipitate was filtered and recrystallized (EtOH, 95%) to give 0.66 g (23.2% from **1d** ⇄ **3d** and 60% from the intermediate yellow oil) of a white solid **4g**: mp 244–245 °C; IR (film) cm^{-1} 3342, 3319, 3067, 3005, 3010 , 2986, 2947, 2833, 1672 , 1086, 730, 700; ^1H NMR (DMSO-d_6) δ 1.18 (d, 6 H, *J* = 6.1, 6 H), 2.63 (m, 1 H), 2.79 (m, 2 H), 3.21 (m, 1 H), 3.34–3.69 (m, 9 H), 7.34–7.47 (m, 5 H), 8.39 (m, 1 H), 11.50 (bs, 1 H); ^{13}C NMR (DMSO-d_6) δ 15.89, 16.29, 41.68, 43.43, 48.92 , 52.47, 54.41, 57.47, 58.24, 60.98, 127.99, 128.48, 129.67, 135.45, 174.77. Anal. Calcd for $C_{17}H_{26}ClN_3O_5$: C, 52.64; H, 6.76. Found: C, 52.41; H, 6.68.

7-Benzyl-3-isopropyl-9-oxa-3,7-diazabicyclo[3.3.2]decan-10-one Hydroperchlorate (4h). The procedure used to prepare lactone **4b** was followed using ketone **1d** ⇄ **3d** (1.0 g, 3.7 mmol), concd H_2SO_4 (5.4 g, 55.0 mmol), and peracetic acid (32%, 3.49 g, 14.68 mmol) in $HCCl_3$ (40 mL). After completion of the workup, concentration gave a dark oil which was purified [Chromatotron with $HCCl_3$/MeOH (20:1) as the eluent]. One fraction [R_f 0.65, in $HCCl_3/H_3COH$ (20:1)] was evaporated to a light yellow oil (0.224 g, 21%). To a chilled (5 °C) solution of the expected lactone (0.23 g, 0.78 mmol) in ether was added $HClO_4$ (60%, 0.16 g, 0.98 mmol) over a 5-min period. The white precipitate was filtered and recrystallized (EtOH, 95%) to give 0.168 g (11.7 % from **1d** ⇄ **3d** and 55.4% from the intermediate yellow oil) of white needles of **4h**: mp 125–126 °C; IR (KBr) cm^{-1} 3428, 3027, 2978, 2841, 1744, 1084, 730, 701; ^1H NMR (DMSO-d_6) δ 1.18 (d, 6 H,J = 6.0), 2.83 (m, 1 H), 2.94 (m, 1 H), 3.32–3.75 (m, 10 H), 4.74 (m, 1 H,), 7.36–7.44 (m, 5 H), 11.14 (bs, 1 H); ^{13}C NMR (DMSO-d_6) δ 16.18, 40.96, 48.20, 52.19, 53.39, 57.03, 57.65, 60.56, 69.54, 128.16, 128.64, 129.71, 135.44, 172.71. Anal. Calcd for $C_{17}H_{25}ClN_2O_6 \cdot 0.5H_2O$: C, 51.32; H, 6.59. Found: C, 51.61; H, 6.37.

7-Benzyl-3-methyl-3,7,9-triazabicyclo[3.3.2]decan-10-one (4i). The procedure for the preparation of lactam **4a** was followed using ketone **1e** ⇄ **3e** (1.00 g, 4.09 mmol), NaN_3 (0.53 g, 8.18 mmol), and concd H_2SO_4 (6.02 g, 61.35 mmol). Upon completion of the workup, the off-white solid obtained was recrystallized (EtOH, 95%) to give 0.90 g (84.9%) of white platelettes of **4i**: mp 172–173 °C; IR (KBr) cm^{-1} 3201, 3097, 3054, 2966, 2925, 2804, 1657, 735, 710; ^1H NMR ($DCCl_3$) δ 2.38 (s, 3 H), 2.57–2.80 (m, 8 H), 2.87–2.89 (m, 1 H), 3.44 (m, 1 H), 3.60 (s, 2 H), 6.65 (m, 1 H), 7.25–7.33 (m, 5 H); ^{13}C NMR ($DCCl_3$) δ 45.91, 46.69, 47.86, 52.61, 53.53, 57.70, 57.85, 62.69, 127.08, 128.26, 128.73, 138.66, 178.33. Anal. Calcd for $C_{15}H_{21}N_3O$: C, 69.47; H, 8.16. Found: C, 69.45; H, 8.01.

7-Benzyl-3-methyl-9-oxa-3,7-diazabicyclo[3.3.2]decan-10-one Hydroperchlorate (4j). The procedure for making lactone **4b** was followed using ketone **1e** ⇄ **3e** (2.0 g, 8.18 mmol), peracetic acid (32%; 4.86 g, 20.45 mmol), and concd H_2SO_4 (12.0 g, 122.8 mmol). Standard workup gave a dark oil which was purified [Chromatotron with $HCCl_3$/MeOH (20:1) as the eluent]. Concentration of one fraction [R_f 0.7; silica gel plate] gave a light yellow oil (0.24 g, 11.3%) which was dissolved in ether and cooled

Table I. Crystal Data, Data Collection, and Refinement Parameters

	4a	4c	4d
formula	$C_{14}H_{18}N_2SO$	$C_{21}H_{25}N_3O$	$C_{21}H_{24}N_2O_2$
M_r	262.4	335.4	336.4
space group	$P2_1/n$	$P\bar{1}$	$P\bar{1}$
cell dimensions			
a (Å)	22.388(4)	8.6687(6)	11.091(2)
b	8.6718(6)	16.135(1)	15.756(4)
c	6.8453(6)	6.751(1)	10.717(2)
α (deg)		101.64(1)	99.45(2)
β	96.364(9)	91.07(1)	90.12(2)
γ		92.585(6)	106.19(2)
V (Å^3)	1320.8	923.5	1771.9
Z	4	2	4
D_x (g cm^{-3})	1.319	1.206	1.261
radiation	Cu Kα	Cu Kα	Cu Kα
μ, cm^{-1}	19.7	5.2	5.7
temperature, K	163	293	163
$2\theta_{max}$	150	150	150
h range	−28 to +28	−10 to +10	−13 to +13
k	0 to 10	−20 to +20	−19 to +19
l	0 to 8	0 to 8	0 to 13
scan width (deg)	(1.30 + 0.20) tan θ	(1.20 + 0.20) tan θ	(0.80 + 0.20) tan θ
aperture (mm)	(4.50 + 0.86) tan θ	(4.50 + 0.86) tan θ	(4.50 + 0.86) tan θ
T_{max} (s)	75	60	40
monitors, h	2	2	2
max variation, %	4	1	2
total reflections	2709	3641	6786
no. of obs reflections ($I > 2\sigma(I)$)	1971	2075	4767
R	0.061	0.066	0.055
R_w	0.069	0.068	0.059
$(\Delta/\sigma)_{max}$	0.02	0.04	0.05
S	2.0	2.0	1.8
no. of parameters	240	330	660
(diff map)			
max density (e/Å^3)	0.32	0.20	0.50
min density (e/Å^3)	−0.30	−0.20	−0.40

[ice bath, 5 °C]. Dropwise addition of $HClO_4$ (60%; 0.19 g, 1.15 mmol) over a 5-min period gave a white precipitate which was filtered and recrystallized (EtOH, 95%) to give 0.29 g (10.8% from **1e** ⇄ **3e** and 81.9% from the intermediate yellow oil) of white needles of **4j**: mp 187–188 °C; IR (KBr) cm^{-1} 3444, 3031, 2953, 2839, 1741, 1084, 730, 705; ^{1}H NMR (DMSO-d_6) δ 2.65 (m, 1 H), 2.76 (m, 1 H,), 2.85 (s, 3 H), 3.23–3.44 (m, 4 H), 3.58–3.68 (m, 2 H), 3.70 (s, 2 H), 3.86 (m, 1 H), 4.72 (s, 1 H), 7.34–7.43 (m, 5 H), 10.54 (bs, 1 H); ^{13}C NMR (DMSO-d_6) δ 41.95, 44.23, 51.82, 53.63, 56.68, 58.57, 60.79, 70.22, 127.79, 128.59, 129.49, 135.05, 172.78. Anal. Calcd for $C_{15}H_{21}ClN_2O_6$: C, 49.94; H, 5.97. Found: C, 49.88; H, 5.84.

Single Crystal X-ray Diffraction Analysis. Crystals of **4a,c,d** were grown as described previously and all three showed moderate to large mosaic. The crystal structures were determined by X-ray diffraction with measurements being carried out by using an Enraf Nonius CAD-4 automatic diffractometer fitted with a liquid nitrogen low-temperature device. Crystal data, data collection parameters, and refinement results for **4a,c,d** are given in Table I. The cell parameters of each crystal were determined by a least squares fit to the $\pm 2\theta$ of 48 reflections distributed throughout the reciprocal space and measured using Cu Kα_1 radiation. The intensities were measured for all unique reflections at low temperature employing the θ–2θ scan technique.

The structures were solved by applying the direct methods using the programs SHELXS[33] (**4a** and **4c**) and MITHRIL[34] (**4d**). In **4d**, the two independent molecules in the asymmetric unit are found to be related by a pseudocenter of symmetry; various attempts to generate a cell of higher symmetry failed. The refinement was performed by a full-matrix least squares routine in SHELX76[35] in which the quantity $\Sigma w(F_o - F_c)^2$ was minimized. All hydrogen atoms were located from difference Fourier maps, and they were refined with isotopic temperature factors. Because of disorder in the vicinity of the 9-position, the amide hydrogens in **4a** and **4c** were not included in the refinement. All non-hydrogen atoms were refined anisotopically. In **4c**, one of the phenyl rings showed large thermal motion.

All three structures indicated a common disorder problem. Difference Fourier maps showed an extra peak in the vicinity of the 9-position. This extra peak was included in the refinement for each structure on the assumption that the carbonyl group switched between the 10- and 9-positions. The proportion of disorder was found to be 75–25% in **4a**, 80–20% in **4c**, and 90–10% in **4d**. In each case, atom 011 was refined at two locations with appropriate occupancy factors. The structures refined reasonably well, and the final difference Fouriers showed no disorder in the other parts of each of the structures. The bond distances in the amide group in **4a** and in **4c**, as well as the lactone group in **4d**, showed differences from the accepted values. However, all other bond distances and angles in all three compounds were normal. In all three compounds attempts were made to solve the disorder problem by eliminating the center of symmetry from the space group symmetry. The subsequent refinements yielded higher R values for all three compounds.

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