Regioselective Functionalization. 6.[1] Migratory Preferences in Hydroxylamine-*O*-sulfonic Acid and Schmidt Rearrangements of 7-Substituted Norcamphors

Grant R. Krow,* Osbert H. Cheung, Zilun Hu, and Yoon B. Lee[†]

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122, and Department of Chemical Engineering, Soonchunhyang University, Choongchungnam-do, Korea 336-745

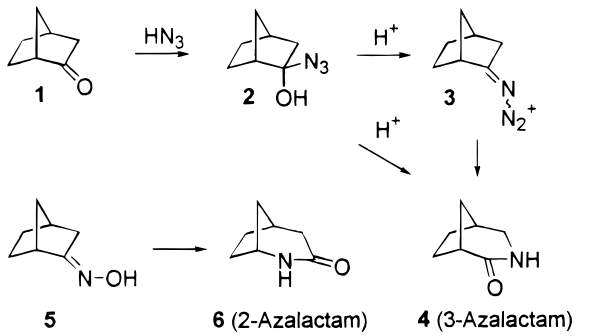
Received April 1, 1996[⊗]

Hydroxylamine-*O*-sulfonic acid reacted with *syn*-7-X- and *anti*-7-Y-substituted norcamphor derivatives [X = H, OMe, Cl, Br, OTos; Y = H, COOMe, Cl, Br, Tos, COOMe(5-*exo*-Br)], to give solely bridgehead migrated 2-azalactams, except for minor amounts of methylene migrated 3-azalactams from norcamphor (**1**) and the *syn*-7-Br ketone **19**. Schmidt reactions of the same ketones provided varying mixtures of methylene and bridgehead migrated lactams, except for norcamphor (**1**) and *anti*-7-Br ketone **31**, which provided solely 3-azalactams. Significant ratios (>0.4) of bridgehead migration to cleavage products were observed in the Schmidt reactions only with 7-OTos ketones **22** and **24** with *exo*-5-bromo-*anti*-7-methoxycarbonyl ketone **37**. The Schmidt rearrangements most likely involve iminodiazonium ion intermediates in light of the large amounts of cleavage observed relative to lactam formation and the insensitivity of methylene migration to the substituent size in the reactions of *syn*-7-substituted norcamphors.

Introduction

Among the arsenal of synthetic methods available for the formation of bridged bicyclic lactams from ketones[2] are the Schmidt rearrangement,[3] the Beckmann rearrangement,[4] and a variety of modifications of these reactions.[5] The power and importance of these synthetic tools for a chosen substrate is dependent upon the efficiency and regioselectivity of heteroatom delivery.[4b] In a noted example of reaction selectivity (Scheme 1), Elderfield and Losin[6] in 1961 and Potti and Nobles[7] in 1968 reported that the lactam formed during the Schmidt reaction of norcamphor (**1**) was solely 3-azalactam **4**, the result of methylene (M) migration. By contrast, the Beckmann rearrangement of norcamphor oxime (**5**) has been reported to give either solely the bridgehead migrated 2-azalactam **6** or a mixture of lactams **4** and **6**.[2,4a,6]

Scheme 1. Lactams from Schmidt and Beckmann Reactions of Norcamphor (1)



A proposed explanation for the difference in the regiochemical outcomes in these reactions was the suggestion that while the Beckmann rearrangement of ketone **1** provides 2-azalactam **6** by stereospecific rearrangement of the trigonal *anti*-oxime **5**, the Schmidt reaction proceeds via a dissimilar pathway *not* involving the iminodiazonium ion **3**. DiMaio and Permutti in 1966 suggested a pinacol-like rearrangement of the protonated azidohydrin **2** as the source of the 3-azalactam **4**.[8] Reagents which react with ketones and which must give ring expansion via tetrahedral intermediates; i.e., *N*-alkyl azides, studied by Aube and co-workers,[5b,9] and *O*-(*p*-nitrobenzenesulfonyl)-*N*-methylhydroxylamine, studied by Hoffman and Salvador,[5e] have been found to react with norcamphor (**1**) to give 3:2 or greater mixtures favoring methylene migrated 3-azalactams. On the other hand, Richard and co-workers have recently shown the competence of iminodiazonium ions, such as **3**, to be the active intermediate of a Schmidt reaction.[10] Despite many decades since the original observations, the mech-

[†] Soonchunhyang University.

[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1996.

(1) For previous papers in this series, see: (a) Krow, G. R.; Szczepanski, S. *J. Org. Chem.* **1982**, *47*, 1153. (b) Krow, G. R.; Lee, Y. B. *Trends Org. Chem.* **1992**, *3*, 289.

(2) For a review of nitrogen insertions in bridged bicyclic ketones, see: Krow, G. R. *Tetrahedron* **1981**, *37*, 1283.

(3) For an early review of the Schmidt reaction, see: (a) Smith, P. A. S. In *Molecular Rearrangements*; de Mayo, P., Ed.; Wiley-Interscience: New York, 1963; Vol. 1, pp 507−526. (b) For a recent discussion of the mechanism of the Schmidt reaction, see: Sprecher, M.; Kost, D. *J. Am..Chem. Soc.* **1994**, *116*, 1016. (c) Shioiri, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 6, pp 798, 820. (d) An efficient asymmetric Schmidt reaction of symmetrical ketones utilizing chiral 1,2-azidohydrins has recently been described: Gracias, V.; Milligan, G. L.; Aube, J. *J. Am. Chem. Soc.* **1995**, *117*, 8047.

(4) (a) Gawley, R. *Org. React.* **1988**, *35*, 1−420. (b) Benz, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 6, p 404. It has been generalized that the regioselectivity of Schmidt and Beckmann reactions with bridged bicyclic ketones is opposite. (c) Maruoka, K.; Yamamota, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 6, pp 763, 773.

(5) (a) Oxime photolysis: Suginome, H.; Furukawa, K.; Orito, K. *J. Chem. Soc., Chem. Commun.* **1987**, 1004. (b) Alkyl azide insertions: Aube, J.; Milligan, G.; Mossman. C. *J. Org. Chem.* **1992**, *57*, 1635. (c) Oxaziridine photolysis: Aube, J.; Hammond, M.; Gherardini, E.; Takusagawa, F. *J. Org. Chem.* **1991**, *56*, 499. (d) Hydroxylamine-*O*-sulfonic acid: Krow, G. R.; Szczepanski, S. *Tetrahedron Lett.* **1980**, *21*, 4593. (e) *N*-alkylhydroxylamine-*O*-*p*-nitrobenzenesulfonate: Hoffman, R. V.; Salvador, J. M. *Tetrahedron Lett.* **1989**, *30*, 4207.

(6) Elderfield, R. C.; Losin, E. T. *J. Org. Chem.* **1961**, *26*, 1703.

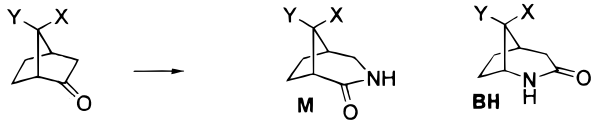
(7) Potti, N.; Nobles, W. *J. Pharm. Sci.* **1968**, *57*, 1785.

(8) DiMaio, G.; Permutti, V. *Tetrahedron* **1966**, *22*, 2059.

(9) The success of the intramolecular version of the Schmidt reaction of alkyl azidoketones has been cited as finally confirming the viability of the direct rearrangement pathway. However, the authors clearly pointed out that this pathway must be considered only a possibility for reactions of HN_3 with ketones. Milligan, G. L.; Mossman, C. J.; Aube, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449. See also ref 3d and Aube, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965.

S0022-3263(96)00604-4 CCC: $12.00

Table 1. Hydroxylamine-*O*-sulfonic Acid Rearrangements of 7-Substituted Norcamphors

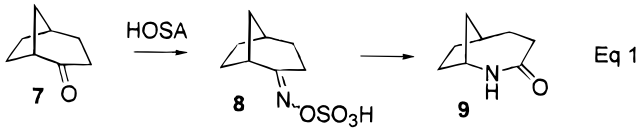


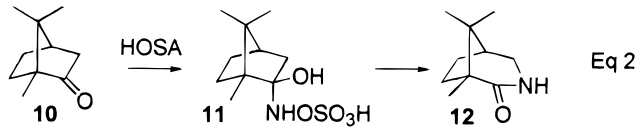
entry	ketone	X	Y	time (h)	lactams yield[a] (%)	type of lactam (%) M:(%) BH[b]
			Syn			
1	**1**	H	H	1	37	10(**4**):90(**6**)[c]
2	**13**	OMe	H	1	27	0(**14**):100(**15**)
3	**16**	Cl	H	2	49	0(**17**):100(**18**)
4	**19**	Br	H	2	53	5(**20**):95(**21**)[c]
5	**22**	OTos	H	1	27	0(**23**):100(**24**)
			Anti			
6	**25**	H	COOMe	2	29	0(**26**):100(**27**)
7	**28**	H	Cl	3	23	0(**29**):100(**30**)
8	**31**	H	Br	1.5	57[d]	0(**32**):100(**33**)
9	**34**	H	OTos	1	38	0(**35**):100(**36**)
10	**37**	H(*exo*-5-Br)	COOMe	2	64	0(**38**):100(**39**)

[a] Yields following chromatography unless otherwise noted. [b] M = methylene migration (3-azalactam). BH = bridgehead migration (2-azalactam). Ratios were determined by comparison of H8 protons; entries of 0 were not observed by NMR and are <2%. [c] Crude and isolated ratios are within 1%. [d] Crude lactam was clean by ^{1}H-NMR.

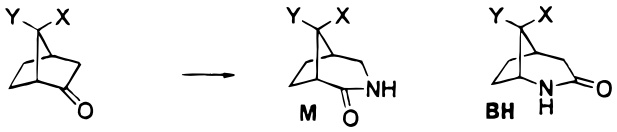
anism of the Schmidt rearrangement of norcamphor (**1**) remains controversial.[9]

In an investigation of the hydroxylamine-*O*-sulfonic acid (HOSA) modification of the Beckmann rearrangement, we found that bicyclo[3.2.1]octan-2-one (**7**) reacts to form primarily (95:5) the 2-azalactam **9** (eq 1).[1a] This result is as expected for rearrangement of a mixture of oxime sulfonic acids **8**, in which bridgehead migration of the *anti*-isomer is favored. However, camphor (**10**), which has a 7-*syn*-methyl group, reacts to give α-camphidone (**12**) (eq 2).[5d] It has been postulated that the 7-substituent in camphor causes *endo*-directed attack of HOSA to give **11**, which rearranges directly to lactam **12** by preferred methylene migration.[11,12]





As part of an effort to identify, to expand the scope, and to clarify the mechanisms of synthetically significant regioselective heteroatom insertion methods, we have tested the application of HOSA and Schmidt reactions to derivatives of norcamphor (**1**). Both *syn*- and *anti*-7-substituted norcamphors have been prepared in order to determine migratory preferences.



1	X = H, Y = H	**4**	**6**
13	X = OMe, Y = H	**14**	**15**
16	X = Cl, Y = H	**17**	**18**
19	X = Br, Y = H	**20**	**21**
22	X = OTos, Y = H	**23**	**24**
25	X = H, Y = COOMe	**26**	**27**
28	X = H, Y = Cl	**29**	**30**
31	X = H, Y = Br	**32**	**33**
34	X = H, Y = OTos	**35**	**36**
37	X = H (*exo*-5-Br), Y = COOMe	**38**	**39**

Results

HOSA Reactions. The *syn*- and *anti*-substituted norcamphors shown in Table 1 were prepared by known methods. Beckmann rearrangements of the ketones were performed using HOSA in acetic acid to afford lactams;[13] no attempt was made to isolate or identify Beckmann cleavage products. Upon workup the crude lactams were subjected to NMR analysis; lactam ratios were determined by comparison of the integrated areas for H8 adjacent to the substituent. The crude lactams were purified by preparative thin layer chromatography, and the purified lactams were again subjected to NMR analysis. Only the 2-azalactams were observed with the exception of the parent ketone **1** (entry 1), which gave a 10:90 ratio of 3-aza-/2-azalactams **4**/**6**, and the *syn*-7-bromoketone **19** (entry 4), which gave a 5:95 ratio of 3-aza-/2-azalactams **20**/**21**.

Schmidt Reactions. Schmidt reactions of the ketones shown in Table 2 were carried out in chloroform with concentrated sulfuric acid and sodium azide to afford lactams; no attempt was made to isolate or identify cleavage products. Although the lactams are formed in the presence of sulfuric acid, their stability to the reaction conditions remained a concern. Accordingly, a 4:96 mixture of lactams **4** and **6**, prepared by chromatographic isomeric enrichment of a 10:90 mixture of these lactams (Table 1, entry 1), was stirred in chloroform with a drop of concentrated sulfuric acid for 3 h. The lactams **4** and **6** were recovered quantitatively in the same ratio. Substituents do have an effect upon the acid stability of the lactams, however, and attention must be paid to the time of reaction. The yields of lactams derived from the *syn*-7-OMe ketone **13** (entry 2) are maximized after 1 h. The *syn*-8-OTos lactams **23** and **24** (entry 8) are similarly unstable in the reaction medium. The lactams derived from the *syn*- and *anti*-7-halo norcamphor derivatives (**16**,

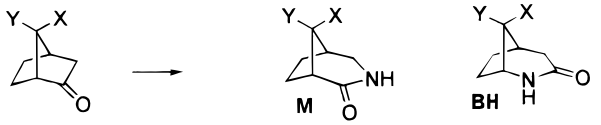
(10) Richard, J. P.; Amyes, T. L.; Lee, Y.-G.; Jagannadham, V. *J. Am. Chem. Soc.* **1994**, *116*, 10833.

(11) A number of carbon ring expansions in norcamphor systems, in which migration occurs toward an *endo*-oriented methylene group, show an increased tendency toward methylene migration relative to their *exo*-substituted counterparts. There is almost all methylene migration in the solvolysis of *endo*-2-norbornylcarbinyl brosylates and in the deamination of *endo*-2-norbornylcarbinylamine; the *exo* isomers give predominant, but less, methylene migration; Krow, G. R. *Tetrahedron* **1987**, *43*, 3, especially footnote 18.

(12) Sterically demanding *syn*-7-substitution has been found to result in a preference for methylene migrated lactones in the Baeyer–Villiger reaction, which proceeds by rearrangement of a tetrahedral intermediate.[1b] (a) For a recent review of the Baeyer–Villiger oxidation, see: Krow, G. R. *Org. React.* **1994**, *43*, 251. (b) Sauers, R. R.; Beisler, J. A. *J. Org. Chem.* **1964**, *29*, 210.

(13) Olah, G. A.; Fung, A. P. *Synthesis* **1979**, 537.

Table 2. Schmidt Reactions of 7-Substituted Norcamphors



entry	ketone	X	Y	time (h)	lactams yield,[a] (%)	type of lactam (%)M:(%)BH[b]
			Syn			
1	**1**	H	H	2	35	100(**4**):0(**6**)
2	**13**	OMe	H	1	48	73(**14**):27(**15**)[c]
3	**16**	Cl	H	12	22	85(**17**):15(**18**)[d]
4				24	28	85(**17**):15(**18**)[e]
5	**19**	Br	H	4	34	81(**20**):19(**21**)[f]
6				12	35	73(**20**):27(**21**)
7				36	37	74(**20**):26(**21**)
8	**22**	OTos	H	2	52	35(**23**):65(**24**)[g]
			Anti			
9	**25**	H	COOMe	2	31	66(**26**):34(**27**)
10	**28**	H	Cl	5	29	83(**29**):17(**30**)[h]
11	**31**	H	Br	12	41	100(**32**):0(**33**)
12	**34**	H	OTos	2	40	36(**35**):64(**36**)[i]
13				10	10[j]	41(**35**):59(**36**)[k]
14	**37**	H(*exo*-5-Br)	COOMe	12	52	52(**38**):48(**39**)

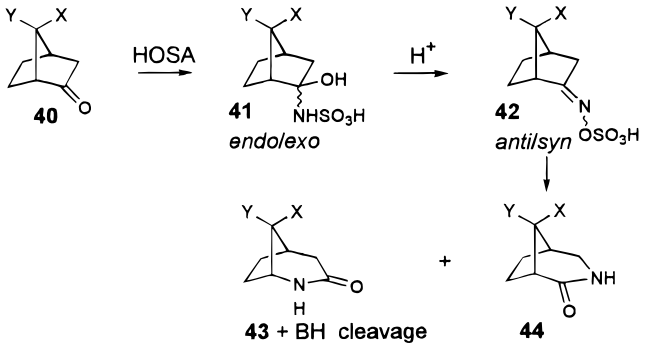
[a] Yields are for purified lactams unless otherwise noted. [b] M = methylene migration (3-azalactam). BH = bridgehead migration (2-azalactam). Ratios were determined by comparison of H8 protons and crude and isolated ratios are within 2% unless otherwise noted. [c] Comparison of OMe peaks. [d] Crude lactam ratio 70:30. [e] Crude lactam ratio 61:39. [f] Crude lactam ratio 74:26. [g] Comparison of H1 peaks. [h] Crude lactam ratio 68:32. [i] Crude lactam ratio 23:77. [j] Not further purified. [k] Crude lactam ratio 41:59. [l] Comparison of NH peaks.

19, **28**, and **31**) (entries 3−7 and 10−11) and from the *endo*-5-bromo-*anti*-7-COOMe ketone **37** (entry 14) survive extended reaction times. Because the surface of silica gel is mildly acidic,[14] selective decomposition of lactam products during chromatographic purification also was of concern. When purified 3-azalactam parent **4** (entry 1) was placed on silica gel and then extracted, a 96% recovery was observed. However, the *syn*-8-methoxy lactams **14** and **15** (entry 2) are decomposed on silica gel; in eight separate trials most of the lactam product was lost during attempted purification. As shown in Table 2, although the M/BH ratios did change in some cases upon purification of the crude lactams (entries 3−5, 10, 12−13), the variations were not large.

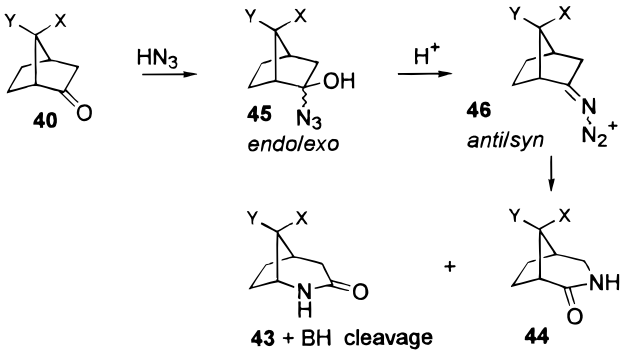
Discussion

HOSA Reactions. A mechanism consistent with the reactions of norcamphor derivatives in Table 1 with HOSA is shown in Scheme 2. Addition of HOSA to ketones **40** to form tetrahedral intermediates **41** is followed by dehydration to give the sulfonated oximes **42**. Bridgehead rearrangement to give lactams **43** and bridgehead cleavage processes via *anti*-oxime-*O*-sulfonic acids **42** account for most of the observed results.[4] Minor amounts (6−10%) of 3-azalactams found with norcamphor (**1**) (entry 1) and 7-*syn*-Br ketone **19** (entry 4) suggest some rearrangement of *syn*-oxime-*O*-sulfonic acid stereoisomers.[15]

Scheme 2. HOSA Rearrangements of Ketones 40



Scheme 3. Schmidt Reactions of Ketones 40



Schmidt Reactions. As pointed out in Scheme 1, the regioselective formation of 3-azalactam **4** in the Schmidt reaction of norcamphor (**1**), but bridgehead migration in the Beckmann reaction to give mainly 2-azalactam **6**, has long been deemed to be of mechanistic significance. The reasonable belief was that *if the mechanisms of the reactions involve the structurally similar oxime derivatives* **5** and *iminodiazonium ions* **3**, then the favored lactam should be the same in both cases.[6,8] The operative postulate was that preferred methylene migration in the Schmidt reaction of the parent norcamphor (**1**) occurred upon rearrangement of a tetrahedral intermediate **2**, without intervention of an iminodiazonium ion **3**. This accepted explanation has been invoked subsequently to rationalize the preference for methylene migration in other Schmidt reactions.[16] Indeed, we have gone so far as to suggest that *insofar as Schmidt reactions of bridged bicyclic ketones occur through tetrahedral intermediates*, methylene migrated lactams are observed.[2] Evidence in support of the viability of rearrangements of azidohydrins has been developed.[9] Nevertheless, on the basis of the present results, we believe that a revision of the original and long accepted mechanism for the Schmidt reaction of norcamphor (**1**) is warranted. A mechanism consistent with the Schmidt reactions of norcamphor derivatives in Table 2 is shown in Scheme 3.

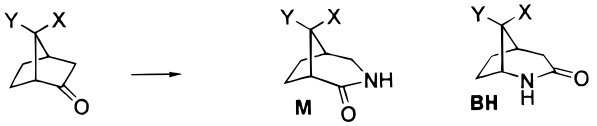
The data in Table 2 show that completely regioselective methylene migration in the Schmidt reaction of norcam-

(14) Kropp, P. J.; Breton, G. W.; Craig, S. L.; Crawford, S. C.; Durland, W. F., Jr.; Jones, J. E., III; Raleigh, J. S. *J. Org. Chem.* **1995**, *60*, 4146.

(15) The reaction of camphor (**10**) (eq 2) to give a mixture of 3-azalactam **12** (48% yield) and cleavage products (52%) has been rationalized as the result of direct rearrangement via a tetrahedral intermediate **11**.[5d] In a reinterpretation consistent with the present findings, the results also can be explained by low stereoselectivity in a rate-determining dehydration step to form *syn*- and *anti*-iminodiazonium ions analogous to **42**. The *syn*-iminodiazonium ion rearranges to give lactam **12**, while the *anti*-isomer gives cleavage products.

(16) (a) Bhaleao, U. T.; Thyagarajan, G. *Can. J. Chem.* **1968**, *46*, 3367. (b) Sasaski, T.; Eguchi, S.; Toru, T. *J. Org. Chem.*, **1970**, *35*, 4109. (c) Fikes, L. E.; Shechter, H. *Tetrahedron Lett.* **1976**, *17*, 2525. (d)) Fikes, L. E.; Shechter, H. *J. Org. Chem.* **1979**, *44*, 741. (e) Arcus, C. J.; Coombs, M. M.; Evans, J. V. *J. Chem. Soc.* **1956**, 1498. (f) Campaigne, E.; Huffman, J. C.; Yodice, R. *J. Heterocycl. Chem.* **1981**, *18*, 135. (g) Hunter, N. R.; Khan, M. Z.; Marat, K.; El-Kabbani, O. A. L.; Delbaere, L. T. *Can. J. Chem.* **1987**, *65*, 137.

Table 3. Summary of Methylene/Bridgehead Migration and Cleavage Processes



entry	ketone	X	Y	M mig.[a] 3-azalactam (%)	BH mig.[a] 2-azalactam (%)	cleavage[a] (%)	ratio BH/ cleavage	σ_I^q
				Syn				
1	1	H	H	35 (**4**)	<2 (**6**)	67	0.00	0
2	13	OMe	H	35 (**14**)[c]	13 (**15**)[c]	52	0.25	0.46
3	16	Cl	H	24 (**17**)	04 (**18**)[c]	72	0.06	0.77
4	19	Br	H	27 (**20**)	10 (**21**)	63	0.16	0.83
5	22	OTos	H	21 (**23**)	31 (**24**)[c]	48	0.65	1.09
				Anti				
6	25	H	COOMe	20 (**26**)	11 (**27**)	69	0.16	0.22[d]
7	28	H	Cl	24 (**29**)	5 (**30**)[c]	71	0.07	0.77
8	31	H	Br	41 (**32**)	<2 (**33**)	59	0.00	0.83
9	34	H	OTos	14 (**35**)	26 (**36**)[c]	60	0.43	1.09
10	37	H (*exo*-5-Br)	COOMe	27 (**38**)	25 (**39**)	48	0.52	

[a] M = methylene migration. BH = bridgehead migration. Yields are for purified lactams; Yields <2% were not observed by NMR; cleavage represents all nonlactam products. [b] Reference 20. Values are for $CH_2X(Y)$. [c] Some decomposition of the lactam occurs on silica gel. [d] The value for CH_2CO_2Me was estimated by subtracting the σ_I^q difference between OAc (1.97) and CH_2Oac (0.69) from the value for COOMe (1.50).

phor (**1**)(entry 1) to give 3-azalactam **4** is unusual. Of the other derivatives studied, only the 7-*anti*-Br derivative **31** (entry 11) did not give mixtures of isomers. In Table 3 a summary of the migration and cleavage processes is shown. A number of important trends can be noted, which are consistent with the iminodiazonium ion mechanism for the Schmidt reaction of norcamphors **40** shown in Scheme 3. First, methylene migration is always minor relative to the sum of the bridgehead migration and the bridgehead cleavage processes.[17] Second, there is not a significant difference between the amount of methylene migration for norcamphor (**1**) (entry 1) and any of its *syn*-7-substituted derivatives (entries 2−5), as would be expected for *endo* attack by azide and rearrangement of the azidohydrin **45** (Scheme 3).[11,12] Dominance of bridgehead processes and failure to observe an increase in methylene migration upon introduction of sterically demanding substituents on the *exo* face of norcamphors **40** is consistent with reaction of iminodiazonium ions **46**. Independent of the stereochemistry of the substituent at C7 of ketones **40**, dehydration of the azidohydrins **45** should give mainly *anti*-iminodiazonium ions **46**,[18] whose expected reactivity is consistent with the dominance of bridgehead cleavage and rearrangement processes observed in Table 2.[19] Methylene migration arises from the *syn*-iminodiazonium ion **46** formed concurrently.

In order to interpret inductive effects upon the course of the Schmidt reaction, σ_I^q value for CH_2X were chosen in Table 3 as a surrogate for substituent inductivity.[20] *If the ketones with 7-chloro or 7-bromo substituents are excluded from the analysis* (entries 3−4, 7−8), several important trends can be noted in the ratio of BH migration to BH cleavage processes. First, there is an increase in the amount of BH migrated 2-azalactam **43** as the inductivity of the norcamphor substituent X(Y) increases (H < COOMe < OMe < COOMe(Br) < OTos). The *syn* or *anti* orientation of the C-7 OTos substituents of ketones **22** and **34** (entries 5 and 9) has no significant additional effect. Second, significant ratios of BH migrated 2-azalactams **43** to cleavage products (>0.4) are observed only upon the introduction of strongly electron-withdrawing substituents (7-OTos and 5-bromo-7-methoxycarbonyl)(entries 5, 9, and 10). Clearly, the electron-withdrawing power of the C-7-substituent decreases the stability of a cation at the adjacent C-1 bridgehead and facilitates BH migration to give 2-azalactams **43** in competion with cleavage. These findings are consistent with either the iminodiazonium ion **46** or the previously accepted tetrahedral **45** rearrangement mechanisms.

As shown in Table 3, the *syn*-7-Cl ketone **16** (entry 3) and *anti*-7-Cl ketone **28** (entry 7) give only 4−5% 2-azalactams **18** and **30**, and the *anti*-7-Br ketone **31** (entry 8) gives no 2-azalactam **33**. The relatively large amounts of cleavage products observed during Schmidt reactions of *anti*-7-Cl ketone **28** and *anti*-7-Br ketone **31** can be rationalized by the speculative suggestion that an electron-withdrawing inductive effect, which facilitates isolation of BH migrated 2-azalactams **43** for the other 7-substituted examples of Table 3, is counterbalanced by anchimeric assistance of BH cleavage by *anti*-7-Br or *anti*-7-Cl substituents, as shown by **47**.[21] Nevertheless, Schmidt reaction of the *syn*-7-halo ketones **16** and **19** (entries 3 and 4), which are not anchimerically assisted, give 6−10% of 2-azalactams **18** and **21**. It is difficult to know

(17) Mehta, G.; Pandey, P. N.; Usha, R.; Venkatesan, K. *Tetrahedron Lett.* **1976**, *17*, 4209.

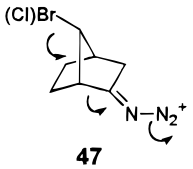
(18) Norcamphor oxime prefers the *anti*-isomer by 85:15. Hawkes, G. E.; Herwig, K.; Roberts, J. D. *J. Org. Chem.* **1974**, *39*, 1017.

(19) Bach, R. D.; Wolber, G. J. *J. Org. Chem.* **1982**, *47*, 239. On the basis of ab initio calculations, rapid isomerization of *syn* and *anti* iminodiazonium ions does not occur at room temperature.

(20) Lowry, T. H.; Richardson, D. S. *Mechanism and Theory in Organic Chemistry*, 3rd Ed., Harper and Row, NY, 1987; p 385.

(21) (a) March, J. *Advanced Organic Chemistry*, 4th ed.; J. Wiley and Sons: NY, 1992; p 312. Iodine and bromine are more effective as neighboring groups than chlorine, which provides anchimeric assistance only when there is a need for it. Anchimeric assistance might be aided in the present instance by poor solvation at C-1 during C−C bond breaking. (b) Duddeck, H.; Brosch, D.; Koppetsch, G. *Tetrahedron* **1985**, *41*, 3753. In methanesulfonic acid-catalyzed Schmidt reactions of 4-substituted adamantanones (*syn*/*anti* 4-OMes, I, Br, Cl, and CN) the *anti*-Cl, Br, and I compounds behaved unusually. Alkene carbonitriles were isolated from cleavage at the bridgehead adjacent to an *anti*-bromo or *anti*-chloro substituent, but not a *syn*-bromo or *syn*-chloro or other substituent. Only *anti*-4-iodoadamantanone gave the regioisomer derived by migration of the C-1 bridgehead distal to the substituent as the major or only lactam isolated. It is suggested that for the adamantanone system, an *anti*-iodo substituent facilitates bridgehead cleavage rather than migration; unfortunately, major amounts of cleavage products from reactions of this substrate have not been identified. For the other 4-substituted adamantanone substrates, the inductive effect of the substituent facilitates the isolation of lactam product (14−44% lactam) when compared to the parent adamantanone (11% lactam).

the significance of these results, since only small quantities of 2-azalactams **43** would be expected on the basis of the inductivity model of Table 3, and the 2-azalactam **18** produced from *syn*-7-Cl ketone **16** is acid sensitive and may have partially decomposed in the reaction medium.



47

In summary, reactions of HOSA with 7-substituted norcamphor derivatives **40** provide a simple and regioselective route to 2-azalactams **43**. The results are consistent with stereoselective formation and rearrangement of *anti*-oxime-*O*-sulfonic acids **42** to give 2-azalactams **43** and cleavage products. Occasionally minor amounts of 3-azalactam **44** are formed from minor reaction of the *syn*-oxime-*O*-sulfonic acid stereoisomers. The reaction of camphor (**10**) to give solely 3-azalactam **12** with HOSA is unusual.[1a] Schmidt reactions of the same ketones **40** provide mixtures of bridgehead **43** and methylene **44** migrated lactams, except for norcamphor (**1**) and *anti*-7-Br norcamphor (**31**), which give only 3-azalactams **44**. Yields of 2-azalactam **43** tend to increase slightly over the parent as the inductive effect of the 7-substituent increases; the 7-OTos derivatives **22** and **34** give mainly bridgehead migrated lactams. The regiochemical outcomes of the Schmidt reactions of norcamphor ketones **40** require a reinterpretation of the mechanism for HN_3 reactions with norcamphor (**1**). The results are best rationalized in terms of a poorly regioselective formation and the subsequent decomposition of *syn*- and *anti*-iminodiazonium ions **46** to give methylene migrated lactams **44**, bridgehead migrated lactams **43**, and cleavage products.

Experimental Section

General Methods. Thin layer chromatography was performed on precoated plates of silica gel GF 250 microns (Analtec, Inc.). Preparative thin layer chromatography was performed on precoated plates of silica gel GF 1000 or 2000 microns (Analtec, Inc.). Melting points are uncorrected. Solvents were removed under reduced pressure. ^{1}H NMR spectra were recorded at 300 and 500 MHz and ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ solvent. Ketones *syn*-7-OMe **13**,[22] *syn*-7-Cl **16**,[23] *syn*-7-Br **19**,[23−25] *syn*-7-OTos **22**,[26] *anti*-7-COOMe **25**,[27−29] *anti*-7-Cl **28**,[30] *anti*-7-Br **34**,[25,30] *anti*-7-OTos **37**,[26] and *exo*-5-Br-*anti*-7-COOMe **40**[27] were prepared by known routes.

General Procedure for the Beckmann Reactions. A mixture of the ketone and excess hydroxylamine-*O*-sulfonic acid (1.2−2.0 equiv) in acetic acid (5−12 mL/mmol) was heated at reflux for 1−4 h. The reaction mixture was basified with saturated $NaHCO_3$ or dilute NaOH and extracted with chloroform. The combined organic layers were washed with water, dried over $MgSO_4$, and filtered. Removal of solvent afforded a crude mixture, which was purified by chromatography or recrystallization. Cleavage products, which primarily remained in the water layer, were not purified or characterized.

3-Aza-2-oxobicyclo[3.2.1]octane (4)[6] and 2-Aza-3-oxobicyclo[3.2.1]octane (6).[6] From norcamphor (**1**) (600 mg, 5.45 mmol) there was obtained after 1 h 425 mg (62%) of a crude mixture containing a 10:90 ratio of lactams **4** and **6**. Further purification by chromatography, R_f = 0.26 (ether), gave 252 mg (37%) of a 10:90 mixture of known lactams **4** and **6**. Data for **4**: ^{1}H NMR δ 6.20 (br, 1H), 3.34 (d, J = 11.1, 3.9 Hz, 1H), 3.01 (dd, 11.1, 1.8 Hz, 1H), 2.60 (br, 1H), 2.46 (br, 1H), 2.03−1.54 (br, 1H); ^{13}C NMR δ 177.7, 49.7, 43.2, 32.5, 32.3, 31.2, 28.8. Data for **6**: ^{1}H NMR δ 6.50 (br, 1H), 3.70 (dd, J = 4.8, 3.9 Hz, 1H), 2.55 (ddd, J = 18, 2.1, 4.8 Hz, 1H), 2.50 (m, 1H), 2.23 (br d, J = 18 Hz, 1H), 2.00−1.59 (br, 6H); ^{13}C NMR δ 172, 53.0, 41.9, 36.0, 35.3, 32.1, 28.8.

***syn*-8-Methoxy-2-aza-3-oxobicyclo[3.2.1]octane (15).** From ketone **13** (300 mg, 2.1 mmol) was obtained after 1 h 175 mg (54%) of crude lactam **15**. Chromatography, R_f = 0.33 (THF/ether 1:1), gave 89 mg (27%) of pure lactam **15**, mp 110−111 °C, ^{1}H NMR δ 6.82 (br, 1H), 3.56 (m, 2H), 3.35 (s, 3H), 2.65 (br dd, J = 18, 2.4 Hz, 1H), 2.37 (m, 1H), 2.05 (dd, J = 18, 1.5 Hz, 1H), 1.93−1.54 (m, 4H); ^{13}C NMR δ 172.0, 79.4, 56.6, 51.9, 36.3, 32.7, 30.6, 25.7. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44, N, 9.02. Found: C, 61.99; H, 8.31; N, 9.07.

***syn*-8-Chloro-2-aza-3-oxobicyclo[3.2.1]octane (18).** From ketone **16** (150 mg, 1.04 mmol) was obtained after 2 h 130 mg (78%) of crude lactam **18**. Recrystallization (EtOAc) gave 81 mg (49%) of white crystals, mp 164−165.5 °C, ^{1}H NMR δ 7.10 (br, 1H), 4.11 (t, J = 4.2 Hz, 1H), 3.65 (q, J = 4.2 Hz, 1H), 2.93 (ddd, J = 18, 4.8, 2.1 Hz, 1H), 2.52 (br dd, J = 6.0, 5.1 Hz, 1H), 2.22 (dd, J = 18, 1.5 Hz, 1H), 2.10−1.81 (m, 4H); ^{13}C NMR δ 1.70.8, 58.2, 56.1, 36.7, 36.3, 31.9, 26.7. Anal. Calcd for $C_7H_{10}NOCl$: C, 52.65; H, 6.32; N, 8.78. Found: C, 52.65; H, 6.49; N, 8.79.

***syn*-8-Bromo-3-aza-2-oxobicyclo[3.2.1]octane (20) and *syn*-8-Bromo-2-aza-3-oxobicyclo[3.2.1]octane (21).** From ketone **19** (21 mg, 0.11 mmol) in acetic acid (5 mL) after 2 h there was obtained 16 mg (71%) of a crude mixture containing lactams **20** and **21** in a 6:94 ratio. Chromatography, R_f = 0.21 (EtOAc), gave 12 mg (53%) of a 5:95 mixture of the lactams as a white solid. Recrystallization ($CHCl_3$:ether) gave pure **21**, mp 166−167.5 °C. Data for **21**: ^{1}H NMR δ 7.45 (br, 1H), 4.12 (t, J = 4.2 Hz, 1H), 3.67 (d, J = 4.2 Hz, 1H), 2.89 (ddd, J = 18.3, 6.9, 2.1 Hz, 1H), 2.53 (d, J = 5.1 Hz, 1H), 2.25 (d, J = 18 Hz, 1H), 2.10−1.82 (br, 4H); ^{13}C NMR δ 171.2, 56.8, 50.4, 38.4, 37.2, 32.6, 27.1. Anal. Calcd for $C_7H_{10}NOBr$: C, 41.18; H, 4.94; N, 6.87. Found: C, 40.91, H, 4.79; N, 6.77.

***syn*-8-(*p*-Toluenesulfonyloxy)-2-aza-3-oxobicyclo[3.2.1]-octane (24).** From ketone **22** (28 mg, 0.106 mmol) in acetic acid (5 mL) there was obtained after 1 h 12 mg (41%) of crude lactam **24**. Chromatography, R_f = 0.18 (EtOAc), afforded 8 mg (27%) of solid, mp 174.5−175.5 °C; ^{1}H NMR δ 7.81 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 5.76 (br, 1H), 4.73 (1H), 3.57 (q, J = 3.9 Hz, 1H), 2.71 (ddd, J = 17.7, 4.8, 2.1 Hz, 1H), 2.47 (s, 3H), 2.20 (dd, J = 18, 1.5 Hz, 1H), 2.20−1.70 (m, 4H); ^{13}C NMR δ 170.1, 145.2, 133.2, 130.0, 127.7, 77.2, 53.2, 36.0, 33.5, 30.1, 25.0, 21.2. Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 56.88; H, 5.99; N, 4.72.

***anti*-8-(Methoxycarbonyl)-2-aza-3-oxobicyclo[3.2.1]-octane (27).** From ketone **25** (70 mg, 0.42 mmol) in acetic acid (15 mL) after 2 h there was obtained 33 mg (43%) of crude lactam **27**. Chromatography, R_f = 0.13 (ether), gave 22 mg (29%) of a solid, mp 123−123.5 °C; ^{1}H NMR δ 6.65 (br, 1H), 3.98 (br, 1H), 3.71 (s, 3H), 2.90 (s, 1H), 2.86 (t, J = 5.4 Hz, 1H), 2.65 (ddd, J = 18, 4.8, 2.1 Hz, 1H), 2.33 (d, J = 18 Hz, 1H), 2.07−1.6 (m, 4 H); ^{13}C NMR δ 171.1, 171.0, 54.4, 51.9, 51.6, 41.3, 34.7, 33.3, 27.4. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.66; H, 7.07; N, 7.63.

***anti*-8-Chloro-2-aza-3-oxobicyclo[3.2.1]octane (30).** From ketone **28** (356 mg, 3.15 mmol) in acetic acid (15 mL) after 3 h there was obtained 151 mg (45%) of crude lactam **30**. Recrystallization (EtOAc) gave 79 mg (23%) of a white solid,

(22) Kagan, J. *Helv. Chim. Acta* **1972**, *55*, 2356.
(23) Roberts, J. D.; Johnson, F. O.; Carboni, R. A. *J. Am. Chem. Soc.* **1954**, *76*, 5692.
(24) Zalkow, L.; Oehlschlager, A. *J. Org. Chem.* **1964**, *29*, 1625.
(25) Dalton, D. R.; Rodebaugh, R. K.; Jefford, C. W. *J. Org. Chem.* **1972**, *37*, 362.
(26) Gassman, P. G.; Marshall, J. L.; Hornback, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 5811.
(27) Grieco, P. A.; Pogonowski, C. S.; Burke, S. D.; Nishizawa, M.; Miyashita, M.; Masaki, Y.; Wang, C.-L. J.; Majetich, G. *J. Am. Chem. Soc.* **1977**, *99*, 4111.
(28) Torii, S.; Tanaka, H.; Mandai, T. *J. Org. Chem.* **1975**, *40*, 2221.
(29) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554.
(30) Werstiuk, N. H.; Timmins, G.; Cappelli, F. P. *Can. J. Chem.* **1980**, *58*, 1709.

mp 129−130 °C; ^{1}H NMR δ 7.21 (br, 1H), 4.30 (s, 1H), 3.69 (br, 1H), 2.70 (ddd, J = 18.0, 4.8, 2.1 Hz, 1H), 2.59 (m, 1H), 2.30−1.71 (br, 5H); ^{13}C NMR δ 170.1, 63.1, 58.0, 40.7, 40.3, 32.0, 26.4. Anal. Calcd for $C_7H_{10}NOCl$: C, 52.65; H, 6.32; N, 8.78. Found: C, 52.27; H, 6.29; N, 8.64.

***anti*-8-Bromo-2-aza-3-oxobicyclo[3.2.1]octane (33).** From ketone **31** (200 mg, 1.05 mmol) in acetic acid (15 mL) after 1.5 h there was obtained 196 mg (92%) of crude lactam **33**. Chromatography, R_f = 0.63 (THF), gave 151 mg (70%) of white solid lactam, mp 109−110 °C (ether/hexanes); ^{1}H NMR δ 7.50 (br, 1H), 4.30 (s, 1H), 3.70 (t, J = 3.0 Hz, 1H), 2.70 (m, 1H), 2.60 (br, 1H), 2.30−1.82 (br, 5H); ^{13}C NMR δ 169.6, 52.8, 50.4, 49.0, 44.0, 39.2, 32.6. Anal. Calcd for $C_7H_{10}NOBr$: C, 41.18; H, 4.94; N, 6.87. Found: C, 40.84, H, 5.08; N, 6.78.

***anti*-8-(*p*-Toluenesulfonyloxy)-2-aza-3-oxobicyclo[3.2.1]-octane (36).** From ketone **34** (15 mg, 0.53 mmol) in acetic acid (5 mL) after 1 h there was obtained 11 mg (70%) of crude lactam **36**. Chromatography, R_f = 0.28 (EtOAc), gave 6 mg (38%) of pure **24** as a white solid, mp 178−179 °C; ^{1}H NMR δ 7.81 (br, J = 8.1 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2 H), 6.90 (br, 1H), 4.76 (s, 1H), 3.67 (br, 1H), 2.61 (ddd, J = 18, 2.1, 1.8 Hz, 1H), 2.49 (br, 4H), 2.30 (dd, J = 18, 1.8 Hz, 1H), 2.07−1.6 (m, 4H); ^{13}C NMR δ 169.5, 144.8, 132.9, 129.6, 127.2, 83.8, 55.0, 39.2, 36.7, 31.9, 26.5, 21.2. Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 57.14; H, 5.72; N, 4.69.

***exo*-6-Bromo-*anti*-8-(methoxycarbonyl)-2-aza-3-oxo-bicyclo[3.2.1]octane (39).** From ketone **37** (200 mg, 0.81 mmol) in acetic acid (15 mL) after 2 h there was obtained 167 mg (79%) of crude lactam **39.** Recrystallization (EtOAc) gave 148 mg (64%) of white solid, mp 164.5−165.5 °C; ^{1}H NMR δ 6.93 (br, 1H), 4.24 (dd, J = 7.8 Hz, 1H), 4.14 (br, 1H), 3.77 (s, 3H), 3.29 (m, 1H), 2.97 (s, 1H), 2.88−2.60 (m, 3H), 2.50 (dd, J = 18, 1.8 Hz, 1H); ^{13}C NMR δ 170.3, 169.8, 53.6, 51.6, 50.3, 48.0, 47.3, 47.2, 40.4. Anal. Calcd for $C_9H_{12}NO_3Br$: C, 41.24; H, 4.61; N, 5.34. Found: C, 41.17, H, 4.69; N, 5.33.

General Procedure for the Schmidt Reactions. To a cold (0 °C) chloroform solution of sodium azide (2 equiv) in concentrated sulfuric acid (1 mL/mmol) was added dropwise a solution of the ketone in chloroform.. After the mixture was stirred at 25 °C for the indicated time (Table 2), the reaction was basified with sodium bicarbonate or sodium hydroxide solution and extracted with chloroform. The combined organic layers were washed with water, dried over $MgSO_4$, and filtered. Removal of solvent gave a crude mixture; lactam products were obtained by chromatography using the appropriate amount of ether. Lactam ratios are reported in Table 2. Cleavage products, which primarily remained in the water layer, were not purified or characterized.

3-Aza-2-oxobicyclo[3.2.1]octane (4).[6] From norcamphor **1** (500 mg, 4.45 mmol) in $CHCl_3$ (15 mL) after 1 h there was obtained 217 mg (39%) of lactam **4**.

***syn*-8-Methoxy-3-aza-2-oxobicyclo[3.2.1]octane (14) and *syn*-8-Methoxy-2-aza-3-oxobicyclo[3.2.1]octane (15).** From ketone **13** (280 mg, 2.0 mmol), sodium azide (1.5 equiv) and sulfuric acid (1 mL) in chloroform (15 mL) after 1 h there was afforded 223 mg (72%) of a mixture of lactams. Chromatography, R_f = 0.40 (THF/ether 1:1), afforded 148 mg of lactams as an oil. Data for **14**: ^{1}H NMR δ 6.82 (br, 1H), 3.75 (dd, J = 4.5, 4.8 Hz, 1H), 3.51 (dd, J = 11.0, 3.3 Hz, 1H), 3.38 (s, 3H), 2.91 (dt, J = 11.0, 1.8 Hz, 1H), 2.70 (t, J = 4.5 Hz, 1H), 2.30 (m, 1H), 1.93−1.70 (m, 4H); ^{13}C NMR δ 174.7, 81.1, 57.1, 44.9, 44.6, 33.1, 26.4, 25.9. Anal. of the mixture calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44, N, 9.02. Found: C, 61.99; H, 8.31; N, 9.07.

***syn*-8-Chloro-3-aza-2-oxobicyclo[3.2.1]octane (17) and *syn*-8-Chloro-2-aza-3-oxobicyclo[3.2.1]octane (18).** From ketone **16** (800 mg, 5.54 mmol) in chloroform (30 mL) after 24 h there was obtained according to the general procedure 364 mg (47%) of a mixture of lactams, which was purified by recrystallization (EtOAc) to afford 250 mg (28%) of white crystals. Further recrystallization gave lactam **17**, mp 161.5−163 °C, ^{1}H NMR δ 6.59 (br, 1H), 4.21 (t, J = 4.5 Hz, 1H), 3.72 (dd, J = 11.4, 3.3 Hz, 1H), 3.07 (d, J = 11.4 Hz, 1H), 2.81 (t, J = 4.5 Hz, 1H), 2.50 (br, 1H), 2.14−1.82 (m, 4H); ^{13}C NMR δ 173.1, 57.7, 48.8, 45.0, 36.2, 27.9, 26.1. Anal. Calcd for $C_7H_{10}NOCl$: C, 52.65; H, 6.32; N, 8.78. Found: C, 52.51; H, 6.30; N, 8.71.

***syn*-8-Bromo-3-aza-2-oxobicyclo[3.2.1]octane (20) and *syn*-8-Bromo-2-aza-3-oxobicyclo[3.2.1]octane (21).** From ketone **19** (100 mg, 0.53 mmol) in chloroform (15 mL) after 4 h there was obtained according to the general procedure 65 mg (60%) of a mixture of lactams. Chromatography, R_f = 0.28 (EtOAc), gave 37 mg (34%). Recrystallization (EtOAc) gave lactam **20**, mp 133−134 °C; ^{1}H NMR δ 5.99 (br, 1H), 4.22 (t, J = 4.2 Hz, 1H), 3.76 (dd, J = 11.4, 3.0 Hz, 1H), 3.14 (d, J = 11.4 Hz, 1H), 2.90, (t, J = 3.9 Hz, 1H), 2.53 (br, 1H), 2.13−1.85 (br, 4H); ^{13}C NMR δ 173.7, 49.6, 48.6, 46.7, 36.9, 29.2, 26.5. Anal. Calcd for $C_7H_{10}NOBr$: C, 41.18; H, 4.94; N, 6.87. Found: C, 41.19, H, 5.03; N, 6.90.

***syn*-8-(*p*-Toluenesulfonyloxy)-3-aza-2-oxobicyclo[3.2.1]-octane (23) and *syn*-8-(*p*-Toluenesulfonyloxy)-2-aza-3-oxobicyclo[3.2.1]octane (24).** From ketone **22** (150 mg, 0.54 mmol) in chloroform (20 mL) after 2 h according to the general procedure there was obtained 130 mg (82%) of a mixture of lactams. Chromatography, R_f = 0.18 (EtOAc), gave 82 mg (52%) of a white solid mixture. Recrystallization gave lactam **23**, mp 169−169 °C; ^{1}H NMR δ 7.81 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 5.60 (br, 1H), 4.85 (dd, J = 5.1, 4.8 Hz, 1H), 3.65 (dd, J = 11.4, 3.0 Hz, 1H), 3.06 (d, J = 11.1 Hz, 1H), 2.57 (t, J = 4.8, 5.1 Hz, 2H), 2.47 (s, 3H), 2.05−1.60 (br, 4H); ^{13}C NMR δ 172.2, 144.8, 132.8, 129.5, 127.7, 79.3, 45.3, 44.5, 33.6, 25.6, 24.7, 21.2. Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 57.14; H, 5.72; N, 4.69.

***anti*-8-(Methoxycarbonyl)-3-aza-2-oxobicyclo[3.2.1]-octane (26) and *anti*-8-(Methoxycarbonyl)-2-aza-3-oxobicyclo[3.2.1]octane (27).** From ketone **25** (100 mg, 0.6 mmol) in chloroform (15 mL) after 2 h according to the general procedure there was obtained 43 mg (39%) of a mixture of crude lactams **26** and **27**. Chromatography, R_f = 0.13 (ether), afforded 34 mg (31%) of a 66:34 mixture of the lactams, mp 102−112 °C. Data for lactam **26**: ^{1}H NMR δ 6.61 (br, 1H), 3.67 (s, 3H), 3.39 (dd, J = 11.4, 3.9 Hz, 1H), 3.05 (dt, 11.1, 2.0 Hz, 1H), 2.93 (br, 1H), 2.90 (s, 1H), 2.81 (m, 1H), 2.30−1.56 (m, 4H); ^{13}C NMR δ 175.2, 171.7, 51.6, 49.0, 47.8, 45.3, 35.0, 29.1, 27.1. Anal. of the mixture of lactams Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.66; H, 7.07; N, 7.63.

***anti*-8-Chloro-3-aza-2-oxobicyclo[3.2.1]octane (29) and *anti*-8-Chloro-2-aza-3-oxobicyclo[3.2.1]octane (30).** From ketone **28** (48 mg, 0.346 mmol) in chloroform (15 mL) after 5 h there was obtained according to the general procedure 29 g (53%) of a mixture of lactams. Chromatography, R_f = 0.20 (EtOAc), gave 16 mg (29%) of a white solid mixture of lactams, mp 145−146.5 °C. Data for lactam **29**: ^{1}H NMR δ 6.53 (br, 1H), 4.38 (s, 1H), 3.42 (dd, J = 11.1, 4.0 Hz, 1H), 3.08 (dt, J = 11.1, 2.1 Hz, 1H), 2.82 (d, J = 4.8 Hz, 1H), 2.69 (br, 1H), 2.43−1.65 (m, 4H); ^{13}C NMR δ 174.3, 61.4, 50.9, 47.5, 41.1, 28.1, 25.7. Anal. Calcd for $C_7H_{10}NOCl$: C, 52.65; H, 6.32; N, 8.78. Found: C, 52.39; H, 6.36; N, 8.60.

***anti*-8-Bromo-3-aza-2-oxobicyclo[3.2.1]octane (32).** From ketone **31** (342 mg, 1.81 mmol) in chloroform (25 mL) after 12 h there was obtained according to the general procedure 210 mg (57%) of crude lactam **32**, mp 140.5−142 °C (EtOAc), ^{1}H NMR δ 6.77 (br, 1H), 4.45 (s, 1H), 3.42 (dd, J = 11.1, 3.3 Hz, 1H), 3.05 (d, J = 11.4 Hz, 1H), 2.87 (d, J = 5.1 Hz, 1H), 2.75 (br, 1H), 2.43−1.65 (m, 4H); ^{13}C NMR δ 174.5, 52.7, 52.0, 48.3, 42.1, 29.2, 26.5. Anal. Calcd for $C_7H_{10}NOBr$: C, 41.18; H, 4.94; N, 6.87. Found: C, 41.03, H, 5.01; N, 6.78.

***anti*-8-(*p*-Toluenesulfonyloxy)-3-aza-2-oxobicyclo[3.2.1]-octane (35) and *anti*-8-(*p*-Toluenesulfonyloxy)-2-aza-3-oxobicyclo[3.2.1]octane (36).** From ketone **34** (100 mg, 0.357 mmol) in chloroform (20 mL) after 2 h there was obtained according to the general procedure 63 mg (64%) of crude lactams. Chromatography, R_f = 0.28 (EtOAc), gave 42 mg (40%) of white solid mixture, mp 153−155 °C. Data for lactam **35**: ^{1}H NMR δ 7.78 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2 H), 5.78 (br, 1H), 4.85 (br, 1H), 3.37 (dd, J = 11.1, 3.6 Hz, 1H), 3.02 (d, J = 11.1 Hz, 1H), 2.60 (br, 2H), 2.47 (s, 3H), 2.20−2.00 (br, 4H); ^{13}C NMR δ 173.3, 132.9, 129.6, 127.2, 82.7, 47.8, 46.1, 38.0, 28.1, 25.7, 21.2. Anal. of the mixture of lactams

Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 57.14; H, 5.72; N, 4.69.

***exo*-6-Bromo-*anti*-8-(methoxycarbonyl)-3-aza-2-oxobicyclo[3.2.1]octane (38) and *exo*-6-Bromo-*anti*-8-(methoxycarbonyl)-2-aza-3-oxobicyclo[3.2.1]octane (39).** From ketone **37** (200 mg, 0.81 mmol) in chloroform (15 mL) after 12 h there was obtained 127 mg (60%) of a mixture of lactams. Chromatography, $R_f = 0.13$ (ether), gave 110 mg (52%) of a solid mixture, mp 135−138 °C. Data for lactam **38**: ^{1}H NMR δ 6.08 (br, 1H), 4.25 (m, 7.8 Hz, 1H), 3.79 (s, 3H), 3.50 (dd, J = 11.7, 4.2 Hz, 1H), 3.41−3.20 (br, 3H), 3.01 (br, 1H), 2.87−2.63 (m, 2H); ^{13}C NMR δ 174.1, 169.1, 51.7, 48.0, 47.7, 47.6, 46.2, 45.0, 42.6. Anal. of the lactam mixture calcd for $C_9H_{12}NO_3Br$: C, 41.24; H, 4.61; N, 5.34. Found: C, 41.17, H, 4.69; N, 5.33.

Acknowledgment. We thank Temple University for financial support and Professor Franklin Davis for helpful suggestions.

Supporting Information Available: ^{1}H NMR peak assignments to new lactams (3 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 the ACS; see any current masthead page for ordering information.

JO960604E