Preparation and characterization of bicyclic amide acetals and monothioacetals[1]

J. Peter Guthrie, Roger T. Gallant, and Michael C. Jennings

Abstract: We have prepared and characterized new examples of 5-substituted-1-aza-4,6-dioxabicyclo[3.3.0]octanes (bicyclic amide acetals) and examples of the new heterocyclic system, 5-substituted-1-aza-4-oxa-6-thiabicyclo[3.3.0]octanes (bicyclic amide monothioacetals). Detailed analysis of NMR coupling constants and X-ray structure determination for an example of each class of compound established the stereochemistry and conformation of these ring systems.

Key words: bicyclic amide acetals, preparation, coupling constants, X-ray structure.

Résumé : On a préparé et caractérisé de nouveaux exemples de 1-aza-4,6-dioxabicyclo[3.3.0]octanes substitués en position 5 (amide acétals bicycliques) et des exemples du nouveau système hétérocyclique 1-aza-4-oxa-6-thiabicyclo[3.3.0]octanes substitués en position 5 (amide monothioacétals bicycliques). Une étude détaillée des constantes de couplage de la RMN et la détermination de la structure, par diffraction des rayons X, d'un exemple de chacune de ces classes de composés permet d'établir la stéréochimie et la conformation de ces composés cycliques.

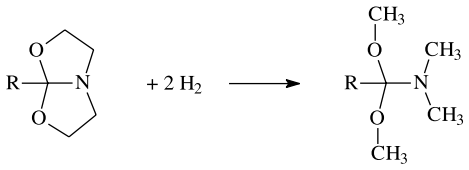
Mots clés : amide acétals bicycliques, préparation, constantes de couplage, structure par diffraction des rayons X.

[Traduit par la Rédaction]

Introduction

We have been interested in determining the energies of tetrahedral intermediates in acyl transfer reactions by an indirect thermochemical approach (1–7). Attempts to extend this approach from simple amides (2) to amides with various substituents on the α-carbon ran into frustrating problems of purification. Amide acetals could be made but could not be purified. In an attempt to overcome this problem we have turned to bicyclic versions of these compounds. Our plan is to determine the heats of hydrolysis and, thus, the heats of formation of the bicyclic acetals and monothioacetals and proceed from these to, first, the heats of formation of the acyclic acetals and monothioacetals, using computational methods to determine the heats of reaction for the hypothetical hydrogenations shown in reactions [1] and [2], and thence, to the free energies of formation of the analogous tetrahedral intermediates.

[1]



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J.P. Guthrie,[2] R.T. Gallant, and M.C. Jennings.
Department of Chemistry, University of Western Ontario, London, ON N6A 5B7, Canada.

[1]This article is part of a Special Issue dedicated to Professor Ed Piers.

[2]Corresponding author (e-mail: peter.guthrie@uwo.ca).

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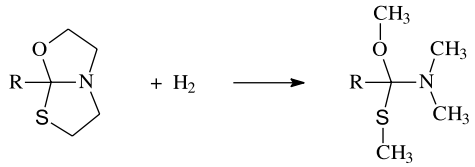

By methods that we have reported (8) and that involve a hypothetical hydrolysis, free energies of the acyclic amide acetals can be used to calculate the free energies of the corresponding amide hemiacetals and amide hydrates.

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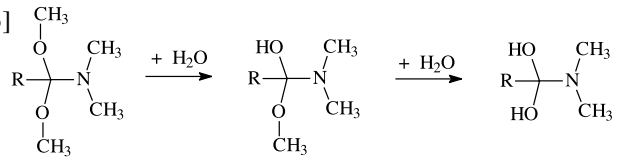

Similarly, the free energies of the acyclic amide monothioacetals can be used to calculate the free energies of the corresponding amide hemithioacetals.

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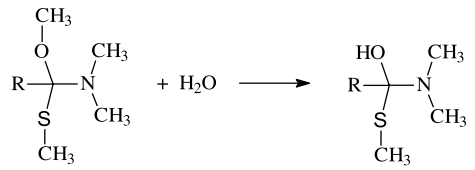

The energies of these adducts can be combined with free energies of the amides to permit calculation of the free energy changes for addition reactions of amides, reactions that are quite unfavorable and difficult to determine experimentally.

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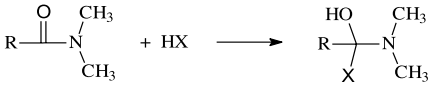
[5] 

X = OH, OCH_3, SCH_3.

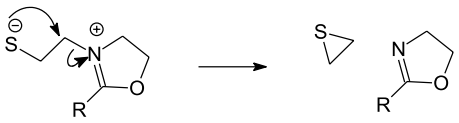
The first stage in this project was to prepare and characterize the bicyclic compounds, only a few of which were known. Calorimetric studies of these compounds are complete and computational studies to complement and in some cases to supplement them are nearly complete. The rest of our studies on these compounds will be reported in due course.

Results

The compounds examined in this work are shown in Scheme 1. The original plan had been to prepare compounds with a range of electron-withdrawing substituents, but difficulties were encountered in some of these attempted preparations, and then it became clear that the rate of hydrolysis was very sensitive to electron withdrawal, such that strong electron-withdrawing groups made hydrolysis too slow for the calorimetric measurements we planned to carry out.

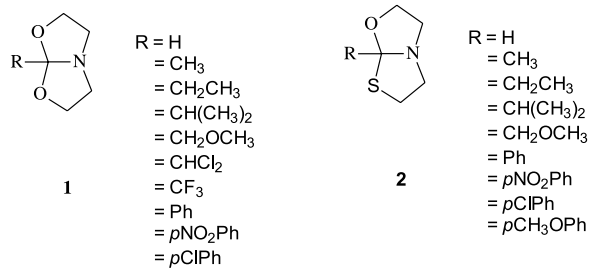
Although some of the bicyclic amide acetals are known compounds, most are novel, and preparations range from very easy to quite difficult.

The standard methods for preparation of compounds **1**, substituted 1-aza-4,6-dioxabicyclo[3.3.0]octanes, involve either reaction of diethanolamine with the corresponding nitrile, using a small amount of sodium as catalyst, or reaction of diethanolamine with the corresponding acyclic amide acetal. Similar methods allowed preparation of the novel compounds **2**, substituted 1-aza-4-oxa-6-thiabicyclo[3.3.0]octanes, by using 2-(2-mercaptoethyl)aminoethanol. The compounds **2** were thermally sensitive and could not be obtained by the standard reaction of a nitrile with 2-(2-mercaptoethyl)aminoethanol at 80 °C; such conditions led only to the oxazoline corresponding to the nitrile. Reaction at room temperature, though slow, led to the desired compounds. Attempted distillation of the crude 5-substituted-1-aza-4-oxa-6-thiabicyclo[3.3.0]octane at temperatures over 110 °C also led to breakdown to the corresponding oxazoline. A reasonable explanation is relatively facile cleavage of ethylene sulfide, e.g., by

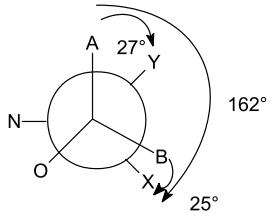


The 5-substituted-1-aza-4-oxa-6-thiabicyclo[3.3.0]octanes were higher boiling than the corresponding oxazolines and so purification by fractional distillation was possible if the temperature could be kept low enough to avoid thermal fragmentation. For the aryl-substituted compounds this was not possible, and pure product could be obtained only when the 5-substituted-1-aza-4-oxa-6-thiabicyclo[3.3.0]octane could be crystallized, as for **2** with R = phenyl and 4-nitrophenyl. In the case of **2** with R = 4-chlorophenyl and 4-methoxyphenyl, crystallization was not achieved, and the best samples were only 94% and 90% pure, with the remainder being the corresponding oxazoline. Details of these preparations and of the preparations of other compounds used in this work are found in the experimental section.

Scheme 1.



The oxazolidinooxazolidine system in the bicyclic amide acetals has two identical five-membered rings — each with four distinctive proton environments — leading to an ABXY pattern, with complicated splitting. The assignment of the methylene signals was based on the ^{1}H, ^{13}C, gCOSY, and gHSQC spectra. The proton NMR spectra of the 5-*R*-1-aza-4,6-dioxabicyclo[3.3.0]octanes are resolved well enough to allow a direct graphical calculation of the true chemical shifts and coupling constants. These calculated values were verified with the use of ACD Labs H NMR spin simulation software (9), as shown in Fig. 1. The worst deviation in chemical shift between the simulated and experimental spectra was approximately 0.002 parts per million (ppm). The chemical shifts and coupling constants resulting from this analysis are summarized in Tables 1 and 2. Analysis of the coupling constants by means of the Karplus–Conroy equation (10–12), using generic values of J° = 8.5 Hz and J^{180} = 9.5 Hz (as recommended when no better estimates are available (13)) led to the conclusion that the geometry of the ring systems for 5-(4-nitrophenyl)- 1-aza-4,6-dioxabicyclo[3.3.0]octane is as shown in



The logic of this assignment is as follows: (*i*) If the AB and XY protons were eclipsed (whether A with X and B with Y or A with Y and B with X), then $^3J_{AX} + {}^3J_{AY} = {}^3J_{BX} + {}^3J_{BY}$, but this is not the case; (*ii*) If the protons are staggered, then one of A and B will be *anti* to one of X and Y and gauche to the other, and the other of A and B will be gauche to both X and Y. Since *J* is largest for protons that are *anti*, the largest of the ^3J coupling constants must be for the pair of protons that are most nearly *anti*. This is $^3J_{AX}$; (*iii*) If A is approximately *anti* to X, then $^3J_{AY} \approx {}^3J_{BX}$, as is found; if instead A and Y were approximately *anti*, then $^3J_{AX} \approx {}^3J_{BY}$, which is not the case.

An X-ray structure was obtained for 5-(4-nitrophenyl)-1-

Fig. 1. Experimental and simulated ^{1}H NMR spectra for 5-isopropyl-1-aza-4,6-dioxabicyclo[3.3.0]octane.

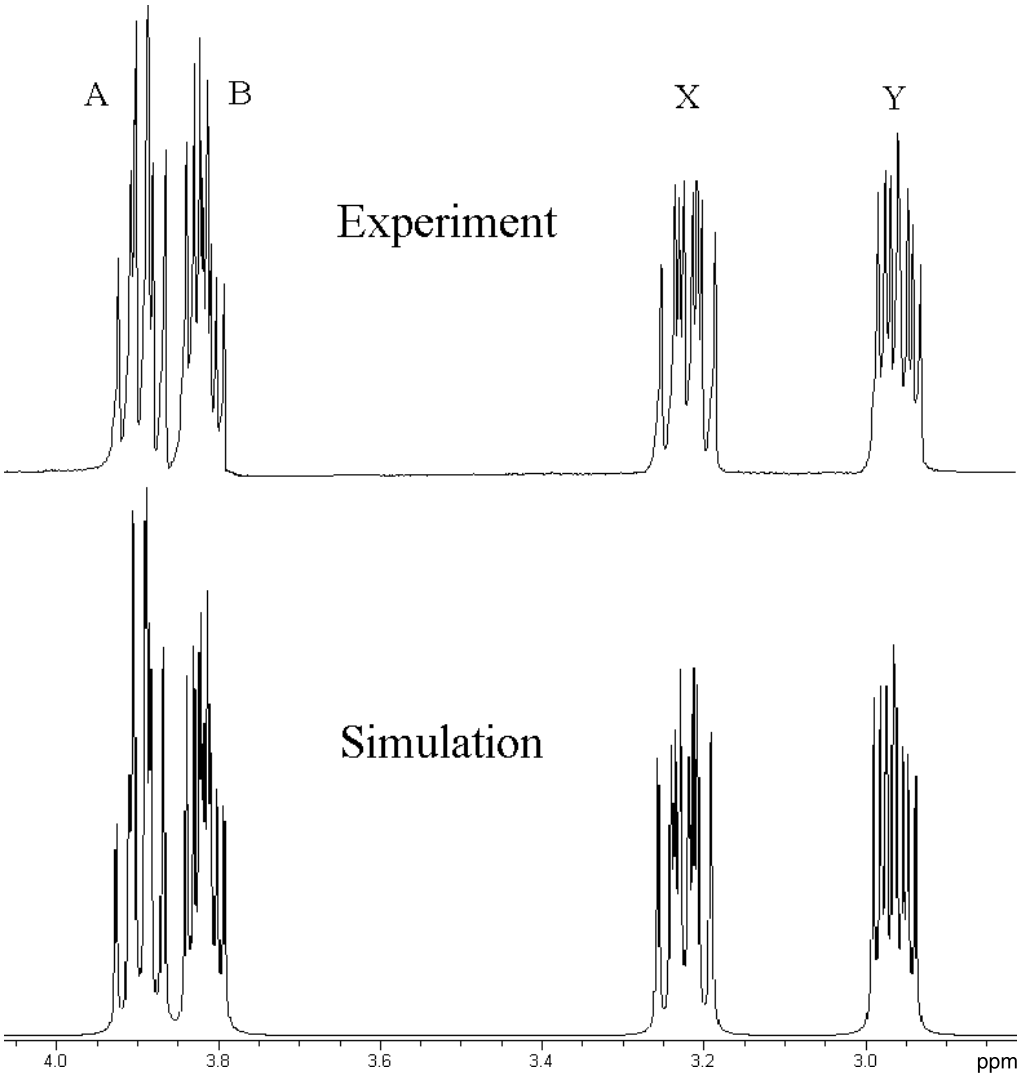


Table 1. Chemical shifts for the 5-*R*-1-aza-4,6-dioxabicyclo-[3.3.0]octanes in $CDCl_3$ (ppm) (Varian Mercury 400).

R	A	B	X	Y
H	3.838	3.796	3.199	2.924
Me	3.865	3.790	3.210	2.909
Et	3.904	3.813	3.219	2.947
i-Pr	3.895	3.816	3.219	2.959
$MeOCH_2$	3.949	3.870	3.275	2.966
Ph	4.119	3.998	3.358	3.094
p-NO_2-Ph	4.115	3.992	3.353	3.127
p-Cl-Ph	4.094	3.968	3.324	3.079
CF_3	4.093	4.012	3.339	3.028
Cl_2CH	4.095	4.055	3.468	3.062

Table 2. Coupling constants for the 5-*R*-1-aza-4,6-dioxabicyclo[3.3.0]octanes (Hz).

R	$^2J_{AB}$	$^3J_{AX}$	$^3J_{AY}$	$^3J_{BX}$	$^3J_{BY}$	$^2J_{XY}$
H	–8.20	8.40	6.04	6.83	4.30	–10.90
Me	–8.20	8.35	6.32	6.67	4.30	–10.95
Et	–8.10	8.25	6.28	6.77	4.10	–10.90
i-Pr	–8.30	8.70	6.28	6.63	3.55	–11.00
$MeOCH_2$	–8.00	7.85	6.24	6.50	4.55	–10.70
Ph	–8.15	8.00	6.56	6.90	4.35	–10.80
p-NO_2-Ph	–8.35	8.30	6.40	6.63	4.25	–11.00
p-Cl-Ph	–8.20	8.15	6.56	6.87	4.30	–11.05
CF_3	–7.95	7.13	6.60	6.50	5.85	–10.88
Cl_2CH	–8.10	7.65	6.54	6.80	4.73	–10.88

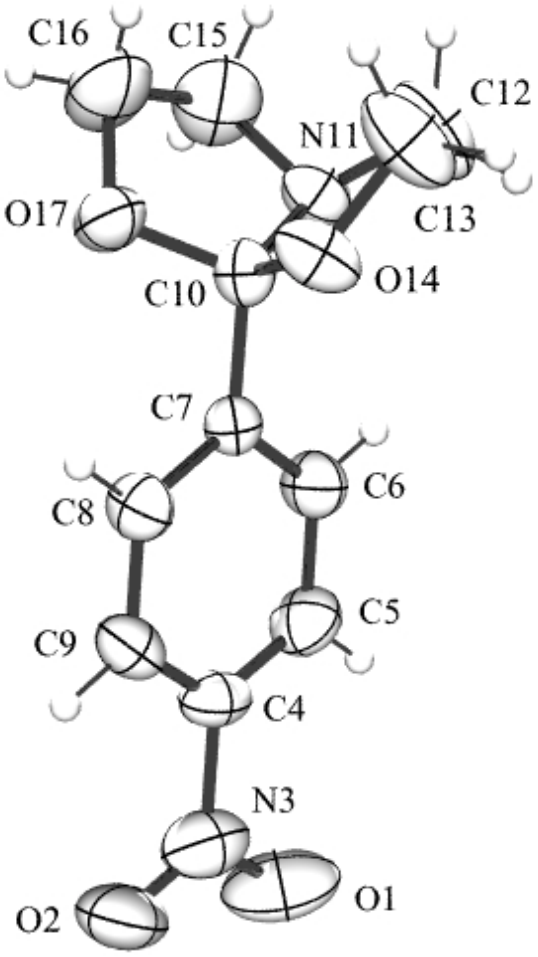
aza-4,6-dioxabicyclo[3.3.0]octane. This structure, Fig. 2, confirms that the bicyclic amide acetals have the five-membered rings *cis*-fused, as Anteunis et al. had concluded (14) based on analysis of the ^{1}H NMR spectra. The dihedral angles were close to, though not identical with, those deduced from the Karplus–Conroy analysis; the worst deviation was for the A–X dihedral, 146° rather than 162°. Examination of bond lengths in the X-ray structure showed no sign of an anomeric effect, which would be expected to cause a shortening of the quaternary carbon–nitrogen bond and a lengthening of at least one of the quaternary carbon–oxygen bonds.

Table 3. MS peak listing of the 5-*R*-1-aza-4,6-dioxabicyclo[3.3.0]octanes.

R	$[M]^+$	$[M - R]^+$	$[M - CH_2O]^+$	$[RCO]^+$	$[C_3H_4NO]^+$	$[C_3H_6N]^+$
H	115(20)	114(8)	85(100)	—	70(3)	56(25)
Me	129(12)	114(12)	99(100)	—	70(12)	56(34)
Et	143(4)	114(100)	113(41)	57(52)	70(34)	56(20)
i-Pr	157(5)	114(16)	127(l)	71(26)	70(8)	56(17)
$MeOCH_2$	158(l)	114(100)	129(2)	—	70(30)	56(7)
CF_3	183(9)	114(100)	153(49)	97(3)	70(43)	56(60)
$C1_2CH$	197(l)	114(100)	167(4)	—	70(29)	—
Ph	191(12)	114(10)	161(61)	105(100)	70(6)	56(19)
p-NO_2-Ph	236(8)	114(8)	206(100)	150(67)	70(6)	—
p-Cl-Ph	225(8)	114(3)	195(37)	139(78)	70(3)	—

Note: Values in table are *m*/*z* (relative intensity (%)).

Fig. 2. Crystal structure of 5-(4-nitrophenyl)-1-aza-4,6-dioxabicyclo[3.3.0]octane.

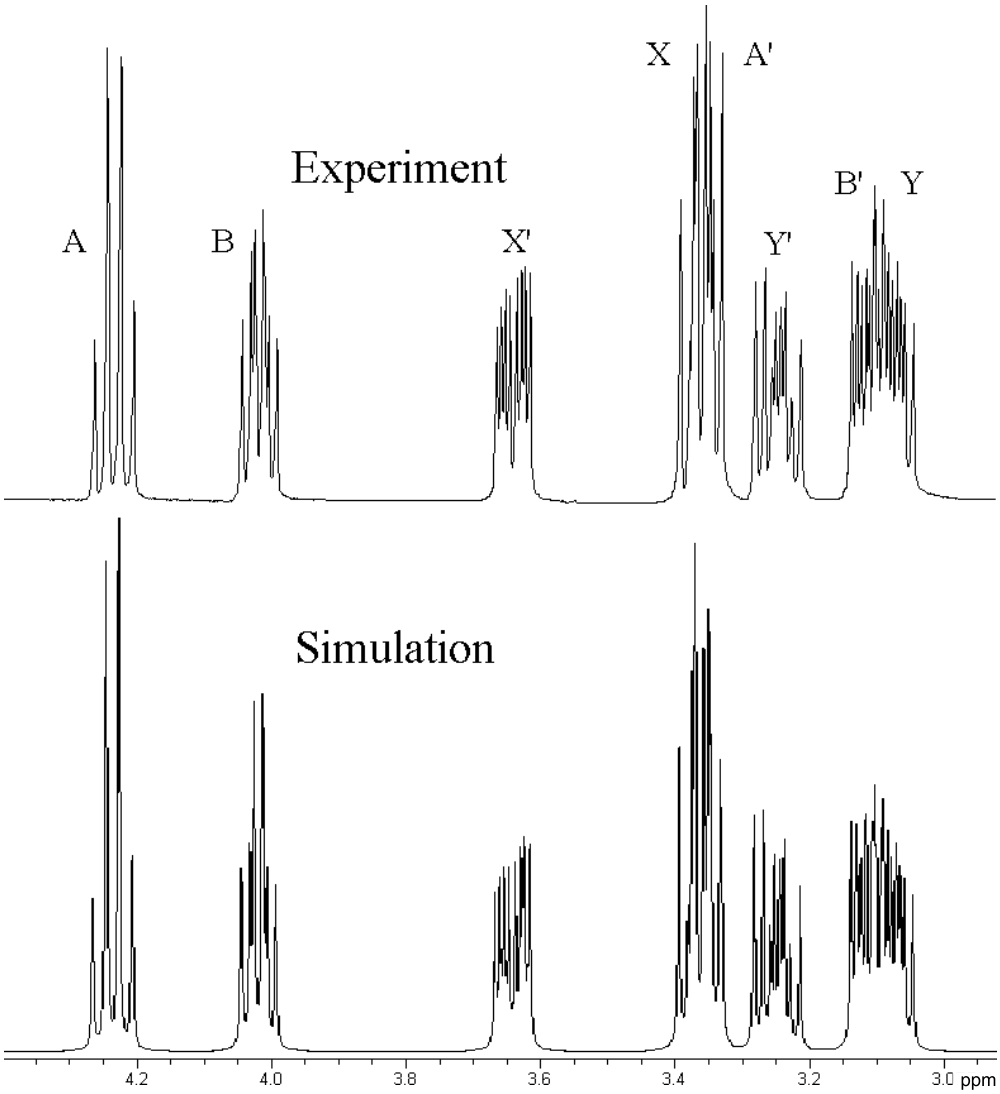


The mass spectra of these compounds were analyzed for characteristic fragmentation patterns. There were differences in fragmentation pattern for 5-aryl- vs. 5-alkyl-substituted 1-aza-4,6-dioxabicyclo[3.3.0]octanes. These results are collected in Table 3. The molecular ion peak for each bicyclic amide acetal was present with low relative intensity. Two primary fragmentation routes appear to be important based on the electron impact studies of these compounds, as follows: cleavage of the ring and elimination of the substituent. In the alkyl-substituted bicyclic amide acetals, the substituent elimination route appears to become more prevalent as R becomes larger. When the substituent was an aryl group, cleavage of the ring was favored, yielding dominant $[M - CH_2O]^+$ and acyl cation fragments.

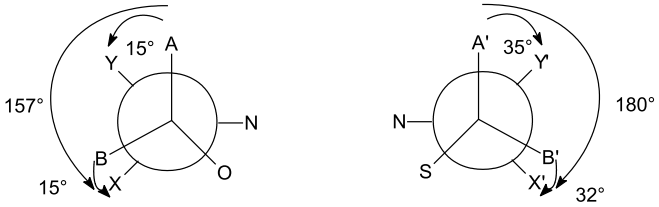
The thiazolidinooxazolidine ring system has a more complicated ^{1}H NMR splitting pattern, with two overlapping ABXY patterns. The pattern for the thiazolidine ring will be labeled A′B′X′Y′; the primes are used to indicate the analogy with the unprimed peak in the oxazolidine ring. This is not the usual convention, where single primes are used to indicate protons that are chemically but not magnetically equivalent, which is not the case here. All the protons are different, and the pattern, though complicated, can be analyzed as in the oxazolidinooxazolidine case. The assignment of the methylene signals was based on the ^{1}H, ^{13}C, gCOSY, and gHSQC spectra. The ^{13}C signal for the methylene at lowest field was assigned to CH_2-O; the ^{13}C signal for the methylene at highest field was assigned to CH_2S. The combination of gCOSY and gHSQC spectra allowed the remaining assignments. Simulated spectra were in good agreement with the observed spectra, as shown in Fig. 3. The chemical shifts and coupling constants are found in Tables 4 and 5.

For most of the 5-substituted-1-aza-4-oxa-6-thiabicyclo-[3.3.0]octanes, the same logic as for the dioxa case can be used to deduce the dihedral angles for the oxazolidino ring from the Karplus–Conroy curve, but for three compounds (R = H, ethyl, and methoxymethyl), all four ^3J values are approximately equal, which leads to a contradiction. If $^3J_{AX} + {}^3J_{AY} \approx {}^3J_{BX} + {}^3J_{BY}$, then one might conclude that the hydrogens were eclipsed, but if so the dihedral angles would be 0° and 120°, leading to distinctly different coupling constants. We are forced to conclude that in fact the structure is partly staggered, and that the Karplus–Conroy curve, especially with generic parameter values, is only an approximate guide. The structures are, in all cases, likely to be staggered but closer to eclipsed than to fully staggered geometry. The approximate nature of the dihedral angles deduced from the Karplus–Conroy curve is shown by comparison with the X-ray structure for R = 4-nitrophenyl, where the AY and BX dihedrals are found to be 27.45° and 26.62°, respectively, and not 15° and 15°, as deduced from the coupling constants. Likewise the AX dihedral is 144.5°, according to the X-ray analysis, rather than 157°, as deduced from coupling constants. The Karplus–Conroy curve is a useful guide but is not exact. The coupling constants for the thiazolidino ring

Fig. 3. Experimental and simulated ^{1}H NMR spectra for 5-(4-nitrophenyl)-1-aza-4-oxa-6-thiabicyclo[3.3.0]octane.



were not all the same, and the logic used for the dioxa case led to a simpler analysis. Analysis of the coupling constants for 6-(4-nitrophenyl)-1-aza-6-thia-4-oxabicyclo[3.3.0]octane by the Karplus–Conroy equation leads to the geometries shown:



An X-ray structure was determined for 6-(4-nitrophenyl)-1-aza-6-thia-4-oxabicyclo[3.3.0]octane; see Fig. 4. Again, the five-membered rings are *cis*-fused, and the dihedral angles are in approximate, though not exact, agreement with the values from the Karplus–Conroy analysis.

The X-ray structure revealed an N-C-S anomeric effect; the quaternary carbon–nitrogen bond is shorter relative to the CH_2—N bonds (1.43 Å vs. 1.46 Å or 1.50 Å), and the quaternary carbon–sulfur bond is longer than the CH_2—S bond (1.93 Å vs. 1.80 Å). The X-ray crystal structure data are found in Tables S-1 to S-10.[3]

The mass spectra of the 5-substituted 1-aza-6-thia-4-oxabicyclo[3.3.0]octanes showed more complex fragmentation patterns, as one might expect for the less-symmetrical structures. Once again there were differences in preferred fragmentation pattern for 5-aryl- vs. 5-alkyl-substituted compounds. These results are found in Table 6. The molecular ion is present in greater amount in the sulfur-containing bicyclic acetals. As for the dioxa series, elimination of the

[3] Supplementary data may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada (http://www.nrc.ca/cisti/irm/unpub_e.shtml for information on ordering electronically). CCDC 214681 and 214682 contain the supplementary data for this paper. These data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, U.K.; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

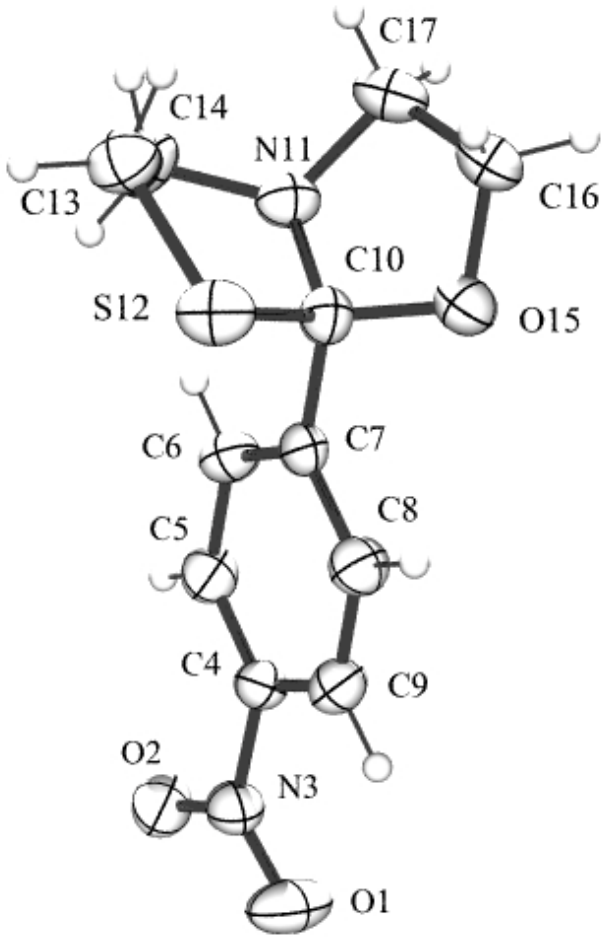
Table 4. Chemical shifts (ppm) for 5-*R*-1-aza-4-oxa-6-thiabicyclo[3.3.0]octanes in $CDCl_3$ (ppm) (Varian Inova 600).

R	A	B	X	Y	A′	B′	X′	Y′
H	4.104	3.947	3.176	2.798	3.122	2.830	3.500	3.054
Me	4.078	3.967	3.230	2.813	3.302	2.921	3.533	3.068
Et	4.053	3.918	3.200	2.816	3.233	2.824	3.509	3.013
i-Pr	4.026	3.884	3.206	2.832	3.183	2.802	3.505	3.026
$MeOCH_2$	4.026	3.930	3.186	2.777	3.137	2.745	3.466	3.002
Ph	4.225	4.029	3.353	3.030	3.346	3.070	3.589	3.211
p-NO_2-Ph	4.217	4.001	3.344	3.058	3.344	3.099	3.623	3.232
p-Cl-Ph	4.207	4.005	3.327	3.018	3.335	3.069	3.567	3.172
p-MeO-Ph	4.213	4.026	3.332	3.009	3.345	3.057	3.552	3.158

Table 5. Coupling constants for 5-*R*-1-aza-4-oxa-6-thiabicyclo [3.3.0] octanes (Hz).

R	$^2J_{AB}$	$^3J_{AX}$	$^3J_{AY}$	$^3J_{BX}$	$^3J_{BY}$	$^2J_{XY}$	$^2J_{A'B'}$	$^3J_{A'X'}$	$^3J_{A'Y'}$	$^3J_{B'X'}$	$^3J_{B'Y'}$	$^2J_{X'Y'}$
H	–7.80	7.58	6.45	6.69	7.65	–9.23	–10.20	4.89	10.20	2.35	5.60	–12.23
Me	–8.03	8.60	7.74	7.55	5.70	–9.15	–10.50	5.57	10.95	1.20	6.15	–12.90
Et	–7.13	7.43	7.56	7.15	7.50	–8.33	–10.20	5.76	10.95	0.00	5.80	–12.60
i-Pr	–7.65	7.35	7.50	7.25	5.57	–9.45	–10.43	5.23	10.88	1.20	5.55	–12.60
$MeOCH_2$	–7.73	7.35	6.60	7.00	7.32	–9.23	–10.43	5.40	10.88	1.28	6.00	–12.83
Ph	–7.73	7.58	7.74	7.60	5.31	–9.68	–10.13	5.49	9.98	2.50	5.90	–12.30
p-NO_2-Ph	–7.73	7.73	7.68	7.65	5.14	–9.98	–9.98	5.52	9.68	3.00	5.80	–12.45
p-Cl-Ph	–7.80	7.50	7.68	7.40	5.06	–9.90	–10.05	5.49	9.75	2.50	6.00	–12.15
p-MeO-Ph	–7.80	7.50	7.80	7.40	5.23	–9.60	–9.48	5.49	9.87	2.45	5.95	–12.83

Fig. 4. Crystal structure of 5-(4-nitrophenyl)-1-aza-4-oxa-6-thiabicyclo[3.3.0]octane.

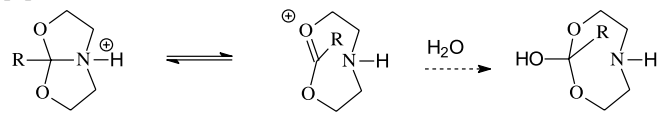


substituent R on C_5 becomes more important as R becomes larger, and ring cleavage is favored when R is an aryl group.

Discussion

As we had hoped, the bicyclic amide acetals and monothioacetals were much easier to purify than the acyclic amide dimethyl acetals and the amide dialkyl monothioacetals, although the bicyclic compounds are still rather sensitive. A range of these compounds has now been prepared, though it proved difficult to prepare even the bicyclic acetals of amides with electron-withdrawing substituents. Although no kinetics were carried out, it is clear that the rate of hydrolysis of these compounds is very sensitive to the nature of the substituent on the 5-carbon, as would be expected, given that this carbon becomes the carbon of an iminium ion during the hydrolysis. It is interesting that the hydrolysis is facile in basic solution, while the corresponding cations (from protonation or alkylation on nitrogen) can be studied in solution (14) or even recrystallized (15). We presume that this is a consequence of the facile reclosure of the cation, resulting from C–N cleavage and the more effective competition by hydroxide to trap the cation from C–O cleavage.

[6]



[7]

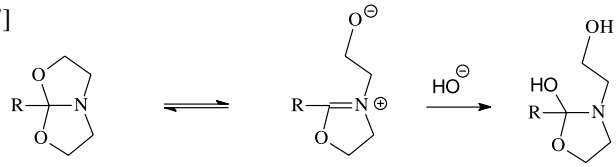


Table 6. MS peak listing of the 5-*R*-1-aza-4-oxa-6-thiabicyclo[3.3.0]octanes.

R	$[M]^+$	$[M - R]^+$	$[M - CH_2S]^+$	$[M - CH_3S]^+$	$[M - C_2H_3S]^+$	
H	131(66)	130(4)	85(70)	84(21)	72(68)	
Me	145(41)	130(6)	99(10)	98(3)	86(31)	
Et	173(49)	130(19)	113(12)	112(23)	100(46)	
i-Pr	173(100)	130(40)	127(4)	126(22)	114(87)	
$MeOCH_2$	175(68)	130(82)	129(l)	128(7)	116(20)	
Ph	207(13)	130(l)	161(3)	160(21)	148(10)	
p-NO_2-Ph	252(21)	130(2)	206(4)	205(20)	193(15)	
p-Cl-Ph	241(18)	130(l)	195(2)	194(12)	182(9)	
p-MeO-Ph	237(2)	130(l)	—	190(l)	178(l)	
R	$[M - C_2H_4S]^+$	$[M - C_2H_3SO]^+$	$[M - C_3H_6SO]^+$	$[RCO]^+$	$[C_3H_4NO]^+$	$[C_3H_6N]^+$
H	71(21)	56(100)	—	—	70(15)	56(100)
Me	85(13)	70(11)	55(36)	—	70(11)	56(100)
Et	99(14)	84(41)	69(21)	57(85)	70(19)	56(100)
i-Pr	113(13)	98(42)	83(10)	71(48)	70(29)	56(92)
$MeOCH_2$	115(3)	100(64)	85(9)	73(2)	70(1)	56(30)
Ph	147(12)	132(l)	117(32)	105(100)	70(2)	—
p-NO_2-Ph	192(8)	177(2)	162(15)	150(100)	70(3)	—
p-Cl-Ph	181(20)	166(l)	151(45)	139(100)	70(3)	—
p-MeO-Ph	177(94)	162(1)	147(100)	135(35)	70(1)	—

We have demonstrated by NMR and X-ray structure determination that both the 5-substituted 1-aza-4,6-dioxabicyclo[3.3.0]octanes and the 5-substituted 1-aza-6-thia-4-oxabicyclo[3.3.0]octanes are *cis* fused, with the ring methylene groups approximately staggered. Examination of the structure of 5-(4-nitrophenyl)-1-aza-4,6-dioxabicyclo[3.3.0]-octane showed no sign of changes in bond lengths attributable to an anomeric effect. All four C—O bonds were essentially the same length, 1.41, 1.41, 1.41, and 1.40 Å, as were all three C—N bonds, 1.47, 1.46, and 1.46 Å. Thus, the bonds that cannot be part of an anomeric effect are the same length as those that, in principle, might be. Consideration of the expected position of the nitrogen lone pair showed that this was not lined up to overlap with the σ* orbital of the C_5—O bond. Since the anomeric effect is attributed to this kind of overlap, the absence of bond length changes becomes reasonable. By contrast, the structure of 5-(4-nitrophenyl)-substituted 1-aza-6-thia-4-oxabicyclo[3.3.0]octane shows definite changes in bond length in the directions expected for an anomeric effect, namely, shortening of the C_5—N bond (1.43 Å vs. 1.46 Å or 1.50 Å) and lengthening of the C_5—S bond (1.80 Å vs. 1.93 Å). There is even a shortening of the C_5—O bond (1.40 Å vs. 1.44 Å). Examination of the structure suggests a dihedral angle between the N lone pair and the C—S bond of 140°. Apparently, this angle, though well short of 180°, is enough to allow for overlap of the lone pair and σ* antibonding orbitals. The longer C—S bonds, relative to C—O bonds, force a loss of symmetry in the bicyclic monothioacetal, and this allows partial overlap of the sort leading to an anomeric effect.

Experimental

General methods

Nuclear magnetic resonance spectra were recorded on a Varian Gemini 200 (^{1}H at 200.1 MHz, ^{13}C at 50.3 MHz), a Varian Gemini 300 (^{1}H at 299.9 MHz, ^{13}C at 75.4 MHz), a Varian Mercury 400 (^{1}H at 400.1 MHz, ^{13}C at 100.6 MHz), a Varian Inova 600 (^{1}H at 599.7 MHz), or a Bruker AMX-500 (University of Ottawa, Ont.) spectrometer (^{1}H at 500.1 MHz, ^{13}C at 125.8 MHz). Mass spectra were recorded on a Finnigan MAT 8200 high-resolution spectrometer. Melting points were recorded on a Gallenkamp melting point apparatus.

Data were collected on a Nonius Kappa-CCD diffractometer (either at the University of Western Ontario or the University of Toronto) using COLLECT software (16). For both compounds, the unit cell parameters were calculated and refined from the full data set. Crystal cell refinement and data reduction were carried out using the Nonius DENZO package (17). The data were scaled using SCALEPACK (18). The SHELXTL 5.1 (19) program package was used to solve the structure by direct methods, followed by successive difference Fouriers. The molecule was very well behaved. All non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were calculated geometrically and were riding on their respective carbon atoms.

Crystals of 5-(*p*-nitrophenyl)-1-aza-4,6-dioxabicyclo-[3.3.0]octane were grown from diethyl ether. A colourless, thin plate was mounted on a glass fibre. Data were collected at low temperature (–73 °C). The crystal data and refinement parameters for $C_{11}H_{12}N_2O_4$ are listed in Table S-1.[3] Interatomic distances and angles are listed in Table S-3. The reflection data and systematic absences were consistent with the monoclinic space group $P2_1/c$. The largest residual electron density peak (0.155 e/A^3) was not associated with anything of significance. Full-matrix least-squares refinement on F^2 gave R_1 = 4.39 and wR_2 = 10.43 at convergence.

Crystals of 5-(*p*-nitrophenyl)-1-aza-4-oxa-6-thiabicyclo-[3.3.0]octane were grown from hexanes. A colourless, thin plate was mounted on a glass fibre and sent to the University

of Toronto. Data were collected at low temperature (–123 °C). The crystal data and refinement parameters for $C_{11}H_{12}N_2O_3S$ are listed in Table S-6. Interatomic distances and angles are listed in Table S-8. The reflection data were consistent with the triclinic space group $P\bar{1}$. The largest residual electron density peak (0.724 e/A^3) was not associated with anything of significance. Full-matrix least-squares refinement on F^2 gave R_1 = 7.94 and wR_2 = 16.88 at convergence.

Materials

1-Aza-4,6-dioxabicyclo [3.3.0] octane

1-Aza-4,6-dioxabicyclo [3.3.0] octane was prepared from diethanolamine (Caledon) and *N*,*N*-dimethylformamide dimethyl acetal (Aldrich) following Arnold and Kornilov (20) in 80.9% yield; bp 68 °C (7.0 torr (1 torr = 133.322 Pa)) (lit. (20) value bp 65 to 66 °C (5 torr)). ^{1}H NMR (400 MHz, $CDCl_3$)[4] δ: 2.90–2.96 (2H, m), 3.16–3.25 (2H, m), 3.77–3.87 (4H, m), 5.80 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 52.53, 64.39, 114.91. Exact mass calcd. for $C_5H_9NO_2$: 115.0633; found: 115.0633.

In the same way were prepared the following two compounds.

1-Aza-4-oxa-6-thiabicyclo[3.3.0]octane

75.8% yield; bp 64 °C (0.050 torr). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.78–2.85 (2H, m), 3.03–3.08 (1H, m), 3.10–3.14 (1H, m), 3.15–3.20 (1H, m), 3.48–3.52 (1H, m),.3.92–3.97 (1H,q), 4.08–4.13 (1H,q). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.08, 49.59, 55.46, 65.37, 106.96. Exact mass calcd. for C_5H_9NOS: 131.0405; found: 131.0398.

5-Methyl-1-aza-4-oxa-6-thiabicyclo[3.3.0]octane

Prepared from from *N*,*N*-dimethylamide dimethyl acetal (21); 90.2% yield; bp 58 °C (0.025 torr). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.81 (3H, s), 2.78–2.85 (1H, m), 2.90–2.95 (1H, m), 3.02–3.12 (1H, m), 3.20–3.35 (2H, m), 3.50–3.58 (1H, m), 3.92–4.02 (1H, q), 4.03–4.12 (1H, q). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.0, 33.8, 50.5, 55.8, 65.7, 119.2. Exact mass calcd. for $C_6H_{11}NOS$: 145.0561; found: 145.0557.

General preparation of 5-substituted-1-aza-4,6-dioxabicyclo[3.3.0]octanes

Diethanolamine (Caledon) (25.0 g, 0.238 mol) and a sliver of sodium metal were placed in a two-necked, round-bottomed flask fitted with a condenser. The system was sealed with the use of septa. An exhaust needle was placed in the septum at the top of the condenser, while a stream of nitrogen was fed through the septum on the neck of the round-bottomed flask. A positive pressure of nitrogen was maintained throughout the remainder of the reaction. A magnetic stirrer and gentle heating with an oil bath (~50 °C) helped dissolve the sodium metal. Once the sodium had completely dissolved, the appropriate nitrile (0.239 mol) was added to the reaction flask with a syringe. The temperature of the oil bath was raised to 100 °C, and the reaction proceeded for 40 h at that temperature. Upon cooling, the reaction mixture was placed in a separatory funnel, and the product was extracted with multiple portions of hexanes. The hexanes were removed by rotary evaporation. The residue was doubly distilled at reduced pressure to give a clear colourless liquid.

In this way were prepared the following five compounds.

5-Methyl-1-aza-4,6-dioxabicyclo[3.3.0]octane

25.5% yield; bp 52 °C (5.0 torr) (lit. (15) value bp 65° (11 torr)). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.49 (3H, s), 2.88–2.96 (2H, m), 3.18–3.26 (2H, m), 3.76–3.83 (2H, m), 3.83–3.90 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.0, 53.0, 64.8, 123.1. Exact mass calcd. for $C_6H_{11}NO_2$: 129.0790; found: 129.0791.

5-Ethyl-1-aza-4,6-dioxabicyclo[3.3.0] octane

17.4% yield; bp 81 °C (9.5 torr) (lit. (15) value bp 72 °C (12 torr)). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96 (3H, t), 1.78 (2H, q), 2.92–3.00 (2H, m), 3.18–3.27 (2H, m), 3.78–3.85 (2H, m), 3.87–3.95 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.7, 30.6, 53.6, 65.0, 125.1. Exact mass calcd. for $C_7H_{13}NO_2$: 143.0946; found: 143.0944.

5-Isopropyl-1-aza-4,6-dioxabicyclo[3.3.0] octane

31.2% yield; bp 86 °C (10 torr). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.97 (3H, s), 0.98 (3H, s), 1.96 (1H, sept), 2.92–2.98 (2H, m), 3.17–3.25 (2H, m), 3.77–3.83 (2H, m), 3.85–3.92 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.4, 35.8, 54.3, 65.2, 126.8. Exact mass calcd. for $C_8H_{15}NO_2$: 157.1103; found: 157.1098.

5-Methoxymethyl-1-aza-4,6-dioxabicyclo[3.3.0] octane

10.1% yield; bp 105 °C (8 torr). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.94–3.00 (2H, m), 3.24–3.31 (2H, m), 3.41 (3H, s), 3.47 (2H, s), 3.84–3.90 (2H, m), 3.92–3.98 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.0, 59.6, 65.2, 73.9, 122.1. Exact mass calcd. for $C_7H_{13}NO_3$: 159.0895; found: 159.0890.

5-Phenyl-1-aza-4,6-dioxabicyclo[3.3.0] octane

17.3% yield; bp 150 °C (5.0 torr) (lit. (15) value bp 79 to 80 °C (0.03 torr)). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.05–3.13 (2H, m), 3.30–3.40 (2H, m), 3.96–4.03 (2H, m), 4.09–4.16 (2H, m), 7.32 (3H, t), 7.61 (2H, d). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.0, 65.7, 123.2, 125.9, 128.1, 128.4, 140.1. Exact mass calcd. for $C_{11}H_{13}NO_2$: 191.0946; found: 191.0943.

5-(*p*-Nitrophenyl)-1-aza-4,6-dioxabicyclo[3.3.0]octane

The experimental procedure followed that of the synthesis of 5-methyl-1-aza-4,6-dioxabicyclo[3.3.0]octane with some modifications. A sliver of sodium metal was dissolved in warm diethanolamine (Caledon) (25.1 g, 0.238 mol), as usual. However, solid *p*-nitrobenzonitrile (Aldrich) (35.0 g, 0.236 mol) was dissolved in 1,4-dioxane (Caledon) prior to addition to the reaction flask. The reaction proceeded for 48 h at 80 °C. Upon removal of the 1,4-dioxane by rotary evaporation, a yellow solid precipitated. The solid was recrystallized from diethyl ether, giving shiny, pale yellow crystals (15.8 g, 28.3% yield); mp 90 to 91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.08–3.14 (2H, m), 3.28–3.38 (2H, m), 3.95–4.00 (2H, m), 4.05–4.14 (2H, m), 7.77 (2H, d), 8.19 (2H, d). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.8, 66.5, 122.4,

[4] Abbreviations used: m, multiplet; s, singlet, d, doublet; t, triplet; q, quartet.

123.9, 127.7, 147.5, 148.1. Exact mass calcd. for $C_{11}H_{12}N_2O_4$: 236.0797; found: 236.0807.

5-(*p*-Chlorophenyl)-1-aza-4,6-dioxabicyclo[3.3.0]octane

Solid *p*-chlorobenzonitrile (Aldrich) (20.0 g, 0.145 mol) was placed in a round-bottomed flask. Enough diethanolamine (Caledon) was added to the reaction flask to completely cover the nitrile. This excess of diethanolamine helped reduce the amount of *p*-chlorobenzonitrile that sublimed onto the upper walls of the reaction flask during the reaction. The round-bottorned flask was fitted with a condenser and kept under an N_2 atmosphere. The oil bath was heated to 50 °C and the reaction proceeded for 4 days. The reaction flask was allowed to cool before addition of hexanes to extract the title compound. Removal of hexanes by rotary evaporation resulted in a white solid that contained the target compound and unreacted nitrile. Recrystallization could not remove all of the nitrile. The white solid was placed in a sublimation apparatus, to take advantage of the willingness of the nitrile to sublime. Reduced pressure (0.025 torr) and very gentle heating removed the nitrile exclusively. The remaining solid was recrystallized in hexanes to give white crystals (2.9 g, 8.9% yield); mp 43–45 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.05–3.12 (2H, m), 3.29–3.37 (2H, m), 3.94–4.00 (2H, m), 4.06–4.13 (2H, m), 7.30 (2H, d), 7.53 (2H, d). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.0, 65.8, 122.8, 127.6, 128.1, 134.3, 138.8. Exact mass calcd. for $C_{11}H_{12}NO_2Cl$: 225.0557; found: 225.0557.

5-Trifluoromethyl-1-aza-4,6-dioxabicyclo[3.3.0]octane

A sliver of sodium metal was dissolved in diethanolamine (Caledon) (28.7 g, 0.273 mol) and placed in a 300 cc Parr Instruments bomb. The bomb was placed into a dry ice – acetone bath to lower the temperature of the bomb and its contents to –78 °C. At that temperature, the contents of the bomb solidified. Freshly prepared, condensed trifluoroacetonitrile (prepared from trifluoroacetamide (22)) (~30 mL, ~0.316 mol) was poured into the chilled bomb. The bomb was then immediately sealed. Undoubtedly some trifluoroacetonitrile was lost during this crude transfer. The bomb was placed into its temperature controller and set to 70 °C. The temperature inside the bomb rose dramatically, requiring cooling of the bomb. Once the temperature was brought under control, the bomb was adjusted to 70 °C where it remained for 48 h. At the end of the reaction period, the bomb was flushed with nitrogen before opening to ensure removal of any remaining trifluoroacetonitrile. Inside the bomb was an orange viscous liquid that was mainly unreacted diethanolamine. Extraction with hexanes resulted in pure 5-trifluoromethyl-1-aza-4,6-dioxabicyclo[3.3.0]octane. The liquid crystallized on its own after sitting on the bench for 2 weeks. Recrystallization from hexanes resulted in translucent crystals (0.25 g, 0.5% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.01–3.09 (2H, m), 3.31–3.40 (2H, m), 3.99–4.06 (2H, m), 4.07–4.15 (2H, m). ^{19}F NMR (300 MHz, $CFCl_3$) δ: 83.0. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 52.5, 66.7, 120.5, 123.3. Exact mass calcd. for $C_6H_8NO_2F_3$: 183.0505; found: 183.0503.

5-Dichloromethyl-1-aza-4,6-dioxabicyclo[3.3.0] octane

The experimental procedure followed that of the synthesis of 5-methyl-1-aza-4,6-dioxabicyclo[3.3.0]octane, with some modifications. Diethanolamine (Caledon) (12.5 g, 0.119 mol) and 75 mL of 1,4-dioxane (Caledon) were placed in the reaction flask with *no catalyst*. Caution: The standard reaction of 1:1 amine:nitrile with sodium catalyst in the absence of solvent resulted in an explosion. Dichloroacetonitrile (Aldrich) (10.0 mL, 0.125 mol) was added slowly to the reaction flask with a syringe. Once the nitrile was completely added, the oil bath was heated gently until it reached 50 °C. The evolution of ammonia appeared to be very rapid, so heating was stopped. The reaction continued at room temperature for 48 h. The 1,4-dioxane solvent was removed by rotary evaporation, leaving a thick residue. It was placed in a separatory funnel for extraction with hexanes. A white solid precipitated in the separatory funnel when hexanes were added. Recrystallization with hexanes resulted in white shiny flakes (5.65 g, 24.0% yield); mp 62 to 63 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.02–3.10 (2H, m), 3.42–3.51 (2H, m), 4.02–4.14 (4H, m), 5.75 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 54.3, 67.2, 74.0, 123.4. Exact mass calcd. for $C_6H_9NO_2Cl_2$: 197.0009; found:. 197.0007.

5-Ethyl-1-aza-4-oxa-6-thiabicyclo[3.3.0]octane

With some heating, a sliver of sodium metal (Aldrich) was dissolved in freshly prepared 2-(2-mercaptoethyl)-aminoethanol (20.0 g, 0.165 mol) in a round-bottomed flask. Propionitrile (Aldrich) (25 mL, 0.328 mol) was added to the reaction flask and allowed to stir for 2 weeks at room temperature under an N_2 atmosphere. It was found that an excess of nitrile made the consistency of the final reaction mixture easier to handle. An extraction with diethyl ether removed the title compound and its corresponding oxazoline. The mixture was doubly distilled at reduced pressure to give a clear colorless fraction (3.5 g, 13.3% yield); bp 50 °C (0.025 torr). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05 (3H, t), 1.99 (2H, m), 2.80–2.88 (2H, m), 2.99–3.09 (1H, m), 3.19–3.29 (2H, m), 3.48–3.57 (1H, m), 3.92 (1H, q), 4.05 (1H, q). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.9, 33.0, 37.0, 51.0, 56.0, 65.5, 123.3. Exact mass calcd. for $C_7H_{13}NOS$: 159.0718; found: 159.0717.

In the same way were prepared the following three compounds.

5-Isopropyl-1-aza-4-oxa-6-thiabicyclo[3.3.0]octane

14.3% yield; bp 53 °C (0.025 torr). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.00 (3H, d), 1.10 (3H, d), 2.06 (1H, sept), 2.78–2.88 (2H, m), 2.98–3.08 (1H, m), 3.14–3.25 (2H, m), 3.47–3.55 (1H, m), 3.90 (1H, q), 4.03 (1H, q). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.1, 18.5, 32.8, 40.2, 52.0, 56.9, 65.8, 126.4. Exact mass calcd. for $C_8H_{15}NOS$: 173.0874; found: 173.0878.

5-Methoxymethyl-1-aza-4-oxa-6-thiabicyclo[3.3.0]octane

19.0% yield; bp 73 °C (0.025 torr). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.75–2.86 (2H, m), 3.00–3.12 (1H, m), 3.15–3.27 (2H, m), 3.40 (3H, s), 3.48–3.55 (1H, m), 3.58 (2H, s), 3.98 (1H, q), 4.08 (1H, q). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 32.0, 51.0, 56.0, 60.0, 66.0, 76.5, 120.0. Exact mass calcd. for $C_7H_{13}NO_2S$: 175.0667; found: 175.0671.

5-Phenyl-1-aza-4-oxa-6-thiabicyclo[3.3.0]octane

The product mixture, after extraction, was distilled at reduced pressure only to remove the by-product, 2-phenyl-

oxazoline (~80 °C at 0.25 torr), leaving relatively pure bicyclic amide acetal in the still-pot. The contents of the still-pot were dissolved in diethyl ether and placed in a freezer. After 5 days, a solid had precipitated and was recrystallized, giving white shiny flakes (12.6% yield); mp 46–48 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.96–3.05 (2H, m), 3.14–3.20 (1H, m), 3.28–3.34 (2H, m), 3.53–3.57 (1H, m), 4.00 (1H, q), 4.19 (1H, q), 7.27 (1H, t), 7.32 (2H, t), 7.63 (2H, d). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 33.74, 50.77, 56.37, 65.16, 120.00, 127.86, 142.92. Exact mass calcd. for $C_{11}H_{13}NOS$: 207.0718; found: 207.0723.

5-(*p*-Nitrophenyl)-1-aza-4-oxa-6-thiabicyclo[3.3.0]octane

With some heating, a sliver of sodium metal was dissolved in freshly prepared 2-(2-mercaptoethyl)-aminoethanol (20.0 g, 0.165 mol) in a round-bottomed flask. In a separate flask, solid *p*-nitrobenzonitrile (Aldrich) (24.5 g, 0.165 mol) was dissolved in 1,4-dioxane (Caledon). The nitrile solution was then added to the reaction flask. The reaction mixture was allowed to stir for 2 weeks at room temperature under an N_2 atmosphere. At the end of the reaction period, rotary evaporation was used to remove the 1,4-dioxane solvent. Diethyl ether was used to extract the title compound from the residue. The ethereal solution was placed in the freezer to facilitate crystallization. Within a short period of time, a yellow solid formed, which was collected and recrystallized from ether to give shiny, pale yellow flakes (5.4 g, 13.0% yield); mp 75 to 76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.05–3.15 (2H, m), 3.20–3.29 (1H, m), 3.33–3.40 (2H, m), 3.61–3.68 (1H, m), 4.02 (1H, q), 4.23 (1H, q), 7.75 (2H, d), 8.18 (2H, d). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.8, 51.8, 57.8, 65.8, 119.0, 124.0, 127.0, 147.9, 150.2. Exact mass calcd. for $C_{11}H_{12}N_2O_3S$: 252.0569; found: 252.0565.

5-(*p*-Chlorophenyl)-1-aza-4-oxa-6-thiabicyclo[3.3.0]octane

The experimental procedure followed that of the synthesis of 5-(*p*-nitrophenyl)-1-aza-4-oxa-6-thiabicyclo[3.3.0]octane, using freshly prepared 2-(2-mercaptoethyl)-aminoethanol (20.0 g, 0.165 mol) and *p*-chlorobenzonitrile (Aldrich) (25.1 g, 0.183 mol) dissolved in 1,4-dioxane. When the ethereal solution from the extraction was placed in the freezer, white needle-like crystals formed. These were later confirmed to be *p*-chlorophenyl-oxazoline. Several attempts at recrystallization successively removed less and less oxazoline. The product mixture still contained oxazoline. Since the oxazoline had a lower boiling point than the bicyclic amide monothioacetal, sublimation was used in a final attempt to remove the oxazoline. The sublimation was carried out under reduced pressure (0.025 torr) with very gentle heating. Before long, the cold finger of the sublimation apparatus was coated with a white solid. The remaining colorless liquid in the sublimation apparatus was determined to be 94% pure by NMR (4.2 g, 10.5% yield). Repeated attempts at sublimation provided no improvement in the purity of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.98–3.11 (2H, m), 3.14–3.22 (1H, m), 3.28–3.38 (2H, m), 3.54–3.61 (1H, m), 4.02 (1H, q), 4.21 (1H, q), 7.28 (2H, d), 7.55 (2H, d). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.01, 51.0, 56.6, 65.5, 119.4, 127.2, 128.3, 133.8, 141.7. Exact mass calcd. for $C_{11}H_{12}ClNOS$: 241.0328; found: 241.0326.

5-(*p*-Methoxyphenyl)-1-aza-4-oxa-6-thiabicyclo[3.3.0]octane

The experimental procedure followed that of the synthesis of 5-(*p*-chlorophenyl)-1-aza-4-oxa-6-thiabicyclo[3.3.0]octane, using freshly prepared 2-(2-mercaptoethyl)-aminoethanol (22.5 g, 0.186 mol) and *p*-methoxybenzonitrile (Aldrich) (25.7 g, 0.193 mol). After sublimation of the product mixture, the remaining colorless liquid was determined to be 90% title compound and 10% *p*-methoxyphenyl-oxazoline (3.4 g, 7.7% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.96–3.07 (2H, m), 3.07–3.20 (1H, m), 3.27–3.37 (2H, m), 3.50–3.60 (1H, m), 3.78 (3H, s), 4.02 (1H, q), 4.20 (1H, q), 6.82 (2H, d), 7.55 (2H, d). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.0, 51.5, 55.5, 56.5, 66.0, 120.4, 127.5, 130.0. Exact mass calcd. for $C_{12}H_{15}NO_2S$: 237.0824; found: 237.0825.

2-(2-Mercaptoethyl)aminoethanol

This procedure was based on a preparation of *N*-(2-methoxyethyl)-*N*-(2-mercaptoethyl)amine (23). Ethanolamine (Aldrich) (25.0 g, 0.409 mol) and 200 mL of 1,4-dioxane (Caledon) were added to a two-necked, round-bottomed flask. A condenser and a dropping funnel, containing roughly 25 mL of 1,4-dioxane, were connected to the round-bottomed flask. Septa were used to seal the system. An exhaust needle was placed in one septum, while nitrogen was introduced through the other. The contents were warmed to a temperature just below that at which refluxing occurred. At this point, ethylene sulfide (Aldrich) (25.0 g, 0.416 mol) was transferred with the use of a cannula to the dropping funnel that contained dioxane. Once transfer was completed, the dropping funnel was opened to allow the dioxane solution containing ethylene sulfide to be added dropwise. On completion of the addition, the reaction mixture was allowed to reflux for 6 h. The reaction mixture was allowed to cool before removal of the dioxane by rotary evaporation. The residue was immediately distilled under reduced pressure. If the residue was not distilled immediately (for instance, if it were distilled the following day), a noticeable reduction in yield was observed. The distillate collected was a clear, colorless liquid and, on occasion, a white solid when returned to atmospheric pressure (23.7 g, 47.8% yield); bp 50 °C (0.050 torr) (lit. (24) value bp 66–69 °C (0.03 torr)). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.97 (3H, br s), 2.66 (2H, t), 2.76 (2H, t), 2.81 (2H, t), 3.63 (2H, t). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.0, 50.4, 51.6, 60.9. Exact mass calcd. for $C_4H_{11}NOS$: 121.0561; found: 121.0558.

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