# Conformational Analysis of Methylthiazanes: The Problem of the Me–C–N–Me *Gauche* Interaction

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The position of conformational equilibria in 2- and 3-methyl-1,4-thiazanes and *cis*- and *trans*-2,3-dimethyl-1,4-thiazanes, their *N*-methyl derivatives, and several of the corresponding sulfoxides and sulfones have been measured. The $\Delta G°$ values for the methyl groups are generally in agreement with what one would expect on the basis of known conformational equilibria in methylthianes, methylpiperidines, and *N*-methylated homologs of the latter; however, the differences in $\Delta G°$ between the 2-methyl and *N*,2-dimethyl homologs are even larger than in the piperidine series. An explanation for these differences is based on MM3 force field calculations of molecular geometry. The sulfoxide and sulfone data throw light on SO/H and SO/Me *syn*-axial as well as SO/Me *gauche* interactions.

## Introduction

While there is an extensive body of data on conformational equilibria in methyl-substituted monohetero- and 1,3-dihetero-substituted cyclohexanes,[2] corresponding data on 1,4-dihetero-substituted analogs are more limited. We have previously reported results in the 1,4-oxathiane series,[3] and data have recently become available for 1,4-dithianes.[4] In this paper we report a conformational study of methyl- and 2,3-dimethyl-substituted 1,4-thiazanes and some of their derivatives (*N*-methyl, sulfoxides, sulfones) by low-temperature $^{13}C$ NMR spectroscopy.

## Synthesis

The 2- and 3-methylthiazanes (**7** and **9**) were prepared from 2-aminoethanethiol hydrochloride and 2-chloroacetone or ethyl 2-bromopropionate, respectively (Scheme I). The synthesis of *cis*- and *trans*-2,3-dimethyl-1,4-thiazanes (**16** and **18**) from *cis*- or *trans*-2-butene has been reported elsewhere.[5] The thiazanes were *N*-methylated following standard procedures; oxidation at sulfur to sulfoxides or sulfones was accomplished with sodium periodate or *m*-chloroperbenzoic acid using 1 mol or excess of oxidizing agent, respectively.

## Low-Temperature $^{13}C$ NMR Spectra: Configurational and Conformational Assignments

For the sake of brevity, we have included in Tables I (chemical shifts) and II (equilibrium constants) low-temperature data for only those systems, depicted in Scheme I, which are not conformationally homogeneous; Scheme II depicts the two conformers in equilibrium for all compounds.

From the observed $^{13}C$ chemical shifts of compounds **3**, **4**, and **8–10** (see Scheme II) we have obtained values of the shift parameters $\Delta\delta$ (in brackets in Table I) for equatorial and axial SO and 2- or 3-Me groups relative to unsubstituted thiazane **1** ($\delta_{C(2,6)}$ = 47.3, $\delta_{C(3,5)}$ = 27.8 ppm) and *N*-methylthiazane **2** ($\delta_{C(2,6)}$ = 55.7, $\delta_{C(3,5)}$ = 26.9 ppm). The effect of the two oxygens in sulfones ($\Delta\delta_{C(2,6)}$ = −4.9, $\Delta\delta_{C(3,5)}$ = +25.7 ppm) was computed by subtracting the $^{13}C$ chemical shifts of *N*-methylthiazane **2** from those of its *S*,*S*-dioxide **6** ($\delta_{C(2,6)}$ = 50.8, $\delta_{C(3,5)}$ = 52.6 ppm). The measured $\Delta\delta$'s, which were all similar to values found in the literature for analogous compounds,[6,7] were used to compute the expected chemical shifts (in parentheses) for the remainder of the compounds in Table I. The assignment of the signals were based both on these calculated values and, where appropriate, on DEPT experiments; the calculated chemical shifts also aided in the configurational assignment of epimeric sulfoxides.

The configurations and conformations of the studied compounds follow from their synthesis and from the general proposition that compounds with axial- or *gauche*-disposed substituents have upfield shifts of most of their $^{13}C$ signals relative to their equatorially or *anti*-substituted epimers or conformers. For compounds **16**, **17**, and **21t** we note that while the calculated and experimental shifts at C(2) and C(3) often disagree quantitatively (although the relative trend is correct)—presumably because "vicinal effects"[6] were not taken into account—agreement at C(5) and C(6) is satisfactory and the upfield shifts of the respective axial methyl substituents relative to the corresponding equatorial ones support the assignment. Compound **21c**, which otherwise shows some irregularities, is characterized by a large upfield shift at C(6) (13.5 ppm) in conformer 1 relative to 2; this would be expected on the basis of the two $\gamma_a$ effects (from SO and 2-Me) in conformer

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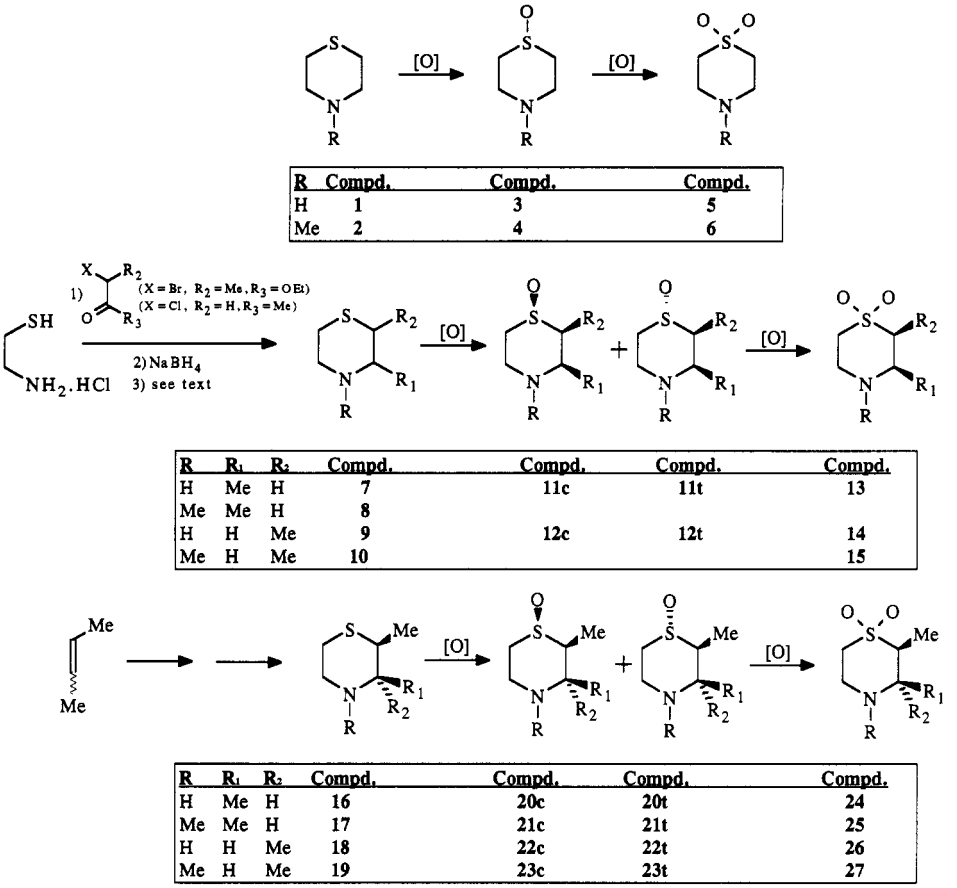
## Scheme I




| R | Compd. | Compd. | Compd. |
|---|---|---|---|
| H | 1 | 3 | 5 |
| Me | 2 | 4 | 6 |

| R | R1 | R2 | Compd. | Compd. | Compd. | Compd. |
|---|---|---|---|---|---|---|
| H | Me | H | 7 | 11c | 11t | 13 |
| Me | Me | H | 8 | | | |
| H | H | Me | 9 | 12c | 12t | 14 |
| Me | H | Me | 10 | | | 15 |

| R | R1 | R2 | Compd. | Compd. | Compd. | Compd. |
|---|---|---|---|---|---|---|
| H | Me | H | 16 | 20c | 20t | 24 |
| Me | Me | H | 17 | 21c | 21t | 25 |
| H | H | Me | 18 | 22c | 22t | 26 |
| Me | H | Me | 19 | 23c | 23t | 27 |

**Table I. Low-Temperature (173–203 K) Chemical Shifts (ppm, $CH_2Cl_2$) of Selected Thiazanes Studied in This Work (Schemes I and II)[a]**

| compd (conf.)[b] | C(2) | C(3) | C(5) | C(6) | 2-Me | 3-Me |
|---|---|---|---|---|---|---|
| **3** (1, major) | 35.0 [−12.3] | 43.9 [+16.1] | | | | |
| **3** (2, minor) | 42.4 [−4.9] | 51.3 [+23.5] | | | | |
| **4** (1, major) | 45.1* [−11.3] | 44.4* [+18.2] | | | | |
| **4** (2, minor) | 52.7* [−5.0] | 50.7* [+25.8] | | | | |
| **8** (1, minor) | 52.5 [−3.2] | 33.8 [+6.9] | 27.2 [+0.3] | 46.4 [−9.3] | | 6.1 |
| **8** (1, major) | 59.4 [+3.7] | 33.8 [+6.9] | 27.2 [+0.3] | 57.3 [+1.8] | | 20.2 |
| **9** (1, minor) | 51.7 [+4.4] | − (27.9) | 22.7 [−5.1] | 48.5 [+1.2] | | 11.4 |
| **9** (2, major) | 55.7 [+8.4] | 36.7 [+8.9] | 28.7 [+0.9] | 47.0 [−0.3] | | 18.4 |
| **10** (1, minor) | 61.6 [+5.9] | 32.0 [+5.1] | 22.7 [−4.2] | 56.3 [+0.6] | | 11.2 |
| **10** (2, major) | 63.6 [+7.9] | 35.1 [+8.2] | 27.2 [+0.3] | 54.8 [−0.9] | | 18.3 |
| **12t** (1, minor) | 40.6* (39.4) | 47.1 (44.0) | 39.4* (38.8) | 35.5 (36.2) | | 11.3 |
| **12t** (2, major) | 49.6* (50.8) | 58.6 (60.2) | 51.4* (52.2) | 43.1 (42.1) | | 12.9 |
| **14** (1, minor) | 49.7 (48.9) | 56.0 (53.3) | 47.6 (48.1) | 45.3 (45.7) | | 12.3 |
| **14** (2, major) | 52.3* (52.9) | 57.4 (62.1) | 51.7* (51.1) | 45.3 (44.2) | | 6.9 |
| **15** (1, minor) | 54.6 (56.7) | 57.6 (57.7) | 45.9 (48.4) | 54.0 (51.4) | | 13.5 |
| **15** (2, major) | 54.7 (58.7) | 59.0 (60.8) | 52.4 (52.9) | 50.0 (49.9) | | 7.2 |
| **16** (1, minor) | 52.0 (52.5) | 40.8 (43.6) | 29.3 (29.0) | 39.0 (37.7) | 11.0 | 18.9 |
| **16** (2, major) | 56.3 (55.4) | 36.7 (34.8) | 21.9 (23.0) | 48.8 (50.3) | 21.4 | 13.7 |
| **17** (1, major) | 57.7 (60.4) | 40.7 (42.0) | 29.0 (27.5) | 45.5 (45.5) | 1.6 | 18.0 |
| **17** (2, minor) | 62.6 (65.3) | 38.0 (38.9) | 22.5 (23.0) | 58.3 (57.9) | 19.8 | 13.7 |
| **19** (1, minor) | 57.5 (58.4) | 38.8 (38.9) | 22.3 (23.0) | 46.1 (47.0) | 8.2 | 19.8 |
| **19** (2, major) | 66.2 (67.3) | 39.2 (42.0) | 27.3 (27.5) | 57.5 (56.4) | 18.2 | 15.6 |
| **21c** (1, minor) | 45.2 (46.4) | 53.7 (58.9) | 50.6 (47.2) | 36.4 (34.2) | 6.1 | 14.6 |
| **21c** (2, major) | 54.3 (57.6) | 58.4 (63.8) | 44.5 (48.3) | 50.9 (53.3) | 19.6 | 1.4 |
| **21t** (1, minor) | 60.3* (52.7) | 60.9* (66.7) | 52.8 (54.8) | 42.9 (40.5) | 5.9 | 13.3 |
| **21t** (2, major) | 50.9 (51.3) | 54.0 (56.2) | 39.9 (40.7) | 46.6 (47.0) | 18.0 | 8.2 |
| **25** (1, minor) | 56.3 (52.8) | 59.6 (66.4) | 49.1 (54.7) | 44.6 (40.6) | 3.9 | 7.2 |
| **25** (2, major) | 58.2* (57.7) | 59.6* (63.7) | 46.0 (48.2) | 53.2 (53.4) | 18.9 | 8.2 |

[a] The numbers in brackets for compounds **3**, **4**, and **8**–**10** are the $^{13}C$ additive parameters for SO, 2Me, and 3Me substituents. The numbers in parentheses for the rest of the compounds are the calculated $^{13}C$ chemical shifts (see text). Asterisks indicate that the pertinent signals may be interchanged. The *N*-methyl derivatives displayed the *N*-Me resonances at 41–44 ppm. [b] Conformations 1 and 2 as shown in Scheme II; major and minor indicate the predominant conformation.

1. Moreover, the methyl groups in **21c** were unequivocally assigned as Me(2) and Me(3), respectively, by a combination of proton coupling and $^1H/^{13}C$ heterocor 2D experiments; their chemical shifts clearly support axial 2-Me in conformer 1 and axial 3-Me in conformer 2. The same identification of methyl groups was made in com-

**Table II. Thermodynamic Parameters of Selected Thiazanes Studied in This Work (Schemes I and II)**

| entry | compd | solvent | $T$ (K) | $N^a$ | $K = [2]/[1]^b$ | $\Delta G°$ (kcal/mol) |
|---|---|---|---|---|---|---|
| 1 | **3** | $CD_2Cl_2$ | 183 | 2 | 0.52 ± 0.03 | −0.23 ± 0.02 |
| 2 | **4** | $CD_2Cl_2$ | 183 | 2 | 0.10 ± 0.00 | −0.84 ± 0.01 |
| 3 | **9** | $CD_2Cl_2$ | 193 | 3 | 40.17 ± 7.25 | 1.41 ± 0.07 |
| 4 | **10** | $CD_2Cl_2$ | 183 | 5 | 45.37 ± 14.17 | 1.37 ± 0.12 |
| 5 | **12t** | $CD_2Cl_2$ | 193 | 4 | 12.01 ± 1.56 | 0.95 ± 0.05 |
| 6 | **14** | $CD_2Cl_2$ | 183 | 3 | 20.23 ± 2.76 | 1.09 ± 0.05 |
| 7 | **15** | $CD_2Cl_2$ | 193 | 5 | 16.76 ± 3.63 | 1.07 ± 0.08 |
| 8 | **8** | $CD_2Cl_2$ | 173 | 2 | 13.71 ± 1.06 | 0.90 ± 0.03 |
| 9 | **16** | $CD_2Cl_2$ | 183 | 5 | 11.03 ± 1.19 | 0.87 ± 0.04 |
| 10 | | acetone-$d_6$ | 183 | 5 | 9.32 ± 2.52 | 0.77 ± 0.07 |
| 11 | | $CD_3OD$ | 183 | 6 | 3.46 ± 0.79 | 0.45 ± 0.08 |
| 12 | **17** | $CD_2Cl_2$ | 183 | 6 | 0.14 ± 0.02 | −0.72 ± 0.01 |
| 13 | | acetone-$d_6$ | 203 | 5 | 0.17 ± 0.03 | −0.72 ± 0.01 |
| 14 | | $CD_3OD$ | 183 | 6 | 0.06 ± 0.01 | −1.03 ± 0.06 |
| 15 | **19** | $CD_2Cl_2$ | 163 | 5 | 3.56 ± 0.76 | 0.40 ± 0.07 |
| 16 | | acetone-$d_6$ | 173 | 3 | 1.56 ± 0.19 | 0.15 ± 0.04 |
| 17 | | $CD_3OD$ | 173 | 3 | 22.90 ± 1.36 | 1.08 ± 0.02 |
| 18 | **21c** | $CD_2Cl_2$ | 193 | 3 | 3.40 ± 0.44 | 0.47 ± 0.05 |
| 19 | | acetone-$d_6$ | 193 | 4 | 5.42 ± 0.67 | 0.65 ± 0.05 |
| 20 | | $CD_3OD$ | 193 | 3 | 1.97 ± 0.05 | 0.26 ± 0.01 |
| 21 | **21t** | $CD_2Cl_2$ | 193 | 3 | 5.66 ± 0.43 | 0.66 ± 0.03 |
| 22 | | acetone-$d_6$ | 193 | 4 | 7.41 ± 0.89 | 0.77 ± 0.05 |
| 23 | | $CD_3OD$ | 193 | 4 | 5.04 ± 0.73 | 0.62 ± 0.06 |
| 24 | **25** | $CD_2Cl_2$ | 203 | 5 | 3.34 ± 0.67 | 0.48 ± 0.08 |
| 25 | | acetone-$d_6$ | 203 | 5 | 4.12 ± 1.03 | 0.56 ± 0.10 |
| 26 | | $CD_3OD$ | 203 | 4 | 2.36 ± 0.39 | 0.34 ± 0.07 |

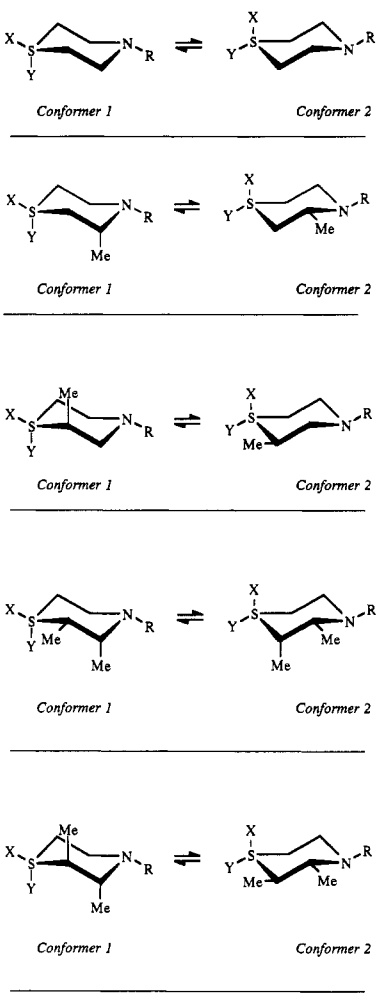
[a] Number of pairs of signals integrated to compute $K$. [b] See Scheme II for conformations 1 and 2.

pound **25** whose ring carbon shifts [again with the possible exception of C(6)] are less than conclusive. Here, again, the large upfield shift of Me(2) identifies it as belonging to conformer 1; Me(3) displays little difference in the two conformers: while it is axial in conformer 3, it has only two *gauche* partners in this conformer whereas the equatorial Me(3) in conformer 1 has three such partners.

## Conformational Free Energies

The conformational energy of 3-Me in 1,4-thiazane, calculated from appropriate signal areas in the low-temperature $^{13}C$ NMR spectra of the two conformers of **9** and **10** (Scheme II), amounts to 1.39 kcal/mol (mean values of entries 3 and 4 of Table II) which is very close to the value of 1.28 kcal/mol expected, based on the known Me/H *syn*-axial interactions in 2-methylthiane (0.55 kcal/mol[8]) and in *N*,3-dimethylpiperidine (0.73 kcal/mol[9]), both present in conformer 1 (Scheme II) of compounds **9** and **10**. The axial SO/H/H interaction in 1,4-thiazane *S*-oxide in $CD_2Cl_2$ is −0.23 kcal/mol (entry 1, Table II), meaning that axial SO is preferred, similarly to the situation in the *S*-oxides of thiane and oxathiane[10] (−0.14 and −0.68 kcal/mol, respectively). Then, comparing the conformational energies of 3-Me in **9** (1.41 kcal/mol) plus SO (−0.23 kcal/mol) with the experimental $-\Delta G°$ value of **12t** (0.95 kcal/mol), one may ascribe the difference of 0.23 kcal/mol to the $(Me/OS)_{gauche}$ interaction present in conformer 2 of **12t**. Similarly, from the averaged data for the sulfones **14** and **15** (Table II, entries 6 and 7) one can calculate the $(Me/OSO)_{gauche}$ interaction, since the conformations with axial and equatorial 3-Me (Scheme II) differ by one such

**Scheme II**




| Compd. | R | X | Y |
|---|---|---|---|
| **3** | H | : | O |
| **4** | Me | : | O |
| **5**[a] | H | O | O |
| **6**[a] | Me | O | O |

| Compd. | R | X | Y |
|---|---|---|---|
| **7**[b] | H | : | : |
| **8** | Me | : | : |
| **11c**[b] | H | : | O |
| **11t**[b] | H | O | : |
| **13**[b] | H | O | O |

| Compd. | R | X | Y |
|---|---|---|---|
| **9** | H | : | : |
| **10** | Me | : | : |
| **12c**[b] | H | O | : |
| **12t** | H | : | O |
| **14** | H | O | O |
| **15** | Me | O | O |

| Compd. | R | X | Y |
|---|---|---|---|
| **16** | H | : | : |
| **17** | Me | : | : |
| **20c**[b] | H | : | O |
| **20t**[b] | H | O | : |
| **21c** | Me | : | O |
| **21t** | Me | O | : |
| **24**[b] | H | O | O |
| **25** | Me | O | O |

| Compd. | R | X | Y |
|---|---|---|---|
| **18** | H | : | : |
| **19** | Me | : | : |
| **22c**[b] | H | O | : |
| **22t**[b] | H | : | O |
| **23c**[b] | Me | O | : |
| **23t**[b] | Me | : | O |
| **26**[b] | H | O | O |
| **27**[b] | Me | O | O |

[a] Degenerated equilibrium.
[b] Only conformer 2 was observed.

interaction (it is assumed that the $Me_a/SO_e$ and $Me_e/SO_a$ interactions are essentially identical). The result is 1.39 − 1.08 = 0.31 kcal/mol, slightly higher than the same interaction in sulfoxides. The difference is reasonable considering that the S–O bond in sulfones is slightly shorter than that in sulfoxides. The *cis* sulfoxide **12c** is essentially monoconformational with 3-Me equatorial, SO axial (conformer 2, Scheme II). This is as expected, since the alternative conformer 1 (Scheme II), with axial 3-Me (1.41 kcal/mol) and equatorial SO (0.23 kcal/mol), should be less stable by *ca.* 1.6 kcal/mol, which exceeds the detection limit of the low-temperature NMR technique used here.

The conformational energy of 2-Me cannot be extracted from the spectrum of **7** since this compound was found to be essentially conformationally homogeneous at low temperature. From the available literature data [*syn*-axial 2-Me/6-H in 2-methylpiperidine, 1.63 kcal/mol, and $(Me/S)_{gauche}$ in 3-methylthiane, 0.53 kcal/mol], we may estimate the conformational $-\Delta G°_{2\text{-Me}}$ value in **7** to be 2.13 kcal/mol. However, the conformational equilibrium of **8**, the *N*-methyl derivative of **7**, is much less biased ($-\Delta G°$ = 0.90 kcal/mol; entry 8, Table II), *suggesting that the conformational energy of 2-Me in 2-methyl-1,4-thiazane may be lowered by as much as 1.2 kcal/mol when the nitrogen is methylated.* The difference in $-\Delta G°$ values between compounds **16** and **17**, this time based solely on experimental data (entries 9 and 12, Table II), is even greater: 0.87 − (−0.72) = 1.59 kcal/mol in $CD_2Cl_2$. Com-

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**Table III. Torsion Angles ω Calculated by MM3 about the Ring Me–C–C–Me and Me–C(2)–N–Me Bonds of 1,2-Dimethylcyclohexane, Piperidines, and 1,4-Thiazanes**

| entry | compd[a] | $\omega_{MeCCMe}$ (conformer) | | $\omega_{MeCNMe}$ (conformer)[b] | | $\Delta\Delta G°$[c] |
|---|---|---|---|---|---|---|
| 1 | 1,2-DMC | 60.3 (1*e*,2*e*) | 55.1 (1*e*,2*a*) | | | |
| 2 | *trans*-*N*,2,4-TMP | | | 58.1 (2*e*) | 62.1 (2*a*) | 0.63 |
| 3 | *cis*-*N*,2,5-TMP | | | 57.7 (2*e*) | 62.5 (2*a*) | 0.75 |
| 4 | *cis*-*N*,2,3-TMP | 58.1 (2*e*,3*a*) | 56.2 (2*a*,3*e*) | 53.7 (2*e*) | 63.8 (2*a*) | 0.62 |
| 5 | 8 | | | 55.0 (2*e*) | 64.8 (2*a*) | 1.10 |
| 6 | 17 | 62.8 (2*e*,3*a*) | 60.3 (2*a*,3*e*) | 50.8 (2*e*) | 66.1 (2*a*) | 1.60 |
| 7 | 19 | 54.6 (2*e*,3*e*) | 170.0 (2*a*,3*a*) | 52.7 (2*e*) | 67.1 (2*a*) | 2.20 |

[a] Name conventions: DMC, dimethylcyclohexane; TMP, trimethylpiperidine; for compounds 8, 17, and 19 see Schemes I and II. [b] *N*-Me group is always equatorial. [c] Experimental differences (kcal/mol) in conformational energies of 2-methyl NH and NMe compounds (see text).

pound 18 is conformationally homogeneous, but its $-\Delta G°$ value may be estimated as *ca.* 2.78 kcal/mol [axial 2Me + axial 3Me − $(Me/Me)_{gauche}$ = 2.13 + 1.39 − 0.74),[11] which suggests that the difference between it and its *N*-methyl derivative 19 in $CD_2Cl_2$ ($-\Delta G°$ = 0.47 kcal/mol; entry 18, Table II) may be the highest (2.31 kcal/mol) in the series 7/8, 16/17, and 18/19. Presumably, the effect responsible for these differences (NH *vs* NMe) is the dissimilarity between $(Me–C–N–Me)_{gauche}$ interactions in conformers with equatorial and axial 2-methyl substituents, respectively, the *gauche* interaction being substantially greater in the former. This difference was earlier seen in piperidines,[9] but is considerably smaller there (*ca.* 0.62–0.75 kcal/mol) than in 1,4-thiazanes (1.2–2.3 kcal/mol).

To gain some insight into this effect, we have undertaken molecular mechanics calculations (MM3)[12] of optimized structures of appropriately substituted piperidines and 1,4-thiazanes. The results concerning the torsion angles Me–C(2)–N–Me(eq) and Me–C(2)–C(3)–Me are summarized in Table III,[13] which also includes data for *cis*- and *trans*-1,2-dimethylcyclohexane as a comparison standard.

The energy difference calculated by MM3 for the hypothetical *cis*–*trans* isomerization of 1,2-dimethylcyclohexane (1.78 kcal/mol) is almost exactly that of the conformational energy of a methyl group.[14] Therefore, contrary to what we observed in piperidines and 1,4-thiazanes, the program predicts that the *e*,*e* and *a*,*e* $(Me/Me)_{gauche}$ interactions cancel in 1,2-dimethylcyclohexane.

The MM3 program predicts that the inclusion of a nitrogen in a six-membered ring causes the internal C–C–N–C torsion angle to increase by *ca.* 3.4° compared to cyclohexane. This causes the substituents attached to the central N(1) and C(2) atoms to be closer or farther, respectively, in the *e*,*e* and *a*,*e* conformations, thus making the corresponding *gauche* Me–C–N–Me interactions different. MM3 also predicts that the incorporation of sulfur, as in 1,4-thiazanes, causes the ring to pucker further, thereby increasing the ring C–C–N–C torsion angle even more (by *ca.* 7.4°).[15] This would explain why the difference of the *gauche* Me–C–N–Me interactions is greater in 1,4-thiazanes than in piperidines.

Table III contains the torsion ring angles $\omega_{MeCCMe}$ and $\omega_{MeCNMe}$ calculated by MM3. Compared to 1,2-dimethylcyclohexane (entry 1), it can be seen that the 2-Me and NMe groups are predicted to be closer ($\omega_{MeCNMe}$ <60.3°) and further apart ($\omega_{MeCNMe}$ >55.1°), respectively, in the conformers with 2-Me group in equatorial (2*e*) and axial (2*a*) arrangement. This suggests that the energy difference observed experimentally between the $(Me–C–N–Me)_{gauche}$ interactions in piperidines and 1,4-thiazanes is due to an increase of the corresponding *e*,*e* interaction (torsion angle decreased) and a relief of the *a*,*e* interaction (torsion angle increased), compared to those in the MeCCMe fragment of 1,2-dimethylcyclohexane. The torsion angle difference was calculated to be greatest for compounds 17 and 19 (entries 6 and 7, Table III), which are also those showing the largest energy difference between the $(Me–C–N–Me)_{gauche}$ interactions. However, in the latter compounds, the *gauche* interactions between the methyl groups on C(2) and C(3) may also contribute to the observed energy differences: while for *cis*-2,3-dimethyl derivatives (entries 4 and 6; Table III) MM3 predicts a relatively insignificant difference (*ca.* 2°) between the MeCCMe torsional angles in *2e*,*3a* and *2a*,*3e* conformers, for compound 19 an unusually small (54.6°) $Me_{2e}/Me_{3e}$ torsion angle is predicted in its diequatorial conformer, which may lead to additional destabilization of that conformer.

The difference (1.38 kcal/mol) between $-\Delta G°$ values of compounds 17 and 21t (entries 12 and 21 of Table II) is much larger than the difference $(Me/OS)_{gauche} - (SO_{axial})$, which was measured by means of compounds 12t and 9 (vide supra) to be 0.46 kcal/mol. The SO group in 21t may affect the *gauche* interactions between *N*-Me, 2-Me, and 3-Me groups as compared to 17, and the differences might account for the observed discrepancy [0.92 kcal/mol favoring conformer 2 (Scheme II) in 21t]. However, in view of its large value, we further investigated whether this discrepancy was due to an enhancement of $(SO/Me)_{gauche}$ interaction in conformer 1 or a favoring of conformer 2 by additional polar interactions.

To sort out these two possibilities, we prepared *N*-methyl-1,4-thiazane *S*-oxide (4) and measured its $-\Delta G°$ value, which turned out to be −0.84 kcal/mol in $CD_2Cl_2$ (entry 2, Table II); *i.e.*, the axial SO is considerably more favored

(11) For the $(Me/Me)_{gauche}$ interaction see: Manoharan, M.; Eliel, E. L. *Tetrahedron Lett.* **1983**, *24*, 453.

(12) See, for example: Allinger, N. L.; Chen, K.; Rahman, M.; Pathiaseril, A. *J. Am. Chem. Soc.* **1991**, *113*, 4505 and references cited therein.

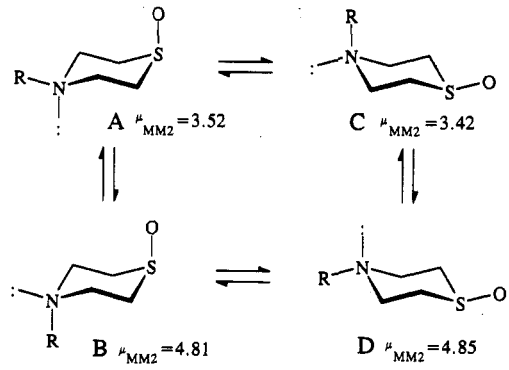
(13) We realized that using internal MM3 parameters led to a poor agreement factor between $-\Delta G°$ and calculated $\Delta E$ values ($R$ = 0.464) for a number of methyl-substituted thianes, piperidines, and 1,4-thiazanes. We thus had to change some torsional parameters (see table in this footnote) to improve the fit ($R$ > 0.92). The torsional angles in Table III have been extracted from the geometries of the best energy fit. Complete details will be published in a separate paper.

| fragment | atom types | $V_1$ | $V_2$ | $V_3$ |
|---|---|---|---|---|
| N–C–C–S | 8–1–1–15 | −0.70 | 0.80 | −0.10 |
| C–C–C–S | 1–1–1–15 | −0.09 | 0.11 | 0.40 |
| C–C–S–C | 1–1–15–1 | −0.18 | 0.00 | 0.60 |
| C–C–C–N | 1–1–1–8 | −0.25 | 0.75 | 0.50 |

(14) Anet, F. A. L.; Bradley, C. H.; Buchanan, G. W. *J. Am. Chem. Soc.* **1971**, *93*, 258. See also: Prosen, E. J.; Johnson, W. H.; Rossini, F. D. *J. Res. Natl. Bur. Stand.* **1947**, *39*, 173.

(15) The calculated MM3 values of the internal torsion angles of cyclohexane, piperidine, thiane, 1,4-oxathiane, and 1,4-thiazane are in agreement with the experimental ones; see: Bastiansen, O.; Fernholt, H.; Seip, H. M.; Kambara, H.; Kuchitsu, K. *J. Mol. Struct.* **1973**, *18*, 163; Lambert, J. B. *Acc. Chem. Res.* **1971**, *4*, 87. Nachtergaele, W. A.; Anteunis, M. J. O. *Bull. Soc. Chem. Belg.* **1980**, *89*, 525.

**Scheme III**




than in the NH analog **3**. Since the electrostatic interactions between SO and the *syn* axial hydrogens should be very similar in both compounds, we have interpreted this behavior on dipolar grounds (Scheme III), in terms of a favoring of the equatorial SO conformer as one goes from NMe to NH.

Proceeding from left to right in Scheme III, the ring flips, whereas going from top to bottom, the nitrogen inverts. When R = H, considerable contribution of C with equatorial SO, the least polar conformer as predicted by MM2,[16] should account for the less negative $-\Delta G°$ value observed in this compound relative to its *N*-methyl counterpart, where the participation of C with axial Me should be negligible and the molecule would be largely in conformation A rather than the much more polar D.[17]

There is still a discrepancy between the calculated conformational energy of **21t** (0.84 kcal/mol for axial SO plus 0.23 kcal/mol for $(SO/Me)_{gauche}$ = 1.07 kcal/mol *vs* 1.38 kcal/mol observed) which suggests small differences in the *gauche* interactions of the methyl groups as between **17** and **21t**.

In the case of sulfoxide **21c** (entry 18 of Table II), the conformational free energy difference $\Delta\Delta G°$ between it and **17** (entry 12 of Table II), 1.19 kcal/mol, should arise from the difference between the interactions (Scheme II) of axial 2-Me with S in **17** (0.52 kcal/mol in 3-methylthiane, *vide supra*) and with axial SO in **21c**, provided again that the methyl *gauche* interactions are the same in **17** and **21c**. Taking the SO/H diaxial interaction in conformer 1 of **21c** as −0.42 kcal/mol, one half of $-\Delta G°$ of *N*-methyl-1,4-thiazane S-oxide (−0.84/2 kcal/mol), one may estimate the SO/Me *syn*-axial interaction ($x$) to amount to *ca.* 2.1 kcal/mol ($x - 0.42 = 1.19 + 0.52$).

Compound **20c** (Scheme II) was conformationally homogeneous; the large shift of equilibrium toward conformer 2 as one passes from **21c** to **20c** is to be expected on the basis of the earlier discussed, corresponding shift as between **17** and **16**. It is noteworthy that the evaluation of the SO/Me *syn*-axial interaction in **21c** has become possible only by the counterpoising action of the $Me_{eq}$-N-C-$Me_{eq}$ interaction (*vide supra*).

The $-\Delta G°$ value for sulfone **25** (entry 24 of Table II) indicates that equilibrium is more on the side of conformer 2 (by 1.20 kcal/mol) than in the parent sulfide **17**, as a result of the *syn*-axial interaction of 2-Me with axial SO, similarly as in sulfoxide **21c**. But conformer 2 of sulfone **25** has two OSO/H axial interactions whereas conformer 1 has only one (see Scheme II). This interaction cannot be measured in 1,4-thiazane *S,S*-dioxide for obvious reasons of symmetry. But, making the approximation that the interactions of the MeNC(2)MeC(3)Me fragment and the OSO/Me *syn*-axial interaction are the same in **21c** and **25**, and taking our above-estimated values for the $(3\text{-Me/O-SO})_{gauche}$ interaction in sulfones (0.31 kcal/mol) and SO/H axial in sulfoxides (−0.42 kcal/mol), one can estimate the OSO/H axial interaction ($y$) in **25** to be *ca.* 0.7 kcal/mol ($\Delta\Delta G°_{(25\text{-}21c)} = 0.01 = -0.31 + y - 0.42$). This value is probably too high, due to the several approximations made and to imperfect additivity of interactions. Nevertheless, the result is clearly a positive number suggesting that this interaction, in contrast to that in sulfoxides, is no longer stabilizing in sulfones.

Finally, compounds **11c**, **11t**, **13**, **20t**, **22–24**, **26**, and **27** are essentially monoconformational (Scheme II) as expected since their calculated $-\Delta G°$ values, from the interactions measured in this work, exceed the detection limit of the low-temperature $^{13}C$ technique.

Solvent effects deserve a brief comment. In $CD_3OD$ all the equilibria are somewhat shifted toward the conformer with equatorial 3-Me. This is reasonable since nitrogen presumably increases its "size" by hydrogen bonding to methanol. In contrast, the effect of acetone-$d_6$ is generally small, suggesting that polar interactions (other than hydrogen bonding) are minor in their effect.

## Experimental Section

**General.** $^1H$ (200 or 250 MHz) and $^{13}C$ NMR (50.3 or 62.9 MHz) were recorded on Bruker AC-200, WP-200-SY, or WM-250 instruments, equipped with 5-mm dual $^1H/^{13}C$ probes. Assignment of proton and carbon signals of room temperature spectra was performed (see text) by DEPT and 2D proton–carbon correlation experiments. Low-temperature spectra were recorded as previously described.[18] IR spectra were measured on a Nicolet-DX FT spectrometer. Mass spectra (electronic impact, 70 eV) were obtained on a Hewlett-Packard 5985 instrument. Elemental analysis were performed out by M-H-W laboratories (USA) and Instituto de Química Orgánica (CSIC, Spain).

**Oxidation of Thioethers to Sulfoxides.** To a dispersion or solution of 10 mmol of the corresponding 1,4-thiazane or its oxalate in 10 mL of water at 0–5 °C was slowly added a cooled, saturated solution of 10 mmol of sodium metaperiodate in water. The mixture was stirred overnight at room temperature. If the starting material was an oxalate, the solution was carefully neutralized with sodium carbonate. Otherwise, the solvent was simply removed at reduced pressure and the residue was extracted with $CH_2Cl_2$ as many times as necessary.

***N*-Methylation of 1,4-Thiazanes.** The appropriate 1,4-thiazane (1.2 mmol) was treated at 0 °C with 0.18 g (3.6 mmol) of 88% formic acid and 0.27 g (3.6 mmol) of 40% formaldehyde.

(16) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

(17) A reviewer has objected to our considering four conformers (Scheme III) for compounds **3** and **12t** and only two for all the others. The reason is as follows: Compounds bearing *N*-Me groups are essentially monoconformational with respect to that moiety; compounds with axial *N*-Me groups are populated negligibly (Crowley, P. J.; Robinson, M. J. T.; Ward, M. G. *Tetrahedron* **1977**, *33*, 915), and one is therefore justified in disregarding them. The opposite is true for the NH group (Anet, F. A. L.; Yavari, I. *J. Am. Chem. Soc.* **1977**, *99*, 2794. Vierhapper, F. W.; Eliel, E. L. *J. Am. Chem. Soc.* **1979**, *44*, 1081). For this reason, for compounds having only a single $R_2NH$ dipole, one need not worry about the two possible conformations which, according to Anet, are very difficult to "freeze out" and have very similar conformational energies. But when there is a second dipole in the molecule, the NH conformation (equatorial or axial) becomes important, since the group dipoles in piperidines with equatorial or axial NH, respectively, are quite differently oriented with respect to whatever other dipole is present in such molecules. It is therefore in such molecules, and such molecules only, that all four conformers need be considered. It happens that in the present paper, of the multiconformational compounds, only **3** and **12t** are the ones in which all four conformers need be considered: all other compounds are either monoconformational, such as **12c** and **20c**, lack sulfoxide SO groups, or bear *N*-Me groups.

(18) Brunet, E.; Eliel, E. L. *J. Org. Chem.* **1986**, *51*, 677.

The mixture was stirred at 80 °C for 24 h, cooled to room temperature, and treated with 1 mL of 20% hydrochloric acid. The resulting mixture was carefully neutralized with sodium bicarbonate, and the solvent was removed at reduced pressure. The residue was extracted with $CH_2Cl_2$ as many times as necessary.

**Oxidation of Thioethers to Sulfones. Procedure A.** To a solution of 10 mmol of 1,4-thiazane in 10 mL of $CH_2Cl_2$ at 0 °C was added a cooled solution of 20 mmol of *m*-chloroperbenzoic acid in 10 mL of $CH_2Cl_2$. The mixture was allowed to warm to room temperature and stirred for 1 h. The solvent was then removed at reduced pressure, and the resulting sulfone was separated from *m*-chlorobenzoic acid by flash chromatography. **Procedure B.** To a solution of 2 mmol of the corresponding *N*-methyl-1,4-thiazane or its oxalate in 2 mL of trifluoroacetic acid was added 1 mL of 30% hydrogen peroxide in a water–ice bath. The mixture was stirred for 1 h at room temperature and then carefully neutralized with sodium bicarbonate. The solvent was removed at reduced pressure, and the residue was extracted with $CH_2Cl_2$ as described above.

**2-Methyl-1,4-thiazane (7).** To a solution of 25.7 g (0.39 mol) of 85% potassium hydroxide in 400 mL of methanol were added 21.7 g (0.19 mol) of 2-aminoethanethiol hydrochloride, in small portions, followed by a solution of 17.6 g (0.19 mol) of chloroacetone in 100 mL of methanol at 0–5 °C. After being stirred for 90 min at the same temperature the solution was acidified with 75 mL of 8 N HCl in methanol at 0–5 °C and stirred for 1 h. Sodium borohydride (14.4 g, 0.38 mol) was then added in small portions below 5 °C, and the mixture was stirred for 30 min. Excess reducing agent was destroyed with diluted HCl, the solution was concentrated at reduced pressure, and the residue was extracted with $CH_2Cl_2$ (3 × 50 mL). The organic extract was dried (anhydrous $Na_2SO_4$) and concentrated; the crude product was then dissolved in ethanol and treated with a slight excess of oxalic acid. The solvent was evaporated at reduced pressure, the residue was dissolved in water, and the solution was extracted several times with $CH_2Cl_2$. The organic layer was discarded, and the aqueous phase was carefully neutralized with sodium bicarbonate and extracted with $CH_2Cl_2$ (3 × 50 mL). Usual workup of the organic extract yielded 6.6 g (30%) of pure product: mp (acid oxalate) 118–119 °C; $^1$H NMR ($CDCl_3$) δ 1.11 (d, 3H, Me), 2.37 (m, 1H, $C_5H$), 2.41 (m, 2H, $C_3H_2$), 2.75 (m, 1H, $C_5H$), 2.94 (m, 1H, $C_2H$), 3.02 (m, 1H, $C_6H$), 3.33 (m, 1H, $C_6H$); $^{13}$C NMR ($CDCl_3$) δ 22.5 (Me), 26.9 ($C_5$), 33.9 ($C_3$), 47.8 ($C_6$), 52.3 ($C_2$). Anal. Calcd for $C_7H_{13}O_4NS$ (acid oxalate): C, 40.57; H, 6.32. Found: C, 40.66; H, 6.49.

**2-Methyl-1,4-thiazane *S*-oxides (11c and 11t)** were obtained from **3** as an oil (see general procedure) as a 3.5:1 mixture of diastereoisomers (**11t** major) which could not be separated in our hands, yield 84%. Compound **11t**: $^1$H NMR ($CDCl_3$) δ 1.09 (d, Me), 2.25 (m, 1H, $C_3H$), 2.51 (m, 1H, $C_5H$), 2.77 (m, 1H, $C_5H$), 3.01 (m, 1H, $C_6H$), 3.59 (m, 1H, $C_2H$), 3.65 (m, 1H, $C_6H$); $^{13}$C NMR ($CDCl_3$) d 22.1 (Me), 36.4 ($C_6$), 41.3 ($C_2$), 44.5 ($C_5$), 51.3 ($C_3$). Compound **11c**: $^1$H NMR ($CDCl_3$) δ 1.20 (d, Me), 2.32 (m, 1H, $C_3H$), 2.45 (m, 1H, $C_5H$), 2.85 (m, 1H, $C_6H$), 2.89 (m, 1H, $C_2H$), 3.29 (m, 1H, $C_3H$), 3.31 (m, 1H, $C_6H$), 3.32 (m, 1H, $C_5H$); $^{13}$C NMR ($CDCl_3$) d 22.1 (Me), 41.9 ($C_6$), 49.0 ($C_2$), 51.0 ($C_5$), 58.3 ($C_3$); IR (mixture of isomers) $\nu_{SO}$ = 1010 cm$^{-1}$.

**2-Methyl-1,4-thiazane *S,S*-dioxide (13)** was obtained from **7** as an oil following procedure A (see above), yield 86%: $^1$H NMR ($CDCl_3$) δ 1.22 (d, Me), 2.73 (m, 1H, $C_3H$), 2.95 (m, 2H, $C_5H_2$), 3.00 (m, 1H, $C_3H$), 3.20 (m, 1H, $C_6H$) 3.27 (m, 1H, $C_2H$), 3.42 (m, 1H, $C_6H$); $^{13}$C NMR ($CDCl_3$) δ 21.6 (Me), 43.7 ($C_6$), 50.9 ($C_2$), 51.9 ($C_5$), 59.2 ($C_3$); MS *m/z* 149 (M, 13.1), 134 (B, 13.1); IR $\nu_{SO_2}$ = 1312, 1127 cm$^{-1}$.

***N*,2-Dimethyl-1,4-thiazane (8)** was obtained from **7** as an oil following the general methylation procedure, yield 89%: $^1$H NMR ($CDCl_3$) δ 1.17 (d, Me), 2.30 (s, Me) 2.45 (m, 1H, $C_2H$), 2.50 (m, 1H, $C_5H$), 2.52 (m, 2H, $C_3H$ and $C_6H$), 2.55 (m, 1H, $C_3H$), 2.83 (m, 1H, $C_5H$), 3.08 (m, 1H, $C_6H$); $^{13}$C NMR ($CDCl_3$) δ 17.8 (Me), 27.1 ($C_5$), 34.0 ($C_3$), 42.8 (Me) 55.7 ($C_6$), 58.4 ($C_2$).

**3-Methyl-1,4-thiazane (9).** A mixture of 4 g (22 mmol) of ethyl 2-bromopropionate, 2.51 g (22 mmol) of 2-aminoethanethiol hydrochloride, and 3.08 g (22 mmol) of potassium carbonate in 50 mL of ethanol was refluxed overnight with stirring. The solvent was removed, and the residue was extracted with 3 × 50 mL of $CH_2Cl_2$. Usual workup of the organic extracts yielded 2.5–2.8 g of 3-methyl-2-oxo-1,4-thiazane which was sufficiently pure for the next step but may be recrystallized from a 1:1 mixture of hexane–acetone (mp 77–80 °C). To a suspension of 2.5 g (18.8 mmol) of 3-methyl-2-oxo-1,4-thiazane and 7.2 g (18.8 mmol) of sodium borohydride in 75 mL of dioxane, 11.4 g (18.8 mmol) of glacial acetic acid in 40 mL of dioxane was slowly added. The mixture was refluxed for 5 h, and the solvent was removed at reduced pressure. The excess of reducing agent was then destroyed with *ca.* 40 mL of water, and the mixture was extracted with 3 × 50 mL of $CH_2Cl_2$. Usual workup of the extracts yielded 2.48 g (99%) of the **5**·$BH_3$ complex: IR $\nu_{BH}$ = 2370, 2315, 2271 cm$^{-1}$; MS *m/z* 131 (M, 14), 130 (B, 100), 117 (62). The amine was liberated by stirring its borane complex overnight in 25 mL of 10% hydrochloric acid. The mixture was carefully neutralized with sodium bicarbonate and extracted with 3 × 50 mL of $CH_2Cl_2$. Workup of the extracts yields 2.2 g (100%) of **5**: mp (acid oxalate) 159–161 °C; $^1$H NMR ($CDCl_3$) δ 1.14 (d, Me), 2.50 (m, 1H, $C_5H$), 2.65 (m, 1H, $C_2H$), 2.85 (m, 2H, $C_5H$, $C_6H$), 2.90 (m, 1H, $C_3H$), 3.26 (m, 1H, $C_2H$); $^{13}$C NMR ($CDCl_3$) δ 18.8 (Me), 28.9 ($C_5$), 35.8 ($C_3$), 46.9 ($C_6$), 55.5 ($C_2$). Anal. Calcd for $C_7H_{13}O_4NS$ (acid oxalate): C, 40.57; H, 6.32. Found: C, 40.76; H, 6.40.

**3-Methyl-1,4-thiazane *S*-oxides (12c and 12t)** were obtained from **9** (see general procedure) as a 4.9:1 mixture of diastereoisomers. The major isomer (**12c**, mp 128 °C) was separated by repeated crystallization from ethyl acetate. The minor isomer (**12t**, oil) was purified from the mother liquors by flash chromatography (acetone-water (2:1)). Compound **12c**: $^1$H NMR ($CDCl_3$) δ 1.26 (d, Me), 2.64 (m, 1H, $C_3H$), 2.67 (m, 1H, $C_5H$), 2.82 (m, 1H, $C_2H$), 2.95 (m, 2H, $C_5H$ and $C_6H$), 3.28 (m, 1H, $C_2H$), 3.45 ($C_6H$); $^{13}$C NMR ($CDCl_3$) δ 12.6 (Me), 34.9 ($C_6$), 42.9 ($C_2$), 45.0 ($C_5$), 48.5 ($C_3$); IR $\nu_{SO}$ = 1011 cm$^{-1}$. Compound **12t**: $^1$H NMR ($CDCl_3$) δ 1.35 (d, Me), 2.50 (m, 1H, $C_2H$), 2.63 (m, 2H, $C_3H$ and $C_5H$), 2.89 (m, 1H, $C_6H$), 3.20 (m, 1H, $C_5H$), 3.27 (m, 1H, $C_2H$), 3.31 (m, 1H, $C_6H$); $^{13}$C NMR ($CDCl_3$) δ 12.3 (Me), 41.5 ($C_6$), 48.1 ($C_2$), 49.2 ($C_5$), 56.4 ($C_3$); IR $\nu_{SO}$ = 1022 cm$^{-1}$; MS (mixture of diastereoisomers) *m/z* 133 (M, B, 100), 116 (32).

**3-Methyl-1,4-thiazane *S,S*-dioxide (14)** was obtained from **9** following procedure A (see above): mp 196–197 °C; $^1$H NMR ($CDCl_3$) δ 1.22 (d, Me), 2.82 (m, 1H, $C_2H$), 2.95 (m, 2H, $C_5H_2$), 2.97 (m, 1H, $C_3H$), 3.07 (m, 1H, $C_6H$), 3.18 (m, 1H, $C_2H$), 3.26 (m, 1H, $C_6H$); $^{13}$C NMR ($CDCl_3$) δ 7.9 (Me), 44.6 ($C_6$), 51.0 ($C_2$), 52.0 ($C_5$), 57.6 ($C_3$); IR $\nu_{SO2}$ = 1300, 1125 cm$^{-1}$; MS *m/z* 149 (M, 14).

***N*,3-Dimethyl-1,4-thiazane (10)** was obtained from **9** following the general methylation procedure, yield 27% after Kugelrohr distillation: bp 80 °C/7 mmHg; mp (acid oxalate) 154–156 °C; $^1$H NMR ($CDCl_3$) δ 1.02 (d, Me), 1.70 (m, 1H, $C_2H$), 1.93 (m, 1H, $C_6H$), 2.03 (s, Me), 2.29 (m, 1H, $C_5H$), 2.56 (m, 1H, $C_5H$), 2.61 (m, 2H, $C_2H$ and $C_3H$), 2.64 (m, 1H, $C_6H$); $^{13}$C NMR ($CDCl_3$) δ 18.6 (Me), 27.9 ($C_5$), 35.3 ($C_3$), 46.5 (Me), 55.6 ($C_6$), 64.3 ($C_2$); MS *m/z* 131 (M, 72), 71 (73). Anal. Calcd for $C_8H_{15}O_4NS$ (acid oxalate): C, 43.42; H, 6.83. Found: C, 43.31; H, 6.98.

***N*,3-Dimethyl-1,4-thiazane *S,S*-dioxide (15)** was obtained as an oil from **10** following procedure B: $^1$H NMR ($CDCl_3$) δ 1.33 (d, Me), 2.39 (s, Me), 2.55 (m, 1H, $C_2H$), 2.86 (m, 1H, $C_5H$), 2.93 (m, 1H, $C_2H$), 3.40 (m, 1H, $C_5H$), 3.05 (m, 2H, $C_6H_2$), 3.20 (m, 1H, $C_3H$); $^{13}$C NMR ($CDCl_3$) δ 8.6 (Me), 45.4 (Me), 50.3 ($C_6$), 53.1 ($C_5$), 55.6 ($C_3$), 59.9 ($C_2$); IR $\nu_{SO_2}$ = 1280, 1150 cm$^{-1}$; MS *m/z* 163 (M, 8).

***cis*- and *trans*-2,3-dimethyl-1,4-thiazanes (16 and 18)** were prepared following the procedure described elsewhere: mp (oxalate) 150–152 °C; $^1$H and $^{13}$C NMR data were previously reported.[5] Anal. Calcd for $C_8H_{15}NO_4S$ (acid oxalate): C, 43.42; H, 6.83. Found for **16**: C, 43.71; H, 6.89. Found for **18**: C, 43.44; H, 6.67.

***cis*-2,3-Dimethyl-1,4-thiazane *S*-oxides (20c and 20t)** were obtained from **16** (see general procedure) as a 4.9:1 mixture of diastereoisomers, which could not be separated in our hands: mp (oxalate, mixture of diastereoisomers) 268–282 °C. Compound **20c**: $^1$H NMR ($CDCl_3$) δ 0.92 (d, Me), 0.98 (d, Me), 2.39 (m, 1H, $C_6H$), 2.55 (m, 1H, $C_5H$), 2.66 (m, 1H, $C_6H$), 2.76 (dq, $C_2H$), 2.87 (dq, $C_3H$), 2.99 (m, 1H, $C_5H$); $^{13}$C NMR ($CDCl_3$) δ 0.0 (Me), 19.2 (Me), 41.3 ($C_6$), 42.4 ($C_5$), 50.8 ($C_2$), 53.2 ($C_3$). Compound **20t**: $^1$H NMR ($CDCl_3$) δ 0.84 (d, Me), 0.96 (d, Me), 2.35 (m, 2H, $C_5H_2$), 2.40 (dq, $C_3H$), 2.73 (m, 1H, $C_6H$), 3.33 (m, 1H, $C_6H$), 3.49 (dq, $C_2H$); $^{13}$C NMR ($CDCl_3$) δ 6.5 (Me), 18.4

(Me), 36.2 ($C_6$), 39.4 ($C_5$), 43.4 ($C_2$), 53.3 ($C_3$); IR (mixture of diastereoisomers) $\nu_{SO}$ = 1032 cm$^{-1}$. Anal. Calcd for $C_{14}H_{28}N_2O_6S_2$ (neutral oxalate): C, 43.37; H, 7.34. Found (mixture of diastereoisomers): C, 43.91; H, 7.17.

***trans*-2,3-Dimethyl-1,4-thiazanes *S*-oxides (22c and 22t)** were obtained from **18** (see general procedure) as a 2.6:1 mixture of diastereoisomers, which could not be separated in our hands: mp (oxalate, mixture of diastereoisomers) 170–197 °C. Compound **22c**: $^1$H NMR ($CDCl_3$) $\delta$ 0.91 (d, Me), 1.03 (d, Me), 2.14 (dq, $C_3H$), 2.70 (m, 1H, $C_5H$), 2.90 (m, 2H, $C_5H$ and $C_6H$), 3.21 (dq, $C_2H$), 3.55 (m, 1H, $C_6H$); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.4 (Me), 18.7 (Me), 35.6 ($C_6$), 46.2 ($C_5$), 46.9 ($C_2$), 54.2 ($C_3$). Compound **22t**: $^1$H NMR ($CDCl_3$) $\delta$ 1.02 (d, Me), 1.11 (d, Me), 2.28 (dq, $C_3H$), 2.60 (dq, $C_2H$), 2.77 (m, 1H, $C_5H$), 2.95 (m, 1H, $C_6H$), 3.38 (m, 2H, $C_5H$ and $C_6H$); $^{13}$C NMR ($CDCl_3$) $\delta$ 11.3 (Me), 18.9 (Me), 41.3 ($C_6$), 51.2 ($C_5$), 53.0 ($C_2$), 63.9 ($C_3$). IR (mixture of diastereoisomers) $\nu_{SO}$ = 1037 cm$^{-1}$. Anal. Calcd for $C_8H_{15}NO_5S$ (acid oxalate): C, 40.49; H, 6.37. Found (mixture of diastereoisomers): C, 40.74; H, 6.38.

***cis*- and *trans*-2,3-dimethyl-1,4-thiazane *S,S*-dioxides (24 and 26)** were obtained from **16** and **18**, respectively, following procedure A. Compound **24**: mp (oxalate) 260–262 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.10 (d, Me), 1.32 (d, Me), 2.77 (m, 2H, $C_3H$ and $C_5H$), 3.00 (m, 1H, $C_5H$), 3.17 (m, 1H, $C_6H$), 3.33 (m, 1H, $C_6H$), 3.54 (m, 1H, $C_2H$); $^{13}$C NMR ($CDCl_3$) $\delta$ 7.0 (Me), 18.8 (Me), 43.0 ($C_6$), 46.7 ($C_5$), 52.2 ($C_2$), 60.4 ($C_3$); IR $\nu_{SO_2}$ = 1286, 1130 cm$^{-1}$; MS *m/z* 163 (M, 26), 148 (17). Anal. Calcd for $C_{14}H_{28}N_2O_8S_2$ (neutral oxalate): C, 40.37; H, 6.77. Found: C, 40.26; H, 6.46. Compound **26**: mp (oxalate) 264–265 °C; $^1$H NMR ($CDCl_3$) $\delta$ 0.92 (d, Me), 1.02 (d, Me), 2.47 (dq, $C_3H$), 2.66 (dq, $C_2H$), 2.77 (m, 2H, $C_5H_2$), 2.94 (m, 1H, $C_6H$), 3.10 (m, 1H, $C_6H$); $^{13}$C NMR ($CDCl_3$) $\delta$ 5.8 (Me), 18.8 (Me), 42.9 ($C_6$), 51.6 ($C_5$), 55.4 ($C_2$), 62.6 ($C_3$); IR $\nu_{SO_2}$ = 1286, 1125 cm$^{-1}$. MS *m/z* 163 (M, 41), 148 (20). Anal. Calcd for $C_{14}H_{28}N_2O_8S_2$ (neutral oxalate): C, 40.37; H, 6.77. Found: C, 40.34; H, 6.57.

***cis*- and *trans*-*N*,2,3-trimethyl-1,4-thiazanes (17 and 19)** were obtained from **16** and **18**, respectively, following the general methylation procedure. Compound **17**: mp (oxalate) 124–125 °C; $^1$H NMR ($CDCl_3$) $\delta$ 0.85 (d, Me), 1.03 (d, Me), 2.18 (s, Me), 2.37 (m, 1H, $C_5H$), 2.41 ($C_6H$), 2.58 (m, 1H, $C_6H$), 2.67 (m, 1H, $C_5H$), 2.69 (dq, $C_2H$), 3.01 (dq, $C_3H$); $^{13}$C NMR ($CDCl_3$) $\delta$ 5.9 (Me), 17.5 (Me), 27.4 ($C_5$), 40.4 ($C_3$), 43.5 (Me), 48.7 ($C_6$), 59.5 ($C_2$). Anal. Calcd for $C_9H_{17}NO_4S$ (acid oxalate): C, 45.94; H, 7.28. Found: C, 45.88; H, 7.18. Compound **19**: mp (oxalate) 71–73 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.09 (d, Me), 1.14 (d, Me), 2.23 (dq, $C_2H$), 2.24 (s, Me), 2.36 (m, 1H, $C_5H$), 2.56 (m, 1H, $C_6H$), 2.65 (dq, $C_3H$), 2.81 (m, 1H, $C_5H$), 2.98 (m, 1H, $C_6H$); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.0 (Me), 18.2 (Me), 24.4 ($C_5$), 37.2 ($C_5$), 40.8 (Me), 54.4 ($C_6$), 63.7 ($C_2$). Anal. Calcd for $C_9H_{17}NO_4S$ (acid oxalate): C, 45.94; H, 7.28. Found: C, 45.56; H, 7.29.

***cis*-*N*,2,3-Trimethyl-1,4-thiazane *S*-oxides (21c and 21t)** were obtained from **17** (see general procedure) as an 8.2:1 mixture of diastereoisomers. The major isomer (**21t**) was separated by flash chromatography (acetone/water (2:1)) as an oil. Compound **21c**: $^1$H NMR ($CDCl_3$) $\delta$ 0.93 (d, Me), 1.08 (d, Me), 2.12 (s, Me), 2.56 (m, 1H, $C_5H$), 2.60 (dq, $C_3H$), 2.77 (m, 2H, $C_6H_2$), 2.83 (m, 1H, $C_5H$), 2.94 (dq, $C_2H$); $^{13}$C NMR ($CDCl_3$) $\delta$ 9.3 (Me), 14.7 (Me), 42.6 (Me), 43.3 ($C_6$), 45.6 ($C_5$), 53.0 ($C_2$), 55.7 ($C_3$). Compound **21t**: $^1$H NMR ($CDCl_3$) $\delta$ 1.03 (d, Me), 1.19 (d, Me), 2.08 (s, Me), 2.35 (m, 2H, $C_5H_2$), 2.37 (dq, $C_3H$), 2.51 (m, 1H, $C_6H$), 2.77 (dq, $C_2H$), 2.82 (m, 1H, $C_6H$); $^{13}$C NMR ($CDCl_3$) $\delta$ 8.0 (Me), 13.8 (Me), 41.8 (Me), 42.1 ($C_6$), 43.6 ($C_5$), 53.8 ($C_2$), 57.9 ($C_3$); IR $\nu_{SO}$ = 1043 cm$^{-1}$; MS *m/z* (mixture of diastereoisomers) 161 (M, 21), 144 (87), 98 (47), 84 (74).

***trans*-*N*,2,3-Trimethyl-1,4-thiazane *S*-oxides (23c and 23t)** were obtained from **19** (see general procedure) as a 3.1:1 mixture of diastereoisomers, which could not be separated in our hands: mp (oxalate, mixture of diastereoisomers) 102–110 °C. Compound **23c**: $^1$H NMR ($CDCl_3$) $\delta$ 1.11 (d, Me), 1.29 (d, Me), 2.30 (s, Me) 2.40 (dq, $C_3H$), 2.72 (m, 1H, $C_6H$), 2.81 (m, 2H, $C_5H_2$), 2.87 (m, 1H, $C_2H$), 3.30 (m, 1H, $C_6H$); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.6 (Me), 15.1 (Me), 40.4 (Me), 42.9 ($C_5$), 44.4 ($C_6$), 51.2 ($C_3$), 53.5 ($C_2$). Compound **23t**: $^1$H NMR ($CDCl_3$) $\delta$ 1.16 (d, Me), 1.33 (d, Me), 2.16 (dq, $C_2H$), 2.26 (s, Me), 2.43 (dq, $C_3H$), 2.59 (m, 1H, $C_5H$), 2.90 (m, 1H, $C_6H$), 3.09 (m, 1H, $C_5H$), 3.24 (m, 1H, $C_6H$); $^{13}$C NMR ($CDCl_3$) $\delta$ 11.8 (Me), 16.0 (Me), 39.9 (Me), 47.3 ($C_5$), 49.9 ($C_6$), 59.5 ($C_2$), 59.8 ($C_3$); IR (mixture of diastereoisomers) $\nu_{SO}$ = 1032 cm$^{-1}$; MS (mixture of diastereoisomers) *m/z* 161 (M, 19), 144 (47), 98 (27), 84 (B, 100). Anal. Calcd for $C_9H_{17}NO_5S$ (acid oxalate): C, 43.01; H, 6.82. Found (mixture of diastereoisomers): C, 43.06; H, 6.97.

***cis*- and *trans*-*N*,2,3-trimethyl-1,4-thiazane *S,S*-dioxides (25 and 27)** were obtained from **17** and **19**, respectively, following procedure B (see above). Compound **25**: mp (oxalate) 192–3 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.11 (d, Me), 1.31 (d, Me), 2.30 (s, Me), 2.52 (dq, $C_2H$), 2.90 (m, 1H, $C_5H$), 2.91 (m, 1H, $C_6H$), 3.09 (m, 3H, $C_3H$, $C_5H$ and $C_6H$); $^{13}$C NMR ($CDCl_3$) $\delta$ 8.0 (Me), 13.8 (Me), 41.8 (Me), 47.8 ($C_6$), 50.4 ($C_2$), 58.9 ($C_5$), 59.3 ($C_3$); IR $\nu_{SO_2}$ = 1292, 1135 cm$^{-1}$; MS *m/z* 177 (M, 40), 162 (52). Anal. Calcd for $C_9H_{17}NO_6S$ (acid oxalate): C, 40.44: H, 6.41. Found: C, 40.48; H, 6.20. Compound **27**: $^1$H NMR ($CDCl_3$) $\delta$ 1.03 (d, Me), 1.14 (d, Me), 2.22 (s, Me), 2.57 (dq, $C_3H$), 2.74 (dq, $C_2H$), 2.81 (m, 1H, $C_5H$), 3.00 (m, 2H, $C_6H_2$), 3.10 ($C_5H$); $^{13}$C NMR ($CDCl_3$) $\delta$ 6.8 (Me), 16.0 (Me), 38.6 (Me), 47.9 ($C_5$), 51.8 (Me), 57.6 ($C_2$), 60.6 ($C_3$); MS *m/z* 177 (M, 36), 162 (62).

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**Supplementary Material Available:** Proton and carbon-13 NMR spectra for compounds **4**, **7c+7t**, **8c**, **9**, **10**, **11**, and **23** (12 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 for ordering information.