Conformational Analysis. 34. Carbon-13 Nuclear Magnetic Resonance Spectra of Saturated Heterocycles. 6. Methylthianes[1,2]

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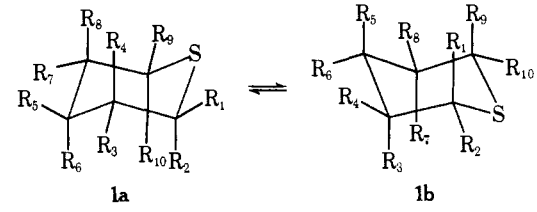
Abstract: The conformational free energies ($-\Delta G°$'s) of methyl groups at the 2-, 3-, and 4-positions of thiane have been determined to be 1.42 ± 0.07, 1.40 ± 0.07, and 1.80 ± 0.10 kcal/mol, respectively, by low temperature ^{13}C NMR. The conformational equilibrium positions in *cis*-2,3-dimethylthiane and *cis*-3,4-dimethylthiane deviate slightly from those predicted on the basis of additivity. The experimentally determined $-\Delta G°$ values are compared to those previously computed by the molecular mechanics method. The ^{13}C NMR spectra of thiane and 20 of its mono-, di-, and trimethyl derivatives along with the 4-*tert*-butyl derivative and two deuterium-labeled analogues have been recorded. The chemical shifts of the ring carbons in the methylthianes have been analyzed in terms of additive parameters for the methyl substituents, which are compared to those previously determined for methylcyclohexanes, methyl-1,3-dithianes, and methyl-1,3-dioxanes. The chemical shifts of equatorial and axial methyl groups at the 2,6-position show that the unusual shifts of methyl groups at the 2- and 4,6-positions of 1,3-dithiane previously reported do not result from electronic interaction of the ring sulfur atoms in the latter.

In previous papers in these series we have reported on the ^{13}C NMR spectra and conformational properties of a variety of saturated heterocyclic systems including *trans*-decahydroquinolines,[3,4] *cis*-decahydroquinolines,[1] 1,3-dithianes,[5,6] and 1,3-dioxanes.[7,8] In this paper we report on a study of the ^{13}C NMR spectra and conformational properties of the thiane ring system and in the following on a conformational study on S-methylthianium salts.[9] The conformational free energies ($-\Delta G$'s) of methyl groups at the 2-, 3-, and 4-positions of the thiane ring may be compared to the values recently calculated by the molecular mechanics method.[10] The NMR study serves to further our understanding of the effects of heteroatoms on ^{13}C chemical shifts; in particular, we were interested to find out if the unusual chemical shifts of equatorial and axial methyl groups at the 2- and 4,6-positions of 1,3-dithiane are related to the known electronic interaction between the ring sulfur atoms.[11]

The thianes investigated in this study are shown in Scheme I. Except for compounds **1, 20,** and **22** (available commercially or from another study), and **23** and **24,** all thianes were synthesized by reaction of the appropriate 1,5-dibromide or 1,5-ditosylate with sodium sulfide (Scheme II). Compounds **23** and **24** were obtained by converting the corresponding perhydro compounds (**1** and **21**) to their *S*-methylthianium iodide derivatives, exchanging the acidic α-hydrogens for deuterium by base-catalyzed H–D exchange in D_2O solutions, followed by reisolation of the salts and dry distillation of the salt yielding the deuterated thiane and methyl iodide-d_3 (Scheme III).[12]

Scheme I

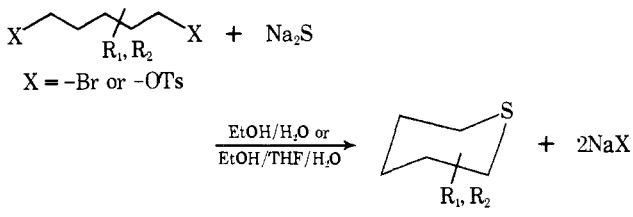


1a **1b**

all R's = H unless noted

2, $R_1 = CH_3$
3, $R_3 = CH_3$
4, $R_5 = CH_3$
5, $R_1 = R_9 = CH_3$
6, $R_1 = R_{10} = CH_3$
7, $R_1 = R_7 = CH_3$
8, $R_1 = R_8 = CH_3$
9, $R_1 = R_5 = CH_3$
10, $R_5 = R_2 = CH_3$
11, $R_1 = R_3 = CH_3$
12, $R_1 = R_4 = CH_3$
13, $R_3 = R_7 = CH_3$
14, $R_3 = R_8 = CH_3$
15, $R_3 = R_5 = CH_3$
16, $R_4 = R_5 = CH_3$
17, $R_3 = R_4 = CH_3$
18, $R_5 = R_6 = CH_3$
19, $R_3 = R_4 = R_7 = CH_3$
20, $R_1 = R_5 = R_6 = CH_3$
21, R_5 = *t*-butyl
22, $R_1 = R_2 = R_5 = CH_3$
23, $R_1 = R_2 = R_9 = R_{10} = D$
24, $R_1 = R_2 = R_9 = R_{10} = D$; R_5 = *tert*-butyl

Scheme II



^{13}C NMR Spectra

In Table I the ^{13}C chemical shift data for compounds **1–24** are summarized along with the corresponding assignments. In Table II, the corresponding chemical shift data for the mobile compounds **3, 6, 8, 10, 12, 14,** and **16** are recorded at room temperature and at −95 °C (−83 °C for **3**) in a different solvent system.

Items 1–3,[13] 4, 9, 11, 15, 20–27, 70–77, 93, 97, 100, 101, 103, 105, 110, 112, 118, 119, 120–123, 125, and 131–136 can be unequivocally assigned to the carbons indicated in Table I on the basis of relative signal intensity, splitting patterns in the off-resonance decoupled spectra, and known effects of deuterium substitution on ^{13}C chemical shifts.[14] The off-resonance decoupled spectra also allowed all other (methyl, methylene, and methine) resonances to be distinguished. From the unequivocal assignments and the assumption that the conformational free energy of 4-methylthiane is similar to that of methylcyclohexane (1.7 kcal/mol) it was possible to develop a set of chemical shift parameters similar to that for methylcyclohexanes.[15] These chemical shift parameters allowed all of the ring carbons in compounds **2, 3, 4, 7, 9, 17, 18, 19, 20,** and **22** and all but the methine carbons in compounds **10, 11,** and **15** to be assigned with a high degree of confidence. The methine carbons in **11** and **15** were assigned by correcting the shifts calculated from the shift parameters by the vicinal e,e parameter for cyclohexane.[15a] This left the methine carbons in compounds **8, 10, 12,** and **16** and the methylene carbons in compounds **8, 12,** and **16** unassigned. These assignments were

Table I. Carbon-13 Chemical Shift Data for the Methylthianes[a]

Item	Compd	Carbon assigned	^{13}C shift, ppm	Calcd shift
1	Thiane (**1**)	2,6	29.06	29.12
2		3,5	27.76	27.72
3		4	26.45	26.35
4	2-Methylthiane (**2**)	2	37.33	37.19
5		3	36.61	36.60
6		4	26.36	26.15
7		5	26.92	26.92
8		6	29.36	29.72
9		Me	21.87	
10	3-Methylthiane (**3**)	2	35.83	35.79
11		3	33.16	33.01
12		4	34.86	34.84
13		5	27.77	27.69
14		6	28.45	28.63
15		Me	22.68	
16	4-Methylthiane (**4**)	2,6	28.80	28.81
17		3,5	36.01	35.98
18		4	32.31	32.23
19		Me	23.01	
20	*cis*-2,6-Dimethylthiane (**5**)	2,6	38.28	38.30
21		3,5	36.00	36.07
22		4	27.05	27.24
23		Me's	21.63	
24	*trans*-2,6-Dimethylthiane (**6**)	2,6	33.36	33.51
25		3,5	34.80	34.75
26		4	20.78	20.75
27		Me's	21.38	
28	*trans*-2,5-Dimethylthiane (**7**)	2	37.10	37.05
29		3	37.36	37.62
30		4	35.52	35.62
31		5	32.91	32.81
32		6	36.56	36.55
33		Me(2)	21.42	
34		Me(5)	22.54	
35	*cis*-2,5-Dimethylthiane (**8**)	2	35.39	35.32
36		3	32.21	32.31
37		4	30.63	30.73
38		5	29.64	29.70
39		6	33.42	33.49
40		Me(2)	20.98	
41		Me(5)	19.65	
42	*cis*-2,4-Dimethylthiane (**9**)	2	37.73	37.66
43		3	45.46	45.35
44		4	32.95	33.02
45		5	35.28	35.28
46		6	29.64	29.90
47		Me(2)	21.79	
48		Me(4)	23.00	
49	*trans*-2,4-Dimethylthiane (**10**)	2	32.48	32.44
50		3	42.15	42.12
51		4	26.39	26.40
52		5	34.56	34.60
53		6	23.72	23.64
54		Me(2)	20.88	
55		Me(4)	21.24	
56	*trans*-2,3-Dimethylthiane (**11**)	2	42.93	
57		3	39.98	
58		4	35.60	35.62
59		5	28.20	
60		6	31.10	
61		Me(2)	19.26	
62		Me(3)	20.37	
63	*cis*-2,3-Dimethylthiane (**12**)	2	40.26	
64		3	34.70	
65		4	31.61	
66		5	23.95	23.89
67		6	27.17	27.07
68		Me(2)	17.17	
69		Me(3)	15.61	

Table I (*Continued*)

Item	Compd	Carbon assigned	^{13}C shift, ppm	Calcd shift
70	*cis*-3,5-Dimethylthiane (**13**)	2,6	35.24	35.30
71		3,5	34.32	34.36
72		4	44.00	44.00
73		Me's	23.00	
74	*trans*-3,5-Dimethylthiane (**14**)	2,6	35.36	35.30
75		3,5	27.52	27.49
76		4	40.75	40.70
77		Me's	20.24	
78	*trans*-3,4-Dimethylthiane (**15**)	2	35.94	35.91
79		3	39.90	
80		4	38.70	
81		5	36.70	36.83
82		6	28.84	28.65
83		Me(3)	[20.10][b]	
84		Me(4)	[20.55][b]	
85	*cis*-3,4-Dimethylthiane (**16**)	2	34.25	
86		3	[34.02][b]	
87		4	[34.13][b]	
88		5	31.16	
89		6	26.79	26.94
90		Me(3)	14.26	
91		Me(4)	17.53	
92	3,3-Dimethylthiane (**17**)	2	41.06	40.98
93		3	29.75	30.11
94		4	39.32	39.43
95		5	23.81	23.63
96		6	28.71	
97		Me's	28.22	
98	4,4-Dimethylthiane (**18**)	2,6	24.38	24.39
99		3,5	39.87	40.05
100		4	29.31	29.71
101		Me's	28.38	
102	3,3,5-Trimethylthiane (**19**)	2	40.42	40.36
103		3	31.20	30.79
104		4	48.41	48.25
105		5	29.45	29.58
106		6	35.59	
107		Me(3,e)	32.65	
108		Me(3,a)	24.28	
109		Me(5)	23.07	
110	2,4,4-Trimethylthiane (**20**)	2	32.65	32.86
111		3	49.48	49.26
112		4	30.56	30.16
113		5	39.14	39.19
114		6	25.31	25.09
115		Me(2)	21.91	
116		Me(4,e)	33.46	
117		Me(4,a)	23.75	
118	4-*tert*-Butylthiane (**21**)	2,6	29.79	
119		3,5	29.06	
120		4	48.02	
121		$C(CH_3)_3$	32.82	
122		Me's	27.33	
123	2,2,4-Trimethylthiane (**22**)	2	40.32	
124		3	50.34	
125		4	28.08	
126		5	35.59	
127		6	26.47	
128		Me(2,e)	32.11	
129		Me(2,a)	27.32	
130		Me(4)	23.22	
131	Thiane-*2,2,6,6*-d_4 (**23**)	3,5	27.55	
132		4	26.30	
133	4-*tert*-Butylthiane-*2,2,6,6*-d_4 (**24**)	3,5	28.82	
134		4	47.86	
135		$C(CH_3)_3$	32.82	
136		Me's	27.31	

[a] In 25% v/v solutions in $CDCl_3$. [b] Brackets indicate that the assignment is not unambiguous.

Table II. Carbon-13 Chemical Shift Data for Mobile Methylthianes at 30 and −95 °C[a]

Item	Compd	Solvent[b]	t, °C	Carbon assigned	^{13}C shift, ppm
137	*trans*-2,6-Dimethylthiane (**6**)	A	30	2,6	35.49
138				3,5	35.13
139				4	21.10
140				Me's	21.47
141		A	−95	2	32.13
142				3	37.24
143				4	20.96
144				5	32.73
145				6	35.01
146				Me(2,e)	22.25
147				Me(6,a)	20.96
148	*trans*-3,5-Dimethylthiane (**14**)	B	30	2,6	35.55
149				3,5	27.52
150				4	41.06
151				Me's	20.34
152		B	−95	2	35.77
153				3	26.80
154				4	40.14
155				5	27.97
156				6	34.13
157				Me(3,e)	23.43
158				Me(5,a)	17.22
159	*cis*-2,3-Dimethylthiane (**12**)	B	30	2	40.69
160				3	35.22
161				4	32.07
162				5	24.47
163				6	27.52
164				Me(2)	17.47
165				Me(3)	15.74
166	*cis*-2,3-Dimethylthiane (**12a**) (major)	B	−95	2	41.60
167				3	33.04
168				4	33.86
169				5	20.49
170				6	30.04
171				Me(2,e)	19.88
172				Me(3,a)	11.28
173	*cis*-2,3-Dimethylthiane (**12b**) (minor)	B	−95	2	38.03
174				3	36.67
175				4	28.70
176				5	27.65
177				6	22.76
178				Me(2,a)	13.79
179				Me(3,e)	22.14
180	*cis*-3,4-Dimethylthiane (**16**)	B	30	2	34.71
181				3	[34.67][c]
182				4	[34.42][c]
183				5	31.50
184				6	27.24
185				Me(3)	14.15
186				Me(4)	17.92
187	*cis*-3,4-Dimethylthiane (**16a**) (major)	B	−95	2	36.91
188				3	32.84
189				4	34.88
190				5	29.46
191				6	28.94
192				Me(3,a)	11.05
193				Me(4,e)	21.34
194	*cis*-3,4-Dimethylthiane (**16b**) (minor)	B	−95	2	27.84
195				3	36.12
196				4	32.15
197				5	34.88[d]
198				6	21.34[d]
199				Me(3,e)	21.34[d]
200				Me(4,a)	11.05[d]
201	*trans*-2,4-Dimethylthiane (**10**)	A	30	2	32.73
202				3	42.42
203				4	26.70
204				5	34.93
205				6	23.91
206				Me(2)	21.04
207				Me(4)	21.33

Table II (*Continued*)

Item	Compd	Solvent[b]	t, °C	Carbon assigned	^{13}C shift, ppm
208	*trans*-2,4-Dimethylthiane (**10a**) (major)	A	−95	2	33.96
209				3	41.68
210				4	27.50
211				5	36.10
212				6	23.72[d]
213				Me(2,a)	20.54
214				Me(4,e)	23.72[d]
215	*trans*-2,4-Dimethylthiane (**10a**) (minor)	A	−95	2	30.18
216				3	41.68[d]
217				4	25.50
218				5	31.69
219				6	23.25
220				Me(2,e)	22.36
221				Me(4,a)	17.09
222	*cis*-2,5-Dimethylthiane (**8**)	A	30	2	35.68
223				3	32.53
224				4	30.96
225				5	29.95
226				6	33.67
227				Me(2)	21.13
228				Me(5)	19.62
229	*cis*-2,5-Dimethylthiane (**8a**) (major)	A	−95	2	38.11
230				3	30.28
231				4	32.37
232				5	25.81
233				6	35.67
234				Me(2,e)	22.36
235				Me(5,a)	16.49
236	*cis*-2,5-Dimethylthiane (**8b**) (minor)	A	−95	2	31.89
237				3	33.84
238				4	28.39
239				5	34.06
240				6	30.06
241				Me(2,a)	19.82
242				Me(5,e)	23.42
243	3-Methylthiane (**3**)	A	30	2	36.00
244				3	33.50
245				4	35.15
246				5	28.18
247				6	28.66
248				Me	22.77
249	3-Methylthiane (**3a**) (major)	A	−83	2	35.47
250				3	33.74
251				4	34.82
252		A	−83	5	[28.24][c]
253				6	[28.29][c]
254				Me	23.42
255	3-Methylthiane (**3b**) (minor)	A	−83	Me	16.49

[a] Solutions are 40–50% v/v in solvent indicated. Temperature measurements are ±5 °C. [b] A is pure CD_2Cl_2, B is 80% CH_2Cl_2 and 20% $(CD_3)_2CO$. [c] Brackets indicate that the assignment is not unambiguous. [d] Overlap with peaks of major isomer.

complicated by the fact that the compounds in question are conformationally inhomogeneous with the conformer populations being initially unknown. However from the free energy differences obtained from the low temperature spectra and the assumption that $\Delta S = 0$[16] the room temperature conformer populations of compounds **8, 10, 12,** and **16** were estimated to be 51:49, 65:35, 57:43, and 73:27, respectively, with the **a** conformers being favored in each case. This information along with the shift parameters (in the case of compounds **12** and **16** the $V_{1,2}$-e,a parameters for cyclohexane) and the low temperature shifts allowed the rest of the assignments to be made for compounds **8, 10, 12,** and **16,** except for the methine carbons in **16** which cannot be unambiguously assigned because of the small shift difference between them.

The assignments of the methyl resonances in compounds **7, 8, 9, 10, 11, 12, 15, 16, 19, 20,** and **23** (which could not be unequivocally assigned) are based on analogy to Dalling and Grant's methylcyclohexane data, the unequivocally assigned methyl resonances (compounds **2, 3, 4, 5, 6, 13, 14, 17,** and **18**), and, in the case of compounds **8, 10, 12,** and **16,** the room temperature conformer populations of these compounds given above.

The assignment of the low temperature ^{13}C NMR spectra (Table II) of compounds **3, 6, 8, 10, 12, 14,** and **16** is based entirely on calculated shifts. In compounds **6** and **14** only one conformer is present, and the assignments are straightforward.

In the low temperature ^{13}C spectrum of compound **12** all 14 resonances of the two conformers are resolved, and a suffrcient free energy difference exists between the two to allow an easy distinction between resonances belonging to the major and minor conformers. The major conformer is assigned the 2-

Table III. Conformational Equilibria in Methylthianes Measured by Low Temperature ^{13}C NMR

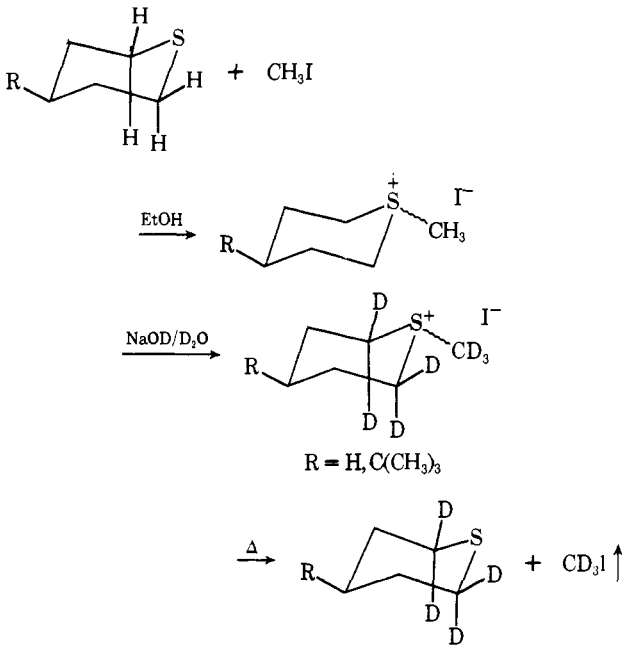
Compd	t, °C	$\Delta G°$, kcal/mol	Preferred conformer, K
3-Methylthiane (**3**)	−83	1.40 ± 0.07	e, 41 ± 7
cis-2,5-Dimethylthiane (**8**)	−95	0.02 ± 0.01	2-CH_3-e, 5-CH_3-a (**8a**), 1.06 ± 0.03
trans-2,4-Dimethylthiane(**9**)	−95	0.38 ± 0.02	2-CH_3-a, 4-CH_3-e (**10a**), 2.92 ± 0.17
cis-2,3-Dimethylthiane (**12**)	−95	0.16 ± 0.02	2-CH_3-e, 3-CH_3-a (**12a**), 1.57 ± 0.09
cis-3,4-Dimethylthiane (**17**)	−95	0.60 ± 0.05	3-CH_3-a, 4-CH_3-e (**16a**), 5.45 ± 0.8

Table IV. Conformational Free Energies of Methyl Groups at the 2-, 3-, and 4-Positions of Thiane[a]

Position	$-\Delta G°$, kcal/mol	$-\Delta G°$, calcd[10]
2-CH_3	1.42 ± 0.07	0.99
3-CH_3	1.40 ± 0.07	1.10
4-CH_3	1.80 ± 0.10	1.59

[a] Calculated from $\Delta G°$'s of **3, 8,** and **9** assuming additivity.

Scheme III



CH_3-e, 3-CH_3-a configuration on the basis of the extremely high field methyl shifts of 11.28 ppm—caused by the γ gauche effect of the heteroatom[17]—(item 172), as compared to the highest field resonance of the minor component (item 178), 13.79 ppm, and the better fit of the calculated vs. experimental shifts.

Integration of the peaks at 41.60 and 38.03 ppm (i.e., C(2) major and minor; items 166 and 173) yields a K_{eq} of 1.55 ± 0.07, corresponding to a ΔG of 0.16 ± 0.02 kcal/mol in favor of the 2-CH_3-e, 3-CH_3-a conformer.

The low temperature spectrum of compound **16** is difficult to interpret because the energy difference between the conformers (≈0.60 kcal/mol) is such that resonances of the minor conformer are small and serious overlap occurs. The assignment of the major conformer to the 3-CH_3-a, 4-CH_3-e structure is based on the better fit of the calculated vs. experimental shifts. From the calculated spectrum several of the overlaps can be spotted, as indicated in the table. Integration of the C(2) resonances in the major and minor conformers (items 187 and 194) yields a K_{eq} of 5.4 ± 0.70, corresponding to a free energy difference of 0.60 ± 0.05 kcal/mol.

In the low temperature ^{13}C spectrum of compound **8** all 14 resonances of the two conformers are resolved, but unfortunately, only a slight (≈0.02 kcal/mol) energy difference exists between them, causing uncertainty in the assignments of items 230 and 240, 237 and 239, and 231 and 236, where insufficient differences exist between the calculated shifts to make an unambiguous choice. Integration of the peaks at 22.36 and 19.82 ppm and at 16.49 and 23.42 ppm (items 234 and 241, 235 and 242) gives a K_{eq} of 1.06 ± 0.02, corresponding to a free energy difference of 0.02 ± 0.01 kcal/mol between the two conformers, favoring the 2-CH_3-e, 5-CH_3-a conformer.

In the low temperature ^{13}C spectrum of **10** only 12 resonances are resolved. Fortunately, the free energy difference between the conformers is such that the overlaps (see table) are easily spotted. Assignment of the minor conformer to the 2-CH_3-e, 4-CH_3-a conformer is based on its having the highest field methyl resonance. Assignment of the resonances is straightforward. Integration of items 208 and 215, and 211 and 218, corresponding to C(2) and C(5), respectively, yields a K_{eq} of 2.84 ± 0.25 and a free energy difference of 0.38 ± 0.02 kcal/mol in favor of the 4-CH_3-e, 2-CH_3-a conformer.

Conformational Equilibria in Methylthianes. In Table III the conformational equilibria of the methylthianes determined by low temperature ^{13}C NMR are summarized. In order to obtain the conformational free energies of methyl groups at the 2- and 4-positions from the experimental $\Delta G°$'s for **3, 8,** and **9,** it is necessary to assume that they are not affected by the remote methyl groups in compounds **8** and **10** (i.e., that additivity holds). In Table IV the conformational free energies of methyl groups at the 2-, 3-, and 4-positions computed on this basis are summarized along with the values recently calculated[10] by the molecular mechanics method. Agreement between the experimental and calculated values is, at best, approximate.

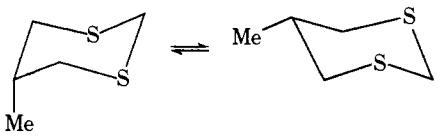
The best agreement is with the values for the 4-methyl group, which is not surprising since this position on the thiane ring is very "cyclohexane-like", and Allinger's force field has been used successfully in the past to calculate conformational energies for pure carbonoid systems.[18a] Allinger and Hickey[10] have not reported the calculated geometry of the parent thiane, but Lambert and co-workers[19] have determined, by the R value method, that the thiane ring is more puckered than cyclohexane ($\Psi_{\alpha\beta}$ = 60°, $\Psi_{\beta\gamma}$ = 61°). The increased puckering causes the axial protons to move closer to one another in the parent thiane, and an axial substituent, such as a methyl group, may be expected to be closer to the syn-axial protons if the same geometry is maintained upon methyl substitution. This may explain why a methyl group in 4-methylthiane has a slightly higher conformational free energy than in methylcyclohexane.

On the basis of essentially the same force field used to calculate the conformational preferences of methyl groups in

thianes, Allinger and Wertz[18a] have recently hypothesized that the major cause of the instability of the *gauche*-butane conformation and the axial conformation of methylcyclohexane is not the gauche interaction of the methyl (or methylene) groups, but the gauche interaction of the vicinal 2,3-hydrogens. On the basis of this hypothesis one may predict a substantial reduction of the conformational preference for substituents when the interaction between a pair of vicinal 2,3-hydrogens is removed. Such is the case in 2-methylthiane. In fact, this is the explanation given[10] for the low conformational free energy (0.99 kcal/mol) calculated[10] for the 2-methyl group in thiane. Allinger and Wertz[18a] claim that the conclusion regarding the origin or cause of the instability of gauche conformations in carbonoid systems is independent of the force field used, but others[18b,20] have disagreed with this point. If, in fact, the conclusion *is* dependent on the force field used, the discrepancy between the experimental and calculated values for the conformational free energy of 2-methylthiane might be lessened by choice of a harder C–C and a softer H–H potential.

Allinger and Hickey[10] attribute the difference (0.47 kcal/mol) between their calculated value for the conformational preference of a methyl group at C(3) (1.10 kcal/mol) in thiane and that calculated for methylcyclohexane (1.57 kcal/mol) to a substantial reduction in the interactions of the axial methyl group by replacement of one of the syn-axial hydrogens with a lone pair. This reduction seems to be slightly overestimated by their force field, however, being in fact only 1.70 − 1.40 = 0.30 kcal/mol. The force field also underestimates the absolute values of the conformational energies not only in methylcyclohexane (1.57 kcal/mol calculated vs. 1.7 kcal/mol experimental) but also in 4-methylthiane (1.59 kcal/mol calculated vs. 1.80 kcal/mol found).

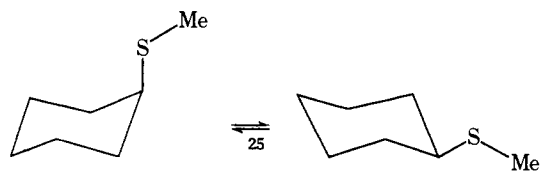
The experimentally determined value for the conformational free energy of a 3-methyl group in thiane (1.40 ± 0.07 kcal/mol) is in good agreement with that estimated by two different methods from known conformational free energies. The conformational free energy of a 5-methyl group in dithiane has been determined to be 1.16 kcal/mol (eq 1).[5,21] If this value



(1)

$\Delta G^\circ = -1.16$ kcal/mol

is assumed to be twice the value of the gauche C–C–C–S interaction, then one can calculate the conformational free energy of the 3-methyl group in thiane to be 0.58 kcal/mol + 0.85 kcal/mol (gauche C–C–C–C), or 1.43 kcal/mol. Again, the conformational free energy of the thiomethyl group in cyclohexane has been determined to be 1.05 ± 0.02 kcal/mol (eq 2),[22,23a] and if this is taken to be twice the gauche C–C–C–S



(2)

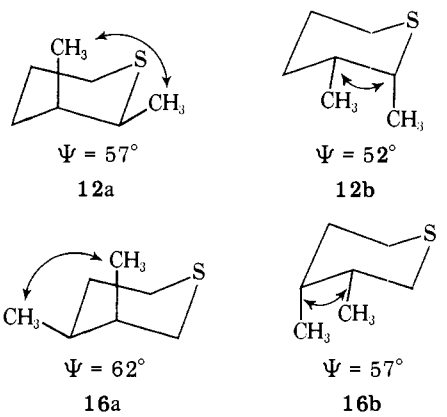
$\Delta G^\circ = -1.05$ kcal/mol

interaction, one can calculate (as above) the conformational free energy of a 3-methyl group to be 1.38 kcal/mol.[23b] Both values are in good agreement with the experimentally determined 1.40 kcal/mol.

However, an analogous estimate of the conformational free energy of the 2-methyl group in thiane, by averaging the $-\Delta G$ of 2-methyl-1,3-dithiane (1.92 kcal/mol)[5,21] with the $-\Delta G$ of methylcyclohexane (1.70 kcal/mol) leads to too high an estimate of $-\Delta G$, 1.81 vs. 1.42 kcal/mol measured. The reason for this discrepancy lies in the difference in the geometry of the rings. Construction of a scale model of the axial conformers of 2-methyl-1,3-dithiane with the bond lengths, bond angles, and torsional angles which have been determined by x-ray crystallographic analysis of 2-*p*-chlorophenyl-1,3-dithiane[24] shows that the distance between the methyl hydrogens and the syn-axial 4,6-hydrogens is about 2.0 Å. Construction of a similar model for the axial conformer of 2-methylthiane indicates a corresponding distance to the C(4) andC(6) syn-axial hydrogens of ca. 2.0 and 2.35 Å, respectively, and by a slight rotation of the methyl group both distances can be brought to about 2.15 Å. This is significantly larger than in either 1,3-dithiane (because of lesser puckering of the thiane) or cyclohexane (because of the longer C–S bond distance) and probably explains why the methyl group in 2-methylthiane has a substantially lower conformational free energy than in either methylcyclohexane or 2-methyl-1,3-dithiane.

The conformational equilibria in *cis*-2,3-dimethylthiane and *cis*-3,4-dimethylthiane (Table III) are interesting. The measured values (Table III) deviate significantly (by 0.14 and 0.20 kcal/mol, respectively) from those calculated (0.02 and 0.40 kcal/mol), assuming additivity of the ΔG's, conformers **12a** and **16a** being preferred. A possible reason for the nonadditivity is seen by inspecting scale models of the two conformers of each compound. The dihedral angle between the exocyclic methyl groups in the 2-CH_3-a, 3-CH_3-e conformer of *cis*-2,3-dimethylthiane (**12b**) is 52°, while the corresponding dihedral angle in the 2-CH_3-e, 3-CH_3-a conformer (**12a**) is 57° (Chart I).[25a] Similarly, the dihedral angles between the methyl groups in the 3-CH_3-e, 4-CH_3-a conformer of *cis*-3,4-dimethylthiane (**16b**) are 57 vs. 62° in the 3-CH_3-a, 4-CH_3-e conformer (**16a**) (Chart I). The nonadditivity thus seems to result from the difference in the interactions of the exocyclic methyl groups in the two conformers due to the different dihedral angles between them.[25b]

Chart I



Ring Carbon Shifts in Methyl-Substituted Thianes. During the course of the assignment of the ^{13}C NMR spectra of the methylthianes, a set of chemical shift parameters was developed. In order to optimize these parameters a multiple-linear regression analysis of the shift data was performed using the program BMD-O2R (UCLA Biomedical Statistical Package).[6,26] The conformationally inhomogeneous compounds (**8, 10, 12,** and **16**) were treated as being composed of appropriate mole fractions of the two conformers, these fractions being calculated from the free energy differences obtained from low temperature spectra and the assumption that $\Delta S = 0$.[16] Compounds **2, 3,** and **4** were also treated as being composed of appropriate mole fractions of the two conformers. In Tables V, VI, and VII the optimized chemical shift parameters for C(2,6), C(3,5), and C(4) in thiane are presented. The shift of

Table V. Chemical Shift Parameters at C(2,6) in Methyl-Substituted Thianes

Parameter[a]	Value of parameter, ppm	No. of occurrences
Parent	29.12 ± 0.11[b]	27
α_e-2	8.47 ± 0.11	8
α_a-2	4.48 ± 0.23	4
β_e-2	6.72 ± 0.12	8
β_a-2	6.18 ± 0.32	5
$\gamma_e{}^4$-2	0.06 ± 0.11	9
$\gamma_a{}^4$-2	−7.42 ± 0.44	7
δ_e-2	−0.54 ± 0.11	8
δ_a-2	−0.01 ± 0.20	5
$\gamma_e{}^6$-2	0.71 ± 0.11	8
$\gamma_a{}^6$-2	−4.89 ± 0.23	4
G^3-2	−1.05 ± 0.31	2
G^4-2	2.62 ± 0.43	2
Standard deviation of fit:	0.18 ppm	
Chemical shift range:	17.34 ppm	

[a] The exponent locates the group causing the shift, the main locant the carbon whose shift was measured. [b] Calculated base value.

Table VI. Chemical Shift Parameters at C(3,5) in Methyl-Substituted Thianes

Parameter[a]	Value of parameter, ppm	No. of occurrences
Parent	27.72 ± 0.14[b]	27
$\beta_e{}^2$-3	9.21 ± 0.14	8
$\beta_a{}^2$-3	5.93 ± 0.32	4
α_e-3	5.95 ± 0.16	8
α_a-3	−0.62 ± 0.39	6
$\beta_e{}^4$-3	8.43 ± 0.15	9
$\beta_a{}^4$-3	5.28 ± 0.65	6
γ_e-3	0.68 ± 0.14	8
γ_a-3	−6.47 ± 0.32	6
δ_e-3	−0.86 ± 0.14	8
δ_a-3	01−0.21 ± 0.29	3
G^3-3	−2.94 ± 0.39	2
G^4-3	−1.38 ± 0.63	2
G^5-3	1.70 ± 0.34	2
Standard deviation of fit:	0.22 ppm	
Chemical shift range:	26.67 ppm	

[a] See footnote *a*, Table V. [b] Calculated base value.

Table VII. Chemical Shift Parameters at C(4) in Methyl-Substituted Thianes

Parameter[a]	Value of parameter, ppm	No. of occurrences
Parent	26.35 ± 0.18[b]	17
γ_e-4	0.45 ± 0.13	6
γ_a-4	−6.04 ± 0.27	4
β_e-4	8.83 ± 0.14	10
β_a-4	5.53 ± 0.27	4
α_e-4	6.22 ± 0.24	4
α_a-4	−0.61 ± 0.95	4
G^3-4	−1.27 ± 0.30	2
G^4-4	−2.24 ± 0.90	2
Standard deviation of fit:	0.25 ppm	
Chemical shift range:	27.59 ppm	

[a] See footnote *a*, Table V. [b] Calculated base value.

Table VIII. Parameters for the Effect of Methyl Substituents (chair conformations)

Parameters[a]	Cyclohexane,[15] ppm	1,3-Dioxane,[27] ppm	1,3-Dithiane,[6] ppm
α_e-2	5.6	5.3	10.27
α_e-4	5.6	5.7	8.33
α_e-5	5.6	3.1	5.56
α_a-2	1.1	0.3	8.30
α_a-4	1.1	0.6	3.20
α_a-5	1.1	3.1	−1.84
β_e-4	8.9	5.8	7.03
β_e-5	8.9	7.3	8.96
β_a-4	5.2	4.5	6.37
β_a-5	5.2	3.7	5.68
γ_e-2	0.0	0.8	0.77
$\gamma_e{}^2$-4	0.0	0.1	1.21
$\gamma_e{}^6$-4	0.0	−0.1	0.62
γ_a-2	−5.4	−9.0	−9.40
$\gamma_a{}^2$-4	−5.4	−7.3	−5.49
$\gamma_a{}^6$-4	−5.4	5.3	−6.53
δ_e-2	0.3	−0.2	−0.41
δ_e-5	0.3	−0.8	−1.25
δ_a-2	0.1	0.4	0.19
δ_a-5	0.1	0.1	−1.10

[a] See footnote *a*, Table V.

the various ring carbons calculated using these parameters are given alongside the experimental shifts in Table I. In Table VIII a summary of the chemical shift parameters which have been derived for methyl-substituted cyclohexanes,[15] 1,3-dioxanes,[27] and 1,3-dithianes[6] are given for comparison.

Comparison of the chemical shift parameters for C(2,6) in thiane (Table V) with the cyclohexane parameters[15] (Table VIII) and the parameters for C(2) and C(4,6) in 1,3-dithiane[6] (Table VIII) shows that the chemical shift parameters for C(2,6) in thiane are similar to the C(4,6)-1,3-dithiane parameters and are an almost perfect average of the cyclohexane and C(2)-1,3-dithiane parameters. The α_e and α_a parameters for C(2,6) in thiane are both larger than those for cyclohexane, while the β_e and β_a effects are smaller and larger, respectively. The larger α_e and α_a effects observed for C(2,6) in thiane and for C(2) and C(4,6) in 1,3-dithiane can be attributed to a decrease in the contribution of the diamagnetic term since the $\beta_e{}^2$-3 and $\beta_a{}^2$-3 effects in thiane and $\beta_e{}^4$-5 and $\beta_a{}^4$-5 effects in 1,3-dithiane are similar to the β_e and β_a effects observed in cyclohexane and only the paramagnetic term contributes significantly to the chemical shift in the β-position.[28] It is also interesting that the $\gamma_a{}^6$-2 and $\gamma_a{}^4$-2 parameters are different in magnitude and are of an order one might predict on the basis of distance between the axial 4- or 6-methyl groups and the axial 2-protons (see section on conformational preferences).

The C(3,5) parameters are much like the cyclohexane parameters except for the α_a-3 parameter, which is slightly negative. This value is intermediate between the α_a of cyclohexane and α_a-5 of 1,3-dithiane.

The C(4) parameters, as expected, are very similar to those for cyclohexane; the significance of the negative α_a value is doubtful in view of its large standard deviation.

Chemical Shifts of Methyl Groups in Methyl-Substituted Thianes. A comparison of the chemical shifts of equatorial and axial methyl groups at the various ring positions of thiane and 1,3-dithiane[6] with the chemical shifts of equatorial and axial methyl groups on cyclohexane[29] is interesting. These data are summarized in Table IX. From the data one can clearly see that the ring sulfur atoms have a palpable effect on the shifts of all but the most remote (C(4) in thiane) methyl groups.

Both an equatorial methyl group at C(2,6) in thiane and one at C(4,6) in 1,3-dithiane are β to one ring sulfur atom and are shifted slightly (1.48 and 1.45 ppm) upfield compared to an equatorial methyl group in cyclohexane, while an equatorial methyl group at C(2) in 1,3-dithiane (which is β to two ring

sulfur atoms) is shifted upfield approximately twice as much (2.90 ppm). An axial methyl group at either C(2,6) in thiane or at C(4,6) in dithiane is β to one ring sulfur atom and is shifted downfield by approximately 3 ppm compared to an axial methyl group in cyclohexane, while an axial methyl group at C(2) in 1,3-dithiane (which is β to two ring sulfur atoms) is shifted downfield by 6.07 ppm compared to an axial methyl group in cyclohexane. The net effect of the upfield shift of the equatorial methyls β to sulfur and the downfield shift of the axial methyls β to sulfur is a large attenuation of the normal 5.7-ppm difference between axial and equatorial methyl groups on cyclohexane to 1.3–1.5 ppm in the case where the methyl group is β to one sulfur. When the methyl is β to two sulfurs, as at C(2) in 1,3-dithiane, a complete reversal of the normal pattern results, with the axial methyl group resonating at higher field than the equatorial one. The intermediacy of the shifts of the equatorial and axial methyl groups at C(2,6) in thiane between those in cyclohexane and those at C(2) in 1,3-dithiane clearly establishes that the unusual shifts of the equatorial and axial methyl groups at C(2) in 1,3-dithiane are not due to the known[11] electronic interaction between the ring sulfur atoms. Similar effects have been observed in the proton shifts of equatorial and axial protons β to sulfur.[6]

The effect of one γ sulfur on the chemical shift of a 3(5)-equatorial methyl group in thiane or two γ sulfurs on a 5-equatorial methyl in 1,3-dithiane is a slight upfield shift of approximately 0.5 ppm per γ sulfur atom. The effect of a γ sulfur on an axial methyl is also an upfield shift, but slightly larger (0.6 ppm/γ sulfur), resulting in the magnitude of the shift difference between axial and equatorial methyl groups being larger at these positions in thiane and 1,3-dithiane than that in cyclohexane.

The shifts of both equatorial and axial methyl groups at C(4) in thiane are almost identical with the shifts of equatorial and axial methyl groups in cyclohexane.

Table IX. Chemical Shifts (in ppm) of Equatorial and Axial Methyl Groups in Methyl-Substituted Cyclohexanes, 1,3-Dithianes, and Thianes

Compound	Position	Equatorial shift	Axial shift	Difference (a − e)
Cyclohexane[29]	All	23.20	17.53	−5.67
1,3-Dithiane[6]	2	20.30	23.60	3.30
	4,6	21.75	20.25	−1.50
	5	22.25	16.40	−5.85
Thiane	2,6	21.72[a]	20.44[b]	−1.28
	3,5	22.82[c]	16.85[d]	−5.97
	4	23.07[e]	17.09[f]	−5.98

[a] Average of 2-methyl equatorial resonances in **2**, **5**, **7**, **9**, and **20** (items 9, 23, 33, 47, and 115). [b] Average of 2-methyl axial resonances in the low-temperature spectra of **6**, **8**, and **10** (items 147, 241, and 213). [c] Average of the 3-methyl equatorial resonances in **3**, **7**, **13**, and **19** (items 15, 34, 73, and 109). [d] Average of 3-methyl axial resonances in the low-temperature spectra of **14** and **8** (items 158 and 235). [e] Average of 4-methyl equatorial resonances in **4**, **9**, and **22** (items 19, 48, and 130). [f] Axial 4-methyl resonance in low-temperature spectra of **10** (item 221).

Experimental Section

Analytical gas liquid partition chromatography was carried out with a Hewlett-Packard 5750 research chromatograph, equipped with a thermal conductivity detector, on ⅛ in. columns. Columns used were a 12-ft, aluminum, 20% Carbowax 20 M + 10% KOH on Chromosorb W, 80/100 mesh; a 20-ft, aluminum, 20% QF-1 on Chromosorb W, 80/100 mesh; and a 6-ft, stainless steel, 10% UC-W-98 Chromosorb W, 80/100 mesh, at temperatures between 70 and 120 °C. A Varian Aerograph Series 2700 and a Varian Aerograph Model 960, with ⅜ in. aluminum columns with matching phase on Chromosorb A were used for preparative VPC.

NMR spectra were recorded on a Varian XL-100 pulsed Fourier transform nuclear magnetic resonance spectrometer. ^{1}H NMR spectra were recorded in either the CW or FT mode, in 5-mm o.d. tubes. ^{13}C NMR spectra were measured at 25.16 MHz, in the pulsed mode, in 10-mm o.d. tubes. The solvent in both cases was $CDCl_3$ [except in the case of the low temperature spectra where the solvent was either CD_2Cl_2 or 80% CH_2Cl_2/20% $(CD_3)_2CO$], with 2–5% Me_4Si admixed as internal reference; the deuterium of the solvent provided the internal lock signal.

Microanalyses were carried out by Galbraith Laboratories, Inc.

General Procedures for Cyclization of 1,5-Dibromides and 1,5-Ditosylates to Thianes. Two procedures were used to convert the 1,5-dibromides and 1,5-ditosylates to the thianes: procedure A (for the dibromides)[30,31] and procedure B (for the ditosylates).

Procedure A. The dibromide was dissolved in approximately five times its volume of absolute alcohol. A 1.5 mol equiv of sodium sulfide nonahydrate was dissolved in enough hot 70% ethanol to make an approximately 2.0 M solution. One-half of the sodium sulfide solution was transferred to a round-bottom three-neck flask equipped with a mechanical stirrer (or a magnetic stirring bar in small-scale reactions), a reflux condenser, and a Claisen adapter to which two constant-rate addition funnels were attached. The solution was stirred and heated to reflux. The ethanol solution of the dibromide and the remainder of the ethanolic solution of sodium sulfide were then added at such rates that both additions were complete in approximately 1 h. The addition funnels were removed and the resulting solution stirred and refluxed for 24 h. The reaction mixture was then steam-distilled until the distillate was clear. The distillate was diluted with three times its volume of water and extracted four times with 100-ml portions of 40–60 °C petroleum ether. The petroleum ether extracts were combined and washed with three 50-ml portions of water and then dried over anhydrous Na_2SO_4. The solution was filtered, concentrated, and the residue distilled.

Procedure B. Procedure B is the same as procedure A except that the 1,5-ditosylates were dissolved in a minimal amount of warm (40 °C) THF for the addition to the sodium sulfide solution.

2-Methylthiane (2). *N*-Benzoyl-2-methylpiperidine was synthesized in 90% yield from 2-methylpiperidine, benzoyl chloride, and sodium hydroxide following a procedure described for *N*-benzoylpiperidine,[32] bp 165–168 °C (1.2 Torr), mp 43–45 °C (lit.[33] 44–45 °C). This material was converted to 1,5-dibromohexane by phosphorus tribromide–bromine in 70% yield,[34] bp 110–113 °C (18 Torr) (lit.[35] 153–154 °C (100 Torr)). The 1,5-dibromohexane was converted to 2-methylthiane following procedure A in 60% yield, bp 156 °C (760 Torr) (lit.[30] 55 °C (26 Torr)).

^{1}H NMR ($CDCl_3$): δ 1.19 (d, J = 7.0 Hz, 3 h, Me), 1.28–2.10 (br, 6 H, H(3,4,5)), 2.40–2.98 (br, 3 H, H(2,6)).

3-Methylthiane (3). 2-Methylglutaric acid was prepared from methyl methacrylate and diethyl malonate in 75% yield[30] and converted to its diethyl ester in 90% yield by refluxing with 3 equiv of triethyl orthoformate with removal of ethyl formate and ethanol,[36] bp 122 °C (14 Torr) (lit.[30] 136 °C (30 Torr)).

The diethyl 2-methylglutarate was reduced to 2-methyl-1,5-pentanediol by $LiAlH_4$ in ether in 85% yield, bp 85–88 °C (0.4 Torr) (lit.[30] 132 °C (10 Torr)).

The diol was converted to 2-methyl-1,5-dibromopentane using phosphorus tribromide in 80% yield,[37] bp 112–114 °C (17 Torr) (lit.[30] 117 °C (21 Torr)). The dibromide was converted to 3-methylthiane by procedure A in 68% yield, bp 155–158 °C (lit.[30] 157.9 °C (760 Torr)).

^{1}H NMR ($CDCl_3$): δ 0.-0–1.20 (m, iH, H(4a)), 0.95 (d, J = 6.5 Hz, 3 H, Me), 1.40–2.15 (br, 4 H, H(3,4e,5)), 2.17–2.73 (br, 4 H, H(2,6)).

4-Methylthiane (4). 3-Methyl-1,5-dibromopentane was synthesized from 4-methylpiperidine in a similar manner as described above for 1,5-dibromohexane, yield 70%, bp 112–114 °C (18 Torr) (lit.[30] 116–117 °C (20 Torr)). The dibromide was converted to 4-methylthiane in 80% yield by procedure A, bp 156–159 °C (760 Torr) (lit.[30] 54 °C (22 Torr)).

^{1}H NMR ($CDCl_3$): δ 0.91 (d, J = 6.0 Hz, 3 H, Me), 1.10–1.60 (br, 3 H, H(3a,4,5a)), 1.98 (brd, J = 13.5 Hz, 2 H, H(3e,5e)), 2.40–2.90 (br, 4 H, H(2,6)).

4-*tert*-Butylthiane (21). 3-*tert*-Butyl-1,5-dibromopentane was synthesized from 4-*tert*-butylpiperidine as described above, yield 70%,

bp 95–97 °C (2 Torr) (lit.[31] 87–88 °C (0.7 Torr)). The dibromide was converted to 4-*tert*-butylthiane in 70% yield by procedure A, bp 88–90 °C (20 Torr) (lit.[31] 47–48 °C (1 Torr)).

^{1}H NMR ($CDCl_3$): δ 0.83 (s, 9 H, Me's), 0.96 (t of t, J = 11.0, 2.5 Hz, 1 H, H(4)), 1.10–1.58 (m, 2 H, H(3a,5a)), 2.07 (brd, J = 13.5 Hz, 2 H, H(3e,5e)), 2.52–2.70 (br, 4 H, H(2,6)).

***cis*-3,5-Dimethylthiane (13).** *meso*-2,4-Dimethylglutaric anhydride, admixed with the *dl* isomer was synthesized from methyl methacrylate and diethyl methylmalonate[38] and separated by crystallization in 25% yield, mp 92–93 °C (lit.[39] 93.5 °C). The anhydride was reduced to pure *meso*-2,4-dimethyl-1,5-pentanediol in 90% yield by aluminum hydride in THF,[40] bp 95–97 °C (1 Torr) (lit.[38] 97–99 °C (2 Torr)). ($LiAlH_4$ reduction of the anhydride in ether led to considerable epimerization, since the produced thiane was contaminated with 25% of the trans isomer, in contrast to previous reports in the literature.[38]) The diol was converted to *meso*-2,4-dimethyl-1,5-dibromopentane in 80% yield by PBr_3, following the general procedure of Kornblum and Eicher,[37] bp 65–66 °C (1 Torr) (lit.[38] 72–73 °C (2 Torr)). The dibromo compound was converted to *cis*-3,5-dimethylthiane in 75% yield by procedure A, bp 170–173 °C (760 Torr).

Anal. Calcd for $C_7H_{14}S$: C, 64.55; H, 10.83. Found: C, 64.76. H, 10.95.

^{1}H NMR ($CDCl_3$): δ 0.65 (ABC$_2$, J_{AB} = 14.0, J_{AC} = 11.0 Hz, 1 H, H(4a)), 0.90 (d, J = 6.5 Hz, 6 H, Me's), 1.52–2.00 (m, 3 H, H(3,4e,5)), 2.16 (ABC, J_{AB} = 13.0, J_{AC} = 11.0 Hz, 2 H, H(2a,6a)), 2.44 (ABCD, J_{AB} = 13.0, J_{BC} ≈ 3.5, J_{BD} ≈ 1.7 Hz, 2 H, H(2e,6e)).

***trans*-3,5-Dimethylthiane (14).** The *dl* rich mixture of *dl*- and *meso*-2,4-dimethylglutaric anhydrides remaining from the previous synthesis was hydrolyzed to the mixed acids, which were converted to the mixed diethyl *meso*- and *dl*-2,4-dimethylglutarates with triethyl orthoformate[36] in 95% yield, bp 142–146 °C (18 Torr). The mixed diethyl esters were reduced in 92% yield by $LiAlH_4$ in ether to a *dl* rich mixture of *meso*- and *dl*-2,4-dimethyl-1,5-pentanediol, bp 93–99 °C, (1 Torr). The diol mixture was treated with a 100% excess of TsCl in pyridine at 0 °C for 48 h, then worked up to give an oily mixture of the *meso*- and *dl*-ditosylates in 85% yield which was converted, in 80% yield, to a trans rich mixture of *cis*- and *trans*-3,5-dimethylthiane by procedure B, bp 168–175 °C. *dl-trans*-3,5-Dimethylthiane was separated from the cis isomer by preparative GLC on a 12 ft × ⅜ in. 20% Carbowax 20M + 10% KOH on 80/100 Chromosorb A column.

Anal. Calcd for $C_7H_{14}S$: C, 64.55; H, 10.83. Found: C, 64.34; H, 10.93.

^{1}H NMR ($CDCl_3$): δ 1.03 (d, J = 6.5 Hz, 6 H, Me's), 1.37 (brt, J = 5.5 Hz, 2 H, H(4)), 1.90–2.25 (m, 2 H, H(3,5)), 2.24 (ABC, J_{AB} = 13.2, J_{BC} = 7.0 Hz, 2 H, H(2c,6c)), 2.64 (ABC, J_{AB} = 13.2, J_{BC} = 3.0 Hz, 2 H, H(2t,6t)).

***cis*- and *trans*-2,6-Dimethylthiane (5, 6).** Heptan-2-ol-6-one was synthesized from 1,3-dibromobutane and ethyl acetoacetate.[41] This material was reduced in 90% yield by $LiAlH_4$ in ether to a mixture of *meso*- and *dl*-2,6-heptanediol, bp 117 °C (40 Torr) (lit.[41] 128 °C (30 Torr)). The diol mixture was treated with a 100% excess of TsCl in dry pyridine at ≈5 °C for 48 h and worked up to yield an oily mixture of ditosylates in 85% yield. The ditosylate mixture was converted to a 50:50 mixture of *cis*- and *trans*-2,6-dimethylthiane in 68% yield by procedure B, bp 170–180 °C (760 Torr). The diastereomeric products were separated by preparative GLC on a 20 ft × ⅜ in. 30% QF-1 on 80/100 mesh Chromosorb A. The product with the shorter retention time was assigned the cis structure, and that with the longer retention time, the trans on the basis of their ^{1}H and ^{13}C NMR spectra.

***cis*-2,6-Dimethylthiane (5).** Anal. Calcd. for $C_7H_{14}S$: C, 64.55; H, 10.83. Found: C, 64.39; H, 10.75. ^{1}H NMR ($CDCl_3$): δ 1.08–1.43 (m, 2 H, H(4)), 1.18 (d, J = 6.8 Hz, 6 H, Me's), 1.70–2.05 (m, 4 H, H(3,5)), 2.61–3.02 (complex m, 2 H, H(2,6)).

***trans*-2,6-Dimethylthiane (6).** Anal. Calcd for $C_7H_{14}S$: C, 64.55; H, 10.83. Found: C, 64.28; H, 10.83. ^{1}H NMR ($CDCl_3$): δ 1.30 (d, J = 7.0 Hz, 6 H, Me's), 1.35–2.03 (m, 6 H, H(3,4,5)), 2.80–3.12 (m, 2 H, H(2,6)).

3,3,5-Trimethylthiane (19). 2,2,4-Trimethyl-1,5-pentanediol was synthesized in 30% yield from 2,2,4-trimethyl-2-pentene and diborane in THF,[42] bp 102–105 °C (1 Torr) (lit.[42] 132–133 °C (8.5 Torr)). The diol was converted to its ditosylate in 85% yield by reaction with a 100% excess of TsCl in dry pyridine for 72 h, followed by the usual workup. The oily ditosylate was cyclized by procedure B in 90% yield to 3,3,5-trimethylthiane, bp 65 °C (18 Torr).

Anal. Calcd for $C_8H_{16}S$: C, 66.66; H, 11.18. Found: C, 66.86; H, 11.37.

^{1}H NMR ($CDCl_3$): δ 0.83 (d of t, J ≈ 13.7 Hz, 1 H, H(4a)), 0.88 (d, J = 6.3 Hz, 3 H, Me(5)), 0.98 (s, 3 H, Me(3e)), 1.12 (brs, 3 H, Me(3a)), 1.43 (d of t, J ≈ 13.7, 2.2 Hz, 1 H, H(4e)), 1.65–1.95 (complex m, 1 H, H(5)), 2.12 (d of d, J = 13.7, 11.0 Hz, 1 H, H(6a)), 2.12 (d of t, J = 13.0, 1.7 Hz, 1 H, H(2e)), 2.43 (d of d of d, J = 13.7, 3.5, 1.7 Hz, 1 H, H(6e)), 2.49 (AB, J_{AB} = 13.0 Hz, 1 H, H(2a)).

4,4-Dimethylthiane (18). 3,3-Dimethylglutaric acid was synthesized[43] by oxidation of dimedone with sodium hypochlorite (Chlorox) in 90% yield, mp 98–99 °C (lit.[43] 100–102 °C). The acid was reduced by $LiAlH_4$ in ether to 3,3-dimethyl-1,5-pentanediol in 90% yield, bp 95–96 °C (1 Torr) (lit.[44] 95 °C (1 Torr). The diol was converted to its ditosylate in 75% yield by reaction with a 100% excess of TsCl in dry pyridine at 5 °C for 72 h. The oily ditosylate was converted to 4,4-dimethylthiane by procedure B in 88% yield, bp 171 °C (760 Torr) (lit.[45] 57–58 °C (13 Torr)).

^{1}H NMR ($CDCl_3$): δ 0.91 (s, 6 H, Me's), 1.58 (m, (A_2B_2) 4 H, H(3,5)), 2.60 (m, (A_2B_2) 4 H, H(2,6)).

3,3-Dimethylthiane (17). Methyl 4,4-dimethylglutaraldehyde was synthesized from the piperidine enamine of isobutyraldehyde and ethyl acrylate,[46] bp 39–41 °C (0.4 Torr) (lit.[46] 40–41 °C (0.5 Torr)). It was then reduced, by $LiAlH_4$ in ether, to 2,2-dimethyl-1,5-pentanediol in 90% yield, bp 135–136 °C (18 Torr) (lit.[47] 130 °C (12 Torr)). The diol was converted to its ditosylate by reaction with a 100% excess of TsCl for 48 h followed by normal workup, yield 85%, mp 76–77 °C. The ditosylate was converted to 3,3-dimethylthiane in 85% yield by procedure B, bp 168 °C (760 Torr).

Anal. Calcd for $C_7H_{14}S$: C, 64.55; H, 10.83. Found: C, 64.34; H, 10.71.

^{1}H NMR ($CDCl_3$): δ 1.05 (s, 6 H, Me's), 1.32 (m, 2 H, H(4)), 1.80 (m, 2 H, H(5)), 2.36 (m, 2 H, H(2)), 2.48 (m, 2 H, H(6)).

***cis*- and *trans*-2,5-Dimethylthiane (8, 7).** Diethyl 2-acetyl-4-methyl glutarate was synthesized[48] by condensing ethyl acetoacetate and methyl methacrylate, bp 115–117 °C (1 Torr) (lit.[48] 122–123 °C (2 Torr)), and was hydrolyzed by concentrated HCl to give 2-methyl-5-ketohexanoic acid (85% yield), bp 113–115 °C (0.5 Torr). The acid was reduced by $LiAlH_4$ in ether to a mixture of *threo*- and *erythro*-2-methyl-1,5-hexanediol, bp 95–98 °C (1 Torr), yield 92%. The mixture of diols was converted to an oily mixture of ditosylates by reaction with a 100% excess of TsCl in dry pyridine at 5 °C for 72 h in 78% yield. The ditosylates were cyclized to a mixture of *cis*- and *trans*-2,5-dimethylthiane in 72% yield by procedure B, bp 165–175 °C (760 Torr). The isomeric products were separated by preparative GLC on a 12 ft × ⅜ in. 20% Carbowax 20M + 10% KOH on Chromosorb A. The short and long retention time products were assigned the trans and cis structures, respectively, on the basis of their ^{1}H and ^{13}C NMR spectra.

***trans*-2,5-Dimethylthiane (7).** Anal. Calcd for $C_7H_{14}S$: C, 64.55; H, 10.83. Found: C, 64.23; H, 10.82. ^{1}H NMR ($CDCl_3$): δ 0.94 (d, J = 6.5 Hz, 3 H, Me(5)), 1.17 (d, J = 6.8 Hz, 3 H, Me(2)), 1.00–2.10 (complex m, 5 H, H(3,4,5)), 2.36 (d of d, J = 13.7, 11.0 Hz, 1 H, H(6a)), 2.46 (d of d of d, J = 13.7, ≈3.5, ≈1.7 Hz, 1 H, H(6e)), 2.60–2.90 (complex m, 1 H, H(2)).

***cis*-2,5-Dimethylthiane (8).** Anal. Calcd for $C_7H_{14}S$: C, 64.55; H, 10.83. Found: C, 64.74; H, 10.99. ^{1}H NMR ($CDCl_3$): δ 1.06 (d, J = 6.5 Hz, 3 H, Me(5)), 1.28 (d, J = 7.0 Hz, 3 H, Me(2)), 1.35–2.10 (complex m, 5 H, H(3,4,5)), 2.41 (ABC, J_{AB} = 13.5, J_{AC} = 6.5 Hz, 1 H, H(6c)), 2.70 (ABC, J_{AB} = 13.5, J_{BC} = 3.5 Hz, 1 H, H(6t)), 2.65–2.95 (complex m, 1 H, H(2)).

***cis*- and *trans*-2,4-Dimethylthiane (9, 10).** Methyl 3-methyl-5-ketohexanoate was synthesized from methyl β,β-dimethylacrylate and acetyl chloride,[49] bp 102–103 °C (18 Torr) (lit.[49] 97 °C (13 Torr)). The ester was reduced by $LiAlH_4$ in ether to a mixture of *threo*- and *erythro*-3-methyl-1,5-hexanediol, bp 97–98 °C (0.4 Torr), yield 90%. The diol mixture was converted to an oily mixture of ditosylates (80% yield) by reaction with a 100% excess of TsCl in dry pyridine at 5 °C for 72 h. The ditosylate mixture was cyclized to a mixture of *cis*- and *trans*-2,4-dimethylthiane by procedure B, yield 75%, bp 165–170 °C. The isomeric *cis*- and *trans*-2,4-dimethylthianes were separated by preparative GLC on a 12 ft × ⅜ in. 20% Carbowax 20M + 10% KOH column on 80/100 Chromosorb A. The short and long retention time products were assigned the cis and trans structures, respectively, on the basis of their ^{1}H and ^{13}C NMR spectra.

***cis*-2,4-Dimethylthiane (9).** Anal. Calcd for $C_7H_{14}S$: C, 64.55; H, 10.83. Found: C, 64.60; H, 10.75. ^{1}H NMR ($CDCl_3$): δ 0.80–1.60

(complex m, 3 H, H(3a,4,5a)), 0.91 (d, J = 6.5 Hz, 3 H, Me(4)), 1.18 (d, J = 7.0 Hz, 3 H, Me(2)), 1.80–2.03 (complex m, 2 H, H(3e,5e)), 2.42–2.92 (complex m, 3 H, H(2,6)).

***trans*-2,4-Dimethylthiane (10).** Anal. Calcd for $C_7H_{14}S$: C, 64.55; H, 10.83. Found: C, 64.69; H, 10.77. ^1H NMR ($CDCl_3$): δ 0.93 (d, J = 6.0 Hz, 3 H, Me(4)), 1.23–2.07 (complex m, 5 H, H(3,4,5)), 1.31 (d, J = 7.0 Hz, 3 H, Me(2)), 2.48–2.78 (complex m, 3 H, H(2,6)).

***cis*- and *trans*-3,4-Dimethylthiane (16, 15).** *erythro*- and *threo*-2,3-Dimethylglutaric acid were synthesized by condensing ethyl crotonate and diethyl methylmalonate followed by hydrolysis and decarboxylation.[50] The mixture was converted to a mixture of diethyl esters by refluxing with triethyl orthoformate (95% yield),[36] bp 125–130 °C (1 Torr). The mixture of diethyl esters was reduced (90% yield) by $LiAlH_4$ in ether to a mixture of *erythro*- and *threo*-2,3-dimethyl-1,5-pentanediol, bp 95–97 °C (0.4 Torr). The diol mixture was converted to an oily mixture of *threo*- and *erythro*-2,3-dimethyl-1,5-pentane ditosylates by reaction with a 100% excess of TsCl in dry pyridine at 5 °C for 60 h, followed by normal workup. The ditosylates were converted to a mixture of *cis*- and *trans*-3,4-dimethylthiane by procedure B in 80% yield, bp 168–172 °C. The isomeric products were separated by preparative GLC on a 12 ft × ⅜ in. 20% Carbowax 20M + 10% KOH on 80/100 Chromosorb A. The short and long retention time products were identified as *trans*- and *cis*-3,4-dimethylthiane, respectively, on the basis of their ^1H and ^{13}C NMR spectra.

***trans*-3,4-Dimethylthiane (15).** Anal. Calcd for $C_7H_{14}S$: C, 64.55; H, 10.83. Found: C, 64.47; H, 10.77. ^1H NMR ($CDCl_3$): δ 0.75–1.70 (br, 3 H, H(3,4,5a)), 0.97 (distorted d, J = 6.5 Hz, 6 H, Me's), 1.95 (d of d of d, J = 13.5, 3.5, 1.7 Hz, 1 H, H(2a)), 2.20–2.83 (complex m, 4 H, H(2e,5e,6)).

***cis*-3,4-Dimethylthiane (16).** Anal. Calcd for $C_7H_{14}S$: C, 64.55; H, 10.83. Found: C, 64.35; H, 10.78. ^1H NMR ($CDCl_3$): δ 0.85 (d, J = 7.0 Hz, 3 H, Me(4)), 0.95–1.10 (complex m, 1 H, H(3c)), 1.00 (d, J = 7.0 Hz, 3 H, Me(3)), 1.52–1.77 (complex m, 2 H, H(4,5t)), 1.94 (m, 1 H, H(3)), 2.31–2.75 (complex m, 3 H, H(2t,6)), 2.69 (d of d, J = 13.0, 3.2 Hz, 1 H, H(2c)).

***cis*- and *trans*-2,3-Dimethylthiane (12, 11).** Ethyl 2-methyl-3-ketobutyrate was condensed with ethyl acrylate in ethanol using 0.1 molar equiv of NaOEt as a catalyst, following the general procedure of Eschenmoser,[51] to give diethyl 1-methyl-1-acetyl glutarate in 90% yield, bp 120–121 °C (1 Torr). The keto ester was dissolved in five times its volume of concentrated HCl, and the mixture refluxed for 24 h. The volume was reduced to half by vacuum concentration and the solution then extracted with ether on a continuous extractor for 18 h. The ether solution was dried and concentrated to give crude 4-methyl-5-ketohexanoic acid in 90% yield. The crude acid was reduced with $LiAlH_4$ in ether to give a mixture of *threo*- and *erythro*-2,3-methyl-1,5-hexanediol in 90% yield, bp 92–96 °C (0.4 Torr). The diol mixture was converted to a mixture of ditosylates by reaction with a 100% excess of TsCl in dry pyridine at 5 °C for 72 h followed by normal workup. The mixture of ditosylates was cyclized to a mixture of *cis*- and *trans*-2,3-dimethylthiane contaminated with 15% of 2-methyl-2-ethylthiolane (bp 162–172 °C (760 Torr)) in 65% yield by procedure B. The cis isomer could be obtained nearly pure by preparative GLC on a 12 ft × ⅜ in. 20% Carbowax 20M + 10% KOH Column on 80/100 Chromosorb A. The *trans*-2,3-dimethylthiane was contaminated with approximately 20% 2-ethyl-2-methylthiolane.

The inseparable mixture of the latter two compounds was converted to a mixture of mercuric chloride salts by reaction with 1.5 mol equiv of $HgCl_2$ in ethanol[30] After two recrystallizations from ethanol a mercuric chloride salt of mp 120–122 °C was obtained. The *trans*-2,3-dimethylthiane was regenerated by refluxing the mercuric chloride salt with 10% HCl.

***cis*-2,3-Dimethylthiane (12).** Anal. Calcd for $C_7H_{14}S$: C, 64.55; H, 10.83. Found: C, 64.60; H, 10.94. ^1H NMR ($CDCl_3$): δ 1.00 (d, J = 7.0 Hz, 3 H, Me(3)), 1.20–2.22 (complex m, 5 H, H(3,4,5)), 1.23 (d, J = 7.1 Hz, 3 H, Me(2)), 2.40–2.85 (complex m, 2 H, H(6)), 3.00 (d of q, J = 3.5, 7.2 Hz, 1 H, H(2)).

***trans*-2,3-Dimethylthiane (11).** Anal. Calcd for $C_7H_{14}S$: C, 64.55; H, 10.83. Found: C, 64.30; H, 10.64. ^1H NMR ($CDCl_3$): δ 0.85–2.12 (complex m, 5 H, H(3,4,5)), 0.96 (d, J = 6.5 Hz, 3 H, Me(3)), 1.20 (d, J = 6.8 Hz, 3 H, Me(2)), 2.35–2.87 (complex m, 2 H, H(6)), 2.49 (d of q, J = 9.2, 6.8 Hz, 1 H, H(2)).

2,2,4-Trimethylthiane (22). This compound was a gift from Dr. F. Vierhapper. ^1H NMR ($CDCl_3$): δ 0.90 (d, J = 6.3 Hz, 3 H, Me(4)), 0.95–2.08 (complex m, 5 H, H(3,4,5)), 1.26 (s, 3 H, Me(2e)), 1.26 (brs, 3 H, Me(2a)), 2.48 (d of brt, J = 13.7, 3.7 Hz, 1 H, H(6e)), 2.83 (d of d of d, J = 13.7, 12.5, 2.5 Hz, 1 H, H(6a)).

2,4,4-Trimethylthiane (20). This compound was a gift from Dr. F. Vierhapper. ^1H NMR ($CDCl_3$): δ 0.89 (brs, 3 H, Me(4a)), 0.93 (s, 3 H, Me(4e)), 1.19 (distorted t, J = 12.5 Hz, 1 H, H(3a)), 1.59 (d of brd, J = 12.5, 4.0 Hz, 1 H, H(3e)), 1.52–1.78 (complex m, 2 H, H(5)), 2.40 (d of brt, J = 13.7, 3.7 Hz, 1 H, H(6e)), 2.89 (d of d of d, J = 13.7, 12.5, 3.5 Hz, 1 H, H(6a)), 2.94 (d of d of q, J = 11.2, 2.8, 7.0 Hz, 1 H, H(2)).

Thiane-*2,2,6,6-d*$_4$ (23).[12] In a 50-ml round-bottom flask was placed 1-methylthianium iodide (6.1 g, 0.025 mol) and 28 ml of 2.5 N NaOD in D_2O. The solution was stoppered and stirred at 60 °C for 48 h. The solution was quickly neutralized with HI and the solvent removed at reduced pressure. The resulting powder was placed in a 15-ml round-bottom flask and dry distilled at 160 °C. Nitrogen was bubbled through the distillate to remove the CD_3I, and the crude thiane-*2,2,6,6-d*$_4$ was distilled in a micro still and further purified by preparative GLC on a 12 ft × ⅜ in. 20% UC-W-98 on 60/80 Chromosorb A column. ^1H NMR and low-voltage mass spectra indicated that the material was approximately 88% labeled.

^1H NMR ($CDCl_3$): δ 1.20–2.10 (complex m, 6 H), 2.30–2.70 (complex m, 0.42 H).

4-*tert*-Butylthiane-*2,2,6,6-d*$_4$ (24).[12] In a 100-ml well-dried round-bottom flask was placed a mixture of *trans*- and *cis*-1-methyl-4-*tert*-butylthianium iodides (7.9 g, 0.025 mol), 30 ml of 2.5 N NaOD in D_2O, and 25 ml of dry dioxane (distilled from $LiAlH_4$). The solution was stoppered and heated at 60 °C for 48 h and was neutralized with 20% HI. The solvent was removed at reduced pressure and the yellowish powder was washed with ether and dried. The powder was transferred to a 15-ml round-bottom flask and dry distilled at 120 °C. The distillate was mostly CD_3I. The residue in the flask was taken up in ether and washed with water. The ether solution was dried and concentrated. The residue was purified by preparative GLC on a 12 ft × ⅜ in. 20% UC-W-98 on 60/80 Chromosorb A at 160 °C. By both ^1H NMR and low-voltage mass spectra the compound was approximately 90% 4-*tert*-butylthiane-*2,2,6,6-d*$_4$.

^1H NMR ($CDCl_3$): δ 0.88 (s, 9 H), 1.00–1.50 (complex m, 3 H), 1.92–2.30 (brd, $J \approx$ 13.0 Hz, 2 H), 2.4–2.70 (complex m, 0.45 H).

Note Added in Proof. After this paper was submitted, a publication appeared[52] reporting the room-temperature ^{13}C NMR spectra of compounds **1–4, 13, 17,** and **18.** Except for C-2 in **3,** reported[52] as 35.2 ppm, agreement of the shifts is excellent, generally to within ±0.2 ppm. Substitution parameters (α_e, β_e, γ_e, and δ_e) at all positions agree accordingly (there is an apparent discrepancy for α_e-3, α_e-4, and β_e-2, but this is due to the fact that effects in thianes and thianium salts were lumped together;[52] α_e-3 and -4 are, in fact, larger in thianium salts than in thianes and β_e-2 is smaller).[9b] There is also agreement, based on chemical shift considerations,[52] that the experimental $\Delta G°$ values for Me-2, Me-3, and Me-4 are incompatible with the calculated[10] ones.

Acknowledgment. This work was supported by NSF Grant GP-35669X and by a grant-in-aid from the Allied Chemical Corp. We also express our appreciation to Dr. D. L. Harris for instruction on how to operate the XL-100 NMR spectrometer and to Dr. F. W. Vierhapper for samples of compounds **20** and **22.**

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Conformational Analysis. 35. *S*-Alkylthianium Salts[1,2]

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Abstract: *S*-Methylthianium hexafluorophosphates or perchlorates (34) were synthesized by methylation of thiane, 2-, 3-, and 4-methylthiane, *cis*- and *trans*-2,6-, -3,5-, -2,5-, -2,4-, and -3,4-dimethylthiane, 3,3- and 4,4-dimethylthiane, 3,3,5-, 2,4,4-, and 2,2,4-trimethylthiane, and 4-*tert*-butylthiane. Of these 20 thianes, 15 gave diastereomeric pairs of thianium salts and all but one (*trans*-*S*,3,3,5-tetramethylthianium) were obtained though not always in pure form. Also obtained were *S*-phenyl- and *S*-benzylthianium fluoroborate, the diastereomeric 4-*tert*-butyl- and 2,6-dimethyl-*S*-benzylthianium fluoroborates, 4-*tert*-butyl-*S*-ethylthianium perchlorates and the four *S*-methyl-*cis*- and -*trans*-1-thiadecalinium hexafluorophosphates or perchlorates. The position of equilibrium, attained thermally, of a number of diastereomeric *S*-methyl, *S*-ethyl, and *S*-benzylthianium salts was studied as a function of ring substitution. $-\Delta G^\circ$ for ^+S-Me is 0.0–0.3 kcal/mol (apparently depending on temperature, suggesting $\Delta S^\circ \approx 1.5$ Gibbs), for ^+S-Et 0.66 ± 0.06, for ^+S-CH_2Ph 0.82 ± 0.08 kcal/mol. Buttressing by one equatorial methyl group at C(2) boosts $-\Delta G^\circ$ for ^+S-Me to 0.6, two such groups [at C(2) and C(6)] enhance it to 1.0 kcal/mol; the ^+S-CH_2Ph value is enhanced to 1.5 kcal/mol by two such methyl groups. Substantial buttressing of axial Me(2) by equatorial ^+S-Me was also observed, and an earlier reported enhancement of the proportion of axial ^+S-Me by geminal 4,4-dimethyl was confirmed, though its origin may be different from that postulated. Conformational equilibria of several of the above *S*-methylthianium salts were also measured by low-temperature NMR and/or averaged chemical shifts employing model compounds.

The conformational energy ($\Delta G^\circ_{\text{axial} \rightleftharpoons \text{equatorial}}$) of the methyl group in methylcyclohexane, −1.7 kcal/mol, is one of the longest known[3] and most thoroughly studied[4,5] parameters in conformational analysis which still commands interest.[6,7] Much less is known about corresponding conformational energies in 1-methylheterocyclohexanes, although the values for 1-methylsilacyclohexane (0.0[8a] or 0.2[8b] kcal/mol), *P*-methylphosphacyclohexane (−0.68 kcal/mol[9]), and *N*-methylpiperidine[10,11] (−3.0 kcal/mol[11]) have recently been determined. Compounds of this type are of particular interest in connection with the recent postulate of Wertz and Allinger[12,13] that the large preference for the equatorial conformation in methylcyclohexane is due not so much to axial methyl/syn-axial hydrogen repulsion, but to the interaction of four vicinal gauche hydrogen atoms with the methine hydrogen of the axial conformer as compared to only two such interactions in the equatorial.

In this connection we have reported, in a preliminary com-