The Conformational Analysis of Saturated Heterocycles. Part 95.[1] Synthesis and Conformational Analysis of 3,4-Dimethyl-, 2,3,4-Trimethyl-, and 2,2,3,4-Tetramethyl-1-thia-3,4-diazacyclohexanes [2]

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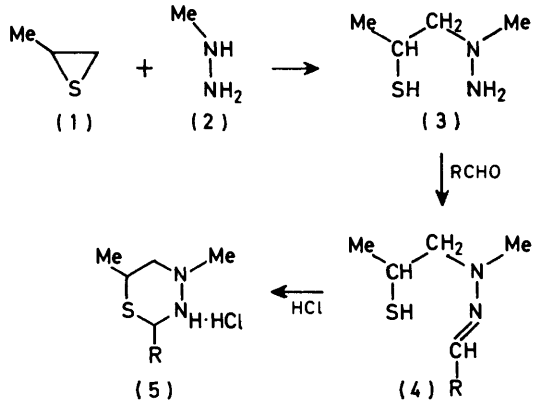
Variable temperature ^1H and ^{13}C n.m.r. spectra elucidate the conformational equilibria and kinetic interconversions for 1,3,4-thiadiazacyclohexanes. The results are compared with those of analogous compounds and the effect of the sulphur atom discussed.

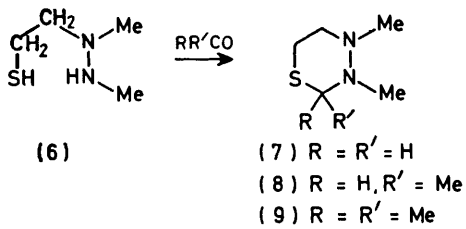
THERE are two previous reports of 1-thia-3,4-diazacyclohexanes, both by Trepanier: propylene sulphide (1) was ring-opened with substituted hydrazines (2) to a thiol (3) which with (a) benzaldehyde [3,4] and (b) pyridine-3-carbaldehyde [3] gave imines (4) that were converted



SCHEME 1

into the ring tautomers (5) with ethereal HCl. The conformations of these 1-thia-3,4-diazacyclohexanes (5) were not discussed.

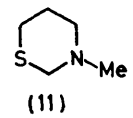
We now find that analogously ethylene sulphide and *sym*-dimethylhydrazine with ammonium chloride in catalytic amounts in refluxing benzene give the obnoxious 2-(*NN'*-dimethylhydrazino)ethanethiol (6). Subsequent reaction with appropriate carbonyl compounds catalysed by toluene-*p*-sulphonic acid forms the novel 1-thia-3,4-diazacyclohexanes (7)—(9). The reaction conditions were similar to those for the synthesis of 1,2,4-triazacyclohexanes,[5] *i.e.* the hydrazine component was freshly distilled, all operations were conducted in an inert atmosphere with rapid work-up, and storage was in the dark under nitrogen. The tetramethyl compound (9) required particular care in that it decomposed rapidly in air. Even with these precautions, accurate chemical analyses to within 0.4% could not be obtained; however, mass spectral and n.m.r. evidence provided conclusive proof for the structures assigned.



SCHEME 2

Background to Conformational Analysis.—3,4-Dimethyl-1-thia-3,4-diazacyclohexane is conveniently regarded as the amalgamation of two heterocyclic units, 1,2-dimethyl-1,2-diazacyclohexane (10) [6] and 3-methyl-1-thia-3-azacyclohexane (11).[7] Nelsen and Weisman have recently interpreted the conformational changes observed in the ^{13}C dynamic n.m.r. spectrum of 1,2-dimethyl-1,2-diazacyclohexane in terms of the earlier postulate [8] of three types of barriers: (a) a high barrier of *ca.* 12 kcal mol^{-1} or more, relating to ring or *N*-inversions involving a crossing or 'passing' of two substituents; (b) an intermediate barrier of *ca.* 10 kcal mol^{-1} for *ee'* $\rightleftharpoons$ *aa* (Scheme 3) ring inversions in saturated systems; and (c) a lower energy barrier (*ca.* 8 kcal mol^{-1} or less) relating to nitrogen inversion not involving 'passing' of substituents.

Sulphur heterocycles have lower ring reversal barriers than the corresponding aza- or oxa-analogues.[9] The



(11)

inclusion of a sulphur atom in the cyclohexane ring leads, because of the longer C–S bonds and the smaller C–S–C angle, to distinct puckering in the thian ring compared with the 'chair' shape of the cyclohexane ring.[10] This puckering results in a smaller ring reversal barrier [11] ($\Delta G_c^{\ddagger}$ 9.4 kcal mol^{-1}) compared with tetrahydropyran [11] ($\Delta G_c^{\ddagger}$ 10.3 kcal mol^{-1}), probably due to the lower barrier of torsion for the C–S bond, compared with the C–O bond. Thus, the 'nonpassing' ring inversion barrier should be less than 10.2 kcal mol^{-1} in 3,4-dimethyl-1-thia-3,4-diazacyclohexane. *N*-Inversion barriers (Table 1) decrease in the series 1-oxa-3-azacyclohexane, 1,3-diazacyclohexane, and 1-thia-3-azacyclohexane.[7] Therefore a value less than 7.5 kcal mol^{-1} (found for 'nonpassing' *N*-inversion in 1,2,4-triazacyclohexane [5]) is expected for

the 'nonpassing' *N*-inversion in 1-thia-3,4-diazacyclohexanes.

The significant distortion of sulphur-containing rings from the classical chair shape also leads to ground-state

TABLE 1

Ring reversal and nitrogen inversion barriers for saturated six-membered heterocycles (kcal mol^{-1})

Group at 3-position	Barrier	Hetero-group at 1-position				
		S	CH_2	O	NH	N–CH_3
CH_2	Ring	9.4 [a]	10.3 [b]	10.3 [a]	10.4 [c]	11.9 [c]
NMe	Ring I	9.8 [d,e]	11.8 [c]	10.0 [f]		11.3 [g]
	N–I	6.9 [d]		7.6 [h]		7.0

[a] Ref. 11. [b] F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc*, 1967, **89**, 760. [c] J. B. Lambert, R. G. Keske, R. E. Carhart, and A. P. Jovanovich, *J. Amer. Chem. Soc.*, 1967, **89**, 3761. [d] Ref. 7; *eq*→ts. [e] Measured for the *N*-ethyl compound. [f] J. M. Lehn, P. Linscheid, and F. G. Riddell, *Bull. Soc. chim. France*, 1968, 1172. [g] F. G. Riddell, *J. Chem. Soc.* (*B*), 1967, 560. [h] A. R. Katritzky, V. J. Baker, and F. M. S. Brito-Palma, in preparation; *ax*→ts 7.6, *eq*→ts 7.5 kcal mol^{-1}. [i] Ref. 16; *ax*→ts.

interactions different from those in the analogous nitrogen or oxygen rings: *e.g.* the free energy differences in the series piperidine, 1,3-diazacyclohexane, 1-oxa-3-azacyclohexane, and 1-thia-3-azacyclohexane and in the corresponding *N*-methyl series show the marked increase in the axial form for the compound with a

indicates the special interactions in the 1-thia-3-azacyclohexane ring.

Strain energy minimisation calculations of ring geometry [12] show that the smaller C–S–C bond angle and the longer C–S bonds cause puckering of the 3-methyl-1-thia-3-azacyclohexane ring in the vicinity of

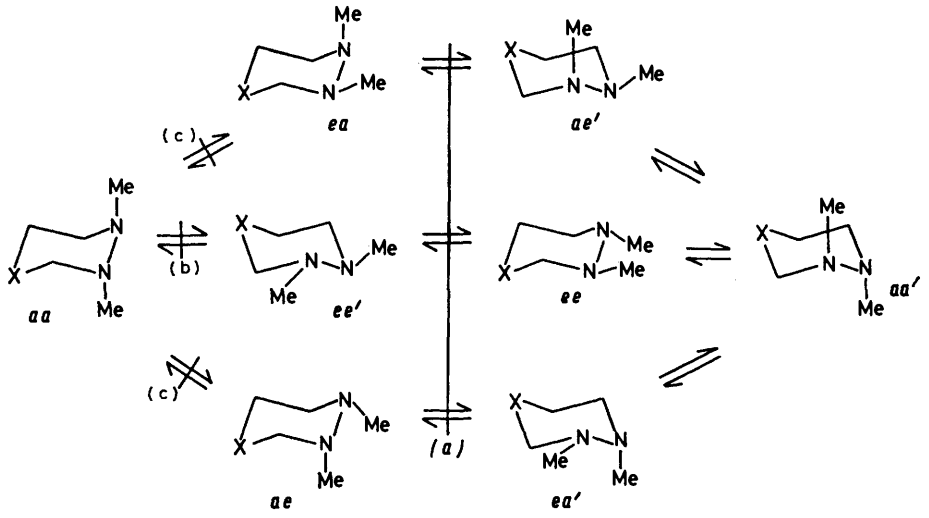
TABLE 2

Free energy differences [$\Delta G°_{298}$ [a] (% *ax*)/kcal mol^{-1}] in piperidines and their 3-hetero-analogues

N-Substituent	Group in 3-position of the ring			
	CH_2	N–CH_3	O	S
H	−0.4 [b]	*a*	0.3 [c]	0.8 [d]
	(34)		(62)	(80)
Me	−2.7 [e]	−0.4 [f]	−0.2 [g]	0.5 [d]
	(<1)	(34)	(44)	(70)
				0.7 [h]
				(90)

[a] In favour of axial conformer. [b] I. D. Blackburne, A. R. Katritzky, and Y. Takeuchi, *Accounts Chem. Res.*, 1975, **8**, 300. [c] M. J. Cook, R. A. Y. Jones, A. R. Katritzky, M. Moreno-Mañas, A. L. Richards, A. J. Sparrow, and D. L. Trepanier, *J.C.S. Perkin II*, 1973, 325. [d] D. M. Read, Ph.D. Thesis, University of East Anglia, 1976, p. 69. [e] P. J. Crowley, M. J. T. Robinson, and M. G. Ward, *Tetrahedron*, 1977, **33**, 915. [f] Ref. 16. [g] I. J. Ferguson, A. R. Katritzky, and D. M. Read, *J.C.S. Chem. Comm.*, 1975, 255. [h] Ref. 7.

the sulphur atom and 'flattening' around the nitrogen atom (Scheme 4). This results in (a) extra torsional strain for an *eq*-*N*-methyl group due to partial eclipsing



X = CH_2 (10)
X = S (7)

SCHEME 3

β-sulphur atom (Table 2). The generalised anomeric effect * should cause increasing *N*-methyl axial for $CH_2 < N–CH_3 \simeq S < O$, dictated by electronegativity. The observed order, $CH_2 \ll N–CH_3 < O < S$, clearly

* The generalised anomeric effect has been described as a stabilising $n \rightarrow \sigma^*$ process for R_2NCH_2X (E. L. Eliel, *et al.*, *J. Amer. Chem. Soc.*, 1975, **97**, 322). In the above 1,3-heteraazacyclohexanes such an interaction exists when the nitrogen lone pair is antiperiplanar to the cyclic C–heteroatom bond.

by the C(4)-axial proton and (b) bending away of an *ax*-*N*-methyl group from the C(5)-*syn*-axial proton.

Thus, flattening at the N-3 atom in 1-thia-3-azacyclohexanes destabilizes the *N*-methyl equatorial position and stabilizes the axial. In addition, the anomeric effect is also operative; as a result the axial *N*-methyl conformer becomes considerably more favoured in the sulphur compound than in the nitrogen and oxygen

TABLE 3

^{1}H Chemical shifts and coupling data of n.m.r. signals [a] at high and low temperatures for 3,4-dimethyl-1-thia-3,4-diazacyclohexanes

Compound	2-Substituent	T (°C)	Methyl protons: 2	Methyl protons: 3,4	Ring protons: 2	Ring protons: 4,5 [b]
(7)		+50		2.48 (s), 2.39 (s)	4.26 (s)	2.73, 2.68 (m)
		−62 [c]		2.55 (s), 2.51 (s)	4.90, 3.86 (q, $^2J_{HH}$ 11.5)	3.02, 2.50 (m)
(8)	Me	+40	1.36 (d, $^3J_{HH}$ 7.0)	2.51 (s), 2.40 (s)	4.95, 4.70 (q, $^3J_{HH}$ 7.1)	3.05, 2.50 (m)
		−54 [c]	1.34 (d, $^3J_{HH}$ 6.8)	2.50 (s), 2.37 (s)	4.95, 4.81 (q, $^3J_{HH}$ 6.7)	3.24, 2.66 (m)
(9)	Me_2	+50	1.49 (s)	2.34 (s)		2.78, 2.40 (m)
		−51 [c]	1.84 (s), 1.30 (s)	2.41 (s)		3.31 (t), 2.68 (t)

[a] All chemical shifts and coupling data in p.p.m. and Hz respectively: solvent $CDCl_3$ (100 MHz). [b] Signals for NCH_2CH_2S protons are quoted as multiplets owing to complexity of coupling. [c] Sufficiently low after coalescence for a well resolved spectrum.

TABLE 4

Coalescence data [a] from variable temperature ^{1}H n.m.r. spectra of 1-thia-3,4-diazacyclohexanes

Compound	2-Substituent	t_c (°C)	Signal observed	$\Delta\nu$/Hz	J/Hz	$\Delta G^{\ddagger}_c$/kcal mol^{-1}
(7)		−5	N–CH_2–S	104	11.5	12.7
(8)	Me	−10< [b] <+10	N–CH–S			*ca.* 13 [c]
(9)	Me_2	−2	C–CH_3	53.2		13.2

[a] Eyring equation employed.[17] [b] Signal exhibits broadening phenomenon in this region. [c] See text.

TABLE 5

^{13}C N.m.r. chemical shifts [a] of the conformers of some six-membered heterocyclohexanes

Compound	N–CH_3 *eq* conformer: N–CH_3	N–CH_2	C–CH_2–C	N–CH_2–S	N–CH_3 *ax* conformer: N–CH_3	N–CH_2	C–CH_2–C	N–CH_2–S
(10) [c]	44.7	58.2	25.4		*eq* 43.5 / *ax* 26.5	43.0 [b] / 54.2 [b]	25.4 [b] / 15.6 [b]	
(11) [d]	47.3	57.0	28.0	58.1	38.6	53.2	18.4	58.1
(12) [e]	47.2	57.9	25.8		37.2	56.1	19.4	

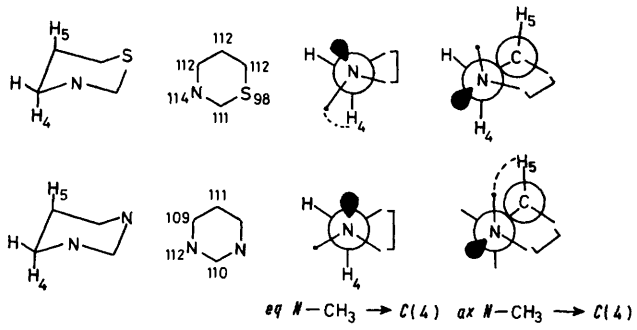
[a] In p.p.m. downfield from Me_4Si. [b] Refers to orientation of closest N–CH_3 group. [c] Ref. 6. [d] Ref. 7. [e] Refs. 5 and 14; E. L. Eliel and F. W. Vierhapper, *J. Org. Chem.*, 1976, **41**, 199.

analogues. The overall order observed (N–CH_3 < O < S) is due to a subtle balance of geometric (dominating in sulphur compounds) and electronic effects.

The conformations (a) N(1)-*eq*, N(2)-*ax*, and N(4)-*eq*, for 1,2,4-triazacyclohexane [5] and (b) N(3)-*ax* and N(4)-*eq* for 1-oxa-3,4-diazacyclohexane [13] are already strongly preferred (*cf. ee* preference by 0.4 kcal mol^{-1} over *ae* in 1,2-dimethyl-1,2-diazacyclohexane [6]). The β-sulphur atom in the 1-thia-3,4-diazacyclohexane ring should induce the *N*(3)-methyl group in 3,4-dimethyl-1-thia-3,4-diazacyclohexane to adopt the axial position even more strongly than found for the oxygen and nitrogen analogues.

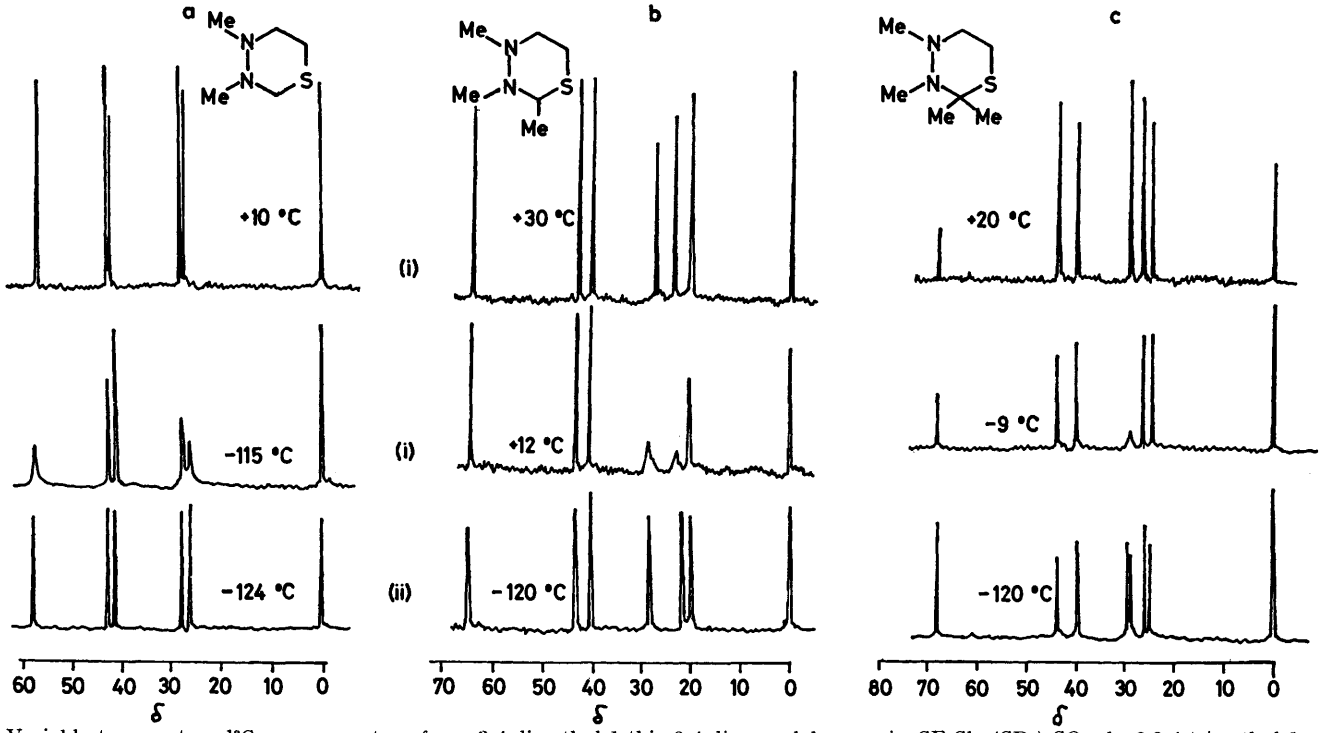
3,4-*Dimethyl*-1-*thia*-3,4-*diazacyclohexane* (7).—The ^{1}H n.m.r. spectrum of (7) at *ca.* +50 °C consists of two N–CH_3 and one N–CH_2–N singlets with a broad overlapping signal for the N–CH_2–CH_2–S protons, and was assigned by integration and chemical shifts (Table 3). The N–CH_2–S signal becomes an AB quartet below −20 °C. The coalescence temperature (Table 4) gives 12.7 ± 0.2 kcal mol^{-1} for the lowest energy passing ring reversal or *N*-inversion barrier (Scheme 3).

The barriers at still lower energies were more conveniently investigated by ^{13}C n.m.r. spectroscopy. The proton noise decoupled ^{13}C spectrum of (7) at high temperatures consists of the expected five lines (Figure a). Assignments were made by reference with the −120 °C spectrum which is that of a single conformer. Tabulation (Table 5) of the chemical shifts of conformers of 1,2-dimethyl-1,2-diazacyclohexane (10),[6] *N*-methyl-1-thia-3-azacyclohexane (11),[7] and *N*-methylpiperidine



SCHEME 4 Values of bond angles for 1,3-thiazane and 1,3-diazine rings and Newman projections along N–CH_3 → C-4 bond for N–CH_3 axial and equatorial.

(12) [5,14],† enables assignment of the effect of sulphur atom substitution on the carbon chemical shifts in *N*-methylpiperidine. Hence the carbon chemical shifts for each of the three most likely conformations of 3,4-dimethyl-1-thia-3,4-diazacyclohexane were calculated (Table 6). By far the best fit with the observed set at



Variable temperature ^{13}C n.m.r. spectra of: a, 3,4-dimethyl-1-thia-3,4-diazacyclohexane in CF_2Cl_2–$(CD_3)_2CO$; b, 2,3,4-trimethyl-1-thia-3,4-diazacyclohexane in (i) $CDCl_3$–$(CD_3)_2CO$, (ii) CF_2Cl_2–$(CD_3)_2CO$; and (c) 2,2,3,4-tetramethyl-1-thia-3,4-diazacyclohexane in CF_2Cl_2–$(CD_3)_2CO$

low temperature is found with the *ae* conformation, as expected.

A dynamic conformational change is observed below −100 °C: the signals for N(3)–CH_3, N(4)–CH_3, C(2), and C(6) each broaden and then resharpen by *ca.* −124 °C (see Figure a). It is known that 1,2-dimethyl-1,2-diazacyclohexane (10) [6] displays two dynamic phenomena on ^{13}C n.m.r.: the higher temperature coalescence (at *ca.* −40 °C) has been ascribed to the ' slowing ' of the ' non-passing ' ring inversion $ee' \rightleftharpoons (ae \rightleftharpoons aa)$ (Scheme 3), ' freezing ' out the *ee'* conformation; the lower temperature coalescence (at *ca.* −100 °C) is thus assigned to ' stopping ' of the $ae \rightleftharpoons ea$ interconversion involving non-passing *N*-inversions *via* intermediate *aa*. These two barriers were also observed in 1,2,4-trimethyl-1,2,4-triazacyclohexane (13) [5] at *ca.* −15 and −95 °C, yielding a non-passing ring inversion barrier of 11.4 and a non-passing *N*-inversion barrier of 7.5 kcal mol^{-1} ($\Delta G_c^{\ddagger}$ 7.5 kcal mol^{-1}); the major form is *ae* (confirmed by ^{13}C chemical shifts correlations) with minor form being *ea*. The presence of any *ee* would have led to a higher temperature broadening at *ca.* −40 °C, as observed for (10) and (13). Application of the Anet equations [15] requires knowledge of $\Delta\nu$, the chemical shift differences, for the carbon resonances undergoing the broadening phenomenon. These were calculated from comparison of the predicted shifts for conformer *ae* and *ea* (Table 6). Note that the N(4)–CH_3 should show the greatest broadening ($\Delta\nu$ predicted is 17 p.p.m. whereas for N(3)–CH_3 $\Delta\nu = 15.6$ p.p.m.): lack of

† These chemical shifts were derived from those for *trans*-perhydroquinoline derivatives. See ref. 5. The effect of an α-sulphur on the ^{13}C chemical shift of C(2) in *N*-methylpiperidine with the N–CH_3 group axial is +2.0 p.p.m. [from comparison of C(2) and C(4) shifts in (12) and (11) respectively]. Similarly, the β-sulphur effect at N–CH_3 and C(3) axial is +1.4 and −1.0 p.p.m. respectively.

TABLE 6

Predicted [a] ^{13}C chemical shifts (δ values) for some conformations of 3,4-dimethyl-1-thia-3,4-diazacyclohexane (7) (*cf.* Scheme 3)

Conformer	(7*ae*)	(7*ee*)	(7*ea*)	Observed [b]
C(2)	56.2	58.4	43.2	58.7(t)
N(3)–C	27.9	44.7	43.5	27.1(q)
N(4)–C	43.5	44.7	26.5	43.8(q)
C(5)	42.0	60.4	56.4	42.2(t)
C(6)	27.0	27.5	17.7	28.4(t)

[a] Using values from Table 5. [b] N.m.r. shifts at −124 °C (multiplicity).

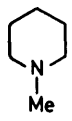
TABLE 7

^{13}C N.m.r. data [a] for 3,4-dimethyl-1-thia-3,4-diazacyclohexane

	T (°C)	C(2)	N(3)–C	N(4)–C	C(5)	C(6)
+25	Chemical shift (δ)	58.1	28.9	43.7	43.0	28.0
	Multiplicity [b]	t	q	q	t	t
−124	Chemical shift (δ)	58.7	27.1	43.8	42.2	28.4
	Broadening data					
	t_c/°C	−113	−116	−118		−113
	$\Delta\omega_{\frac{1}{2}}$ [c]/Hz	7.8	6.8	1.0		7.8
	$\Delta\nu$ [d]/p.p.m.	13.0	15.6	17.0		9.3
	Population [e] (%)	2.4	1.7			3.3
	$\Delta G^{\ddagger}_c$/kcal mol^{-1}	6.7	6.5			6.8
	$\Delta G_c°$/kcal mol^{-1}	1.17	1.26			1.07

[a] Solvent: CF_2Cl_2–$(CD_3)_2CO$, p.p.m. downfield from Me_4Si. [b] Obtained from off resonance spectrum. [c] Corrected for natural line-width (2 Hz). [d] Predicted from model compounds (see Tables 5 and 6). [e] Population of minor form (*ae*).

broadening suggests that the axial C(2)–H and C(6)–H protons which are γ to an axial N(4)–CH_3 group have moved away from their axial position due to ring dis-



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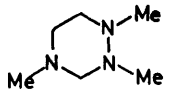

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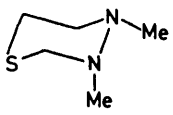
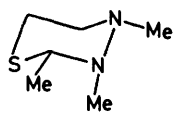
tortion by inclusion of a sulphur atom, reducing the *γ-gauche* upfield shift effect.

An activation energy of 6.7 ± 0.2 kcal mol^{-1} (minor to



(7*ae*)



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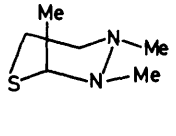

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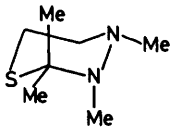
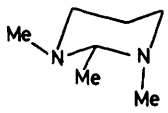
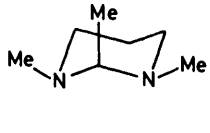


(9*ae*)



(14a)



(14b)

major) was calculated (Table 7) for the non-passing *N*-inversion (*ae* ⇌ *ea*) barrier in (7). Anet's equations [15] also yield the free energy difference between the minor (*ea*) and the major (*ae*) forms ($\Delta G_c°$ 1.1 ± 0.1 kcal mol^{-1} favouring *ae*). The lack of a broadening phenomenon at *ca.* −40 °C indicates that the proportion of *ee* form is very low (<1%). This reflects the destabilization of the *eq*-N(3)–CH_3 group in the 1-thia-3,4-diazacyclohexane ring compared with that in 1,2,4-trimethyl-1,2,4-triazacyclohexane, in accord with the behaviour found for 3-methyl-1-thia-3-azacyclohexane (see above).

2,3,4-*Trimethyl*-1-*thia*-3,4-*diazacyclohexane* (8).—The ^{1}H n.m.r. (Table 3) at *ca.* 40 °C consists of the expected N(3)– and N(4)–CH_3 singlets, N–CH–N AB quartet, methylene multiplet, and *C*-methyl doublet in the correct intensity ratio. In the temperature range +10 to −10 °C conformationally induced broadening was observed, especially in the line width of the N–CH–N AB quartet due to slowing ring reversal and hence the *C*-methyl axial equatorial equilibrium. This dynamic phenomenon was also observed using ^{13}C n.m.r. spectroscopy.

The proton noise decoupled ^{13}C n.m.r. spectrum of 2,3,4-trimethyl-1-thia-3,4-diazacyclohexane (8) at +30 °C consists of six lines (Table 8), assignments by comparison with the dimethyl analogue (7). The signals for N(3)–C, C(2)–*C*, and C(6) broaden in the region +20 to −10 °C and sharpen with further decrease in temperature. No further change is observed at still lower temperatures. Calculation of $\Delta G_c^{\ddagger}$ and $\Delta G_c°$ values for the *C*(2)–CH_3 axial–equatorial equilibrium by Anet's equations [15] requires Δν, which is not obtainable directly because of the low abundance of the minor forms. A calculation based on the temperature of maximum broadening places a rough value of 13.0 ± 1.0 kcal mol^{-1} for the process ' slowed.'

It is well known that adjacent equatorial *C*-methyl groups increase the tendency of *N*-methyl groups to be axial; for example 1,2,3-trimethyl-1,3-diazacyclohexane [16] where the conformer with one *N*-methyl axial and one equatorial and the *C*-methyl also equatorial is strongly preferred (14a). In this example however there is some (10%) contribution from the conformer with *C*-methyl axial and the *N*-methyls diequatorial (14b). These facts exclude all the possible conformers for (8) except (8a and b). A comparison of ^{13}C chemical shifts at low temperature (*ca.* −124 °C) of (7*ae*) and (8) provides conclusive proof that the predominant conformer for (8) is (8a) [*cf.* N(4)–C, C(5), and C(6) at

TABLE 8

^{13}C N.m.r. data [a] at high and low temperatures for methyl-1-thia-3,4-diazacyclohexanes

	2,3,4-Trimethyl (8)				2,2,3,4-Tetramethyl (9)	
	At 30 °C [b]	At −120 °C	t_c/°C	$\Delta\omega_{\frac{1}{2}}$/Hz [c]	At 20 °C	At −122 °C
C(2)	65.3	65.8			68.9	68.7
N(2)–CH_3	20.8	20.5	+20	15.6	29.7 [d]	29.0
						29.6
N(3)–C	23.8	22.1	+5	2.9	25.3	25.3
N(4)–C	43.9	43.8			44.5	44.2
C(5)	41.5	40.8			40.7	40.2
C(6)	28.7	29.0	+16	12.7	26.9	26.3

[a] Solvent CF_2Cl_2–$(CD_3)_2CO$. [b] Solvent: $CDCl_3$–$(CD_3)_2CO$. [c] Corrected for line width in absence of dynamic broadening (2.3 Hz). [d] Signal splits at t_c −9 °C into two equal signals (Δν 0.6 p.p.m., $\Delta G^{\ddagger}_c$ 13.5 kcal mol^{-1}).

δ 43.8, 42.2, and 28.4 p.p.m. respectively in (7*ae*), and C(5) and C(6) at δ 43.8, 40.8, and 29.0 p.p.m. respectively in (8)]. Thus the minor conformer 'freezing' out at *ca.* 0 °C on the ^{13}C n.m.r. spectrum of (8) is assigned to (8b).

2,2,3,4-*Tetramethyl*-1-*thia*-3,4-*diazacyclohexane* (9).—In the ^1H n.m.r. spectrum, the $N(3)$- and $N(4)$-CH_3 groups appear to be equivalent (at δ 2.34): the signals are assigned by relative integration (Table 3). As the temperature is lowered, the signals for the methylene and *C*-methyl protons broaden and collapse into the base line at *ca.* 0 °C: they reappear as a complex triplet and a doublet respectively. The calculated activation energy of 13.2 kcal mol^{-1} (Table 4) is assigned to 'passing' ring inversion. No further change is observed with decreasing temperature.

The room temperature ^{13}C proton noise decoupled spectrum of (9) consists of six lines (Table 8), one of which (δ 29.7) splits by *ca.* −15 °C into a doublet. There are no further changes observable at lower temperatures. The Eyring equation [17] gives a barrier of 13.5 ± 0.2 kcal mol^{-1} (t_c −9 °C, Δν 15 Hz) in agreement with that from ^1H dynamic n.m.r. Again a comparison of ^{13}C n.m.r. shifts at low temperature (−122 °C) of (7) and (9) shows that the preferred conformer for (9) must be (9*ae*) as expected [*cf.* N(4)-C shift in (7)—(9) at *ca.* −120 °C].

Conclusions.—The inclusion of a β-sulphur atom into the 1,2-diazacyclohexane ring forming the 1-thia-3,4-diazacyclohexane ring modifies the geometry such that the $N(3)$-CH_3 group prefers to be axial to the extent of *ca.* 97% at low (−120 °C) temperatures in 3,4-dimethyl-1-thia-3,4-diazacyclohexane (7). This tendency is enhanced to a still greater degree by the adjacent equatorial *C*-methyl groups in the 2,3,4-trimethyl (8) and 2,2,3,4-tetramethyl analogues (9).

The barrier to non-passing *N*-inversion is lower in 3,4-dimethyl-1-thia-3,4-diazacyclohexane ($\Delta G_c^{\ddagger}$ 6.7 kcal mol^{-1}) compared with those in 1,2-dimethyl-1,2-diazacyclohexane (10), and 1,2,4-trimethyl-1,2,4-triazacyclohexane (13) ($\Delta G_c^{\ddagger}$ 7.6 kcal mol^{-1}), possibly because (7) has a 'flat' C-N-N region (angle *ca.* 114° presumably the same as the C-N-C angle in 1-thia-3-azacyclohexane [12]) and thus requires less energy to expand to the planar transition state (angle 120°), compared with the 1,2-diazacyclohexane (10) which probably has a C-N-N angle of 110°.[18]

EXPERIMENTAL

^1H N.m.r. spectra at various temperatures were obtained employing a Varian HA-100 machine following the standard procedure.[19] Proton noise decoupled carbon-13 spectra were obtained using the JEOL FX-100 spectrometer operating at 25.05 MHz and incorporating a JEOL JEC-980B computer. Temperatures are accurate to ±2° and control units were checked with a copper–constantan thermocouple inserted in a standard 10 mm JEOL FX-100 n.m.r. tube. Off resonance decoupling experiments to determine signal multiplicity were conducted using routine JEOL settings (OFR; IRSET 50.8 KHz, power low).

2-(NN'-*Dimethylhydrazino*)*ethanethiol.*—Freshly distilled *sym*-dimethylhydrazine (*ca.* 4.5 g, 70 mmol) was refluxed in sodium dried benzene (50 ml), and ammonium chloride (0.1 g) and thiiran (2 g, 33 mmol) were added. After 1 h, benzene and the excess of hydrazine were removed and the residue distilled to give the *thiol* as a viscous oil (3.5 g, 88%), b.p. 47 °C at 15 mmHg (Found: N, 23.0; S, 27.5. $C_4H_{12}N_2S$ requires N, 23.3; S, 26.7%), $\nu_{max.}$ (film) 2 520w (SH) (broad) and 3 120s cm^{-1} (NH); *m/e* 120 (P^+), 121 ($P^+ + 1$), 122 ($P^+ + 2$), 105 ($P^+ - 15$), and 85 ($P^+ - 30$).

3,4-*Dimethyl*-1-*thia*-3,4-*diazacyclohexane.*— 2-(*NN'*-Dimethylhydrazino)ethanethiol (1.1 g, 8.3 mmol), sodium-dry benzene (25 ml), and paraformaldehyde (0.3 g, 10 mmol) were stirred at 20 °C for 0.25 h, and then slowly heated to reflux. A few drops of water azeotroped over. The mixture was distilled to give 3,4-*dimethyl*-1-*thia*-3,4-*diazacyclohexane* (0.9 g, 83%) as an oil, b.p. 65 °C at 20 mmHg (Found: S, 23.9. $C_5H_{12}N_2S$ requires S, 24.2%); *m/e* 132 (P^+), 133 ($P^+ + 1$), and 134 ($P^+ + 2$).

2,3,4-*Trimethyl*-1-*thia*-3,4-*diazacyclohexane.*— 2-(*NN'*-Dimethylhydrazino)ethanethiol (1.0 g, 8.3 mmol) in sodium dry ether (30 ml), was cooled to −10 °C under nitrogen. Freshly distilled acetaldehyde (1 g, 23 mmol) was added dropwise: the temperature was maintained below 0 °C for 1 h. The mixture was dried (K_2CO_3), the ether removed and the residue distilled to give 2,3,4-*trimethyl*-1-*thia*-3,4-*diazacyclohexane* (1.1 g, 90%) as an oil, b.p. 80 °C at 10 mmHg (Found: C, 50.0; H, 9.3; S, 20.9. $C_6H_{14}N_2S$ requires C, 49.3; H, 9.7; N, 19.2; S, 21.8%); *m/e* 146 (P^+), 147 ($P^+ + 1$), 148 ($P^+ + 2$), and 131 ($P^+ - 15$).

2,2,3,4-*Tetramethyl*-1-*thia*-3,4-*diazacyclohexane.*— 2-(*NN'*-Dimethylhydrazino)ethanethiol (1.2 g, 10 mmol), benzene (25 ml), dry AnalaR acetone (2 g, 34 mmol), and toluene-*p*-sulphonic acid were gently refluxed for 1 h: water (*ca.* 0.1 ml) azeotroped over. The residue was distilled to give 2,2,3,4-*tetramethyl*-1-*thia*-3,4-*diazacyclohexane* (1.0 g, 62%) as an oil, b.p. 57—58 °C at 1.0 mmHg (Found: N, 16.8; S, 20.5. $C_7H_{16}N_2S$ requires N, 17.5; S, 20.0%); *m/e* 160 (P^+), 161 ($P^+ + 1$), and 162 ($P^+ + 2$).

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REFERENCES

[1] The last Part of this series to have been published is F. G. Riddell, E. S. Turner, A. R. Katritzky, R. C. Patel, and F. M. S. Brito-Palma, *Tetrahedron*, 1979, **35**, 1391.

[2] A. R. Katritzky, R. C. Patel, and D. M. Read, *Tetrahedron Letters*, 1977, 3803.

[3] D. L. Trepanier, P. E. Krieger, J. H. Mennear, and J. N. Eble, *J. Medicin. Chem.*, 1967, **10**, 1085.

[4] D. L. Trepanier and P. E. Krieger, *J. Heterocyclic Chem.*, 1967, **4**, 254.

[5] A. R. Katritzky and R. C. Patel, *J.C.S. Perkin II*, 1979, 984.

[6] S. F. Nelsen and G. R. Weisman, *J. Amer. Chem. Soc.*, 1976, **98**, 3281.

[7] A. R. Katritzky, V. J. Baker, F. M. S. Brito-Palma, I. J. Ferguson, and L. Angiolini, in preparation.

[8] (*a*) R. A. Y. Jones, A. R. Katritzky, D. L. Ostercamp, K. A. F. Record, and A. C. Richards, *Chem. Comm.*, 1971, 644; (*b*) R. A. Y. Jones, A. R. Katritzky, and R. Scattergood, *ibid.*, p. 644; (*c*) R. A. Y. Jones, A. R. Katritzky, K. A. F. Record, and R. Scattergood, *J.C.S. Perkin II*, 1974, 406.

[9] J. B. Lambert and S. I. Featherman, *Chem. Rev.*, 1975, **75**, 611.

[10] J. B. Lambert, *Accounts Chem. Res.*, 1971, **4**, 87.

[11] J. B. Lambert, C. E. Mixan, and D. H. Johnson, *J. Amer. Chem. Soc.*, 1973, **95**, 4634.

[12] (*a*) I. D. Blackburne, R. P. Duke, R. A. Y. Jones, A. R. Katritzky, and K. A. F. Record, *J.C.S. Perkin II*, 1973, 332; (*b*) I. D. Blackburne, A. R. Katritzky, D. M. Read, P. J. Chivers, and T. A. Crabb, *ibid.*, 1976, 418.
[13] I. J. Ferguson, A. R. Katritzky, and D. M. Read, *J.C.S. Perkin II*, 1976, 1861.
[14] E. L. Eliel and F. W. Vierhapper, *J. Amer. Chem. Soc.*, 1975, **97**, 2424.
[15] F. A. L. Anet, I. Yavari, I. J. Ferguson, A. R. Katritzky, M. Moreno-Mañas, and M. J. T. Robinson, *J.C.S. Chem. Comm.*, 1976, 399.
[16] A. R. Katritzky, V. J. Baker, I. J. Ferguson, and R. C. Patel, *J.C.S. Perkin II*, 1979, 143.
[17] H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, 1956, **25**, 1228.
[18] G. R. Weisman and S. F. Nelsen, *J. Amer. Chem. Soc.*, 1976, **98**, 7007.
[19] V. J. Baker, A. R. Katritzky, J-P. Majoral, A. R. Martin, and J. M. Sullivan, *J. Amer. Chem. Soc.*, 1976, **98**, 5748.