The Conformational Analysis of Saturated Heterocycles. Part XLV.[1] *N*-Alkyldihydro-1,3,5-dithiazines and *N*-Alkyltetrahydro-1,3,5-thiadiazines [2]

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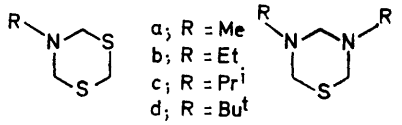
The synthesis, low-temperature n.m.r. spectra, and coalescence $\Delta G^{\ddagger}$ for ring inversion, and dipole moments of the title compounds are discussed, together with the predominant conformations of these compounds.

We recently extended our studies of hetero-analogues of cyclohexane to 1,3,5-trialkylhexahydro-1,3,5-triazines,[3] which were found to present unique features including a considerable preference for at least one axial alkyl group. The present paper is concerned with 5-alkyldihydro-1,3,5-dithiazines (1) and 3,5-dialkyltetrahydro-1,3,5-thiadiazines (2), which have not been previously investigated from a conformational aspect.



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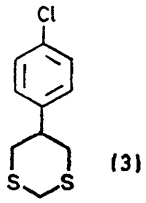

(3)

Preparation of Compounds.—5-Methyldihydro-1,3,5-dithiazine is relatively well known.[4-8] 5-Ethyl- and 5-isopropyl-dihydro-1,3,5-dithiazines have been previously reported in the patent literature [4] but inadequately characterised. We used a procedure similar to that of ref. 4 to prepare the methyl (1a) and also the t-butyl (1d) derivatives; in our hands, this afforded complex mixtures for the other compounds (1b, 1c), but could be suitably modified. The compounds were analysed and further characterised by their n.m.r. spectra (Table 1).

The simple alkyltetrahydrothiadiazines (2a—d) have apparently not previously been prepared, although the cyclohexyl, benzyl, and (substituted) phenyl derivatives had been obtained by treating the corresponding methyleneamines with formaldehyde saturated with hydrogen sulphide;[9,10] the corresponding dithiazines were also produced together with compounds originally formulated [9,10] as thiazetidines, but now known to contain eight-membered rings.[8,11] Further aryl derivatives have also been reported.[12] We have prepared the methyl-, ethyl-, and isopropyl-thiadiazine derivatives (2a—c) by reaction of hydrogen sulphide with formaldehyde and the amine (see ref. 12): the compounds decomposed easily, and could not be analysed satisfactorily, but were characterised adequately by their n.m.r. spectra (Table 2).

TABLE 1

N.m.r. data of 5-alkyldihydro-1,3,5-dithiazines (1)

R	Me	Et	Pr^i	Bu^t
τ_R	7·34 [a] (s, 3 H)	8·95 [a] (t, *J* 7 Hz, 3 H)	8·89 [a] (d, *J* 6·5 Hz, 6 H)	8·64 [a] (s, 9 H)
		6·95 [a] (q, *J* 7 Hz, 2 H)	6·24 [a] (m, *J* 6·5 Hz, 1 H)	
	7·37 [b]	8·96 [b]	8·89 [b]	8·55
		6·94 [b]	6·25 [b]	
$\tau_{H_4(6)}$	5·62 [a] (s, 4 H)	5·61 [a] (s, 4 H)	5·55 [a] (s, 4 H)	5·40 [a] (s, 4 H)
	5·64 [b]	5·62 [b]	5·55 [b]	5·34 [b]
τ_{H_2}	5·96 [a] (s, 2 H)	5·97 [a] (s, 2 H)	5·94 [a] (s, 2 H)	5·77 [a] (s, 2 H)
	5·98 [b]	5·95 [b]	5·92 [b]	5·71 [b]

[a] In $CDCl_3$–$CFCl_3$ 1 : 1, 100 MHz. [b] In CCl_4, 60 MHz.

TABLE 2

N.m.r. data of 3,5-dialkyltetrahydro-1,3,5-thiadiazines (2)

R	Me	Et	Pr^i
τ_R	7·42 [a] (s, 6 H)	8·96 [a] (t, *J* 7 Hz, 6 H)	8·95 [a] (d, *J* 6·5 Hz, 12 H)
		7·14 [a] (q, *J* 7 Hz, 4 H)	6·83 [a] (m, *J* 6·5 Hz, 2 H)
	7·42 [b]	8·98 [c]	8·96 [d]
		7·17 [c]	6·80 [d]
$\tau_{H_2(6)}$	5·89 [a] (s, 4 H)	5·76 [a] (s, 4 H)	5·91 [a] (s, 4 H)
	5·89 [b]	5·82 [c]	5·84 [d]
τ_{H_4}	6·32 [a] (s, 2 H)	6·14 [a] (s, 2H)	6·22 [a] (s, 2 H)
	6·31 [b]	6·20 [c]	6·17 [d]

[a] In $CDCl_3$–$CFCl_3$ 1 : 1, 100 MHz. [b] In $CDCl_3$–$CFCl_3$ 1 : 1, 60 MHz. [c] In CCl_4, 60 MHz. [d] In $CDCl_3$, 60 MHz.

5-*p*-Chlorophenyl-1,3-dithian (3) was prepared by an adapted literature method.[13]

[1] For Part XLIV, see ref. 2.

[2] Part of this work has been described in a preliminary communication: L. Angiolini, R. A. Y. Jones, and A. R. Katritzky, *Tetrahedron Letters*, 1971, 2209.

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EXPERIMENTAL

5-Methyldihydro-1,3,5-dithiazine (1a) (*see* ref. 4).—Aqueous formaldehyde (37%; 81 ml, 1·0 mol) was added with stirring to methylamine hydrochloride (13·5 g, 0·2 mol) and sodium sulphide nonahydrate (108 g, 0·45 mol) in water (200 ml) at 25°. After 15 h, the precipitated dithiazine (17·3 g, 64%) was recrystallised from aqueous ethanol and sublimed at 50°/1 mm; it then had m.p. 64° (lit.,[4] m.p. 65—66°,[5] 63°,[6] 65°,[7] 63—65°,[8] 65·2—66°) (Found: C, 34·8; H, 6·5; N, 10·3; S, 47·7. Calc. for $C_4H_9NS_2$: C, 35·5; H, 6·8; N, 10·3; S, 47·4%).

The *5-t-butyl analogue* (1d) (67%), was prepared similarly, it had b.p. 136—137°/17 mm and crystallised as prisms, m.p. 44—46°, from 95% ethanol; finally it was sublimed at 40°/1 mm, m.p. 46—47° (Found: C, 46·8; H, 8·4; N, 7·7; S, 35·8. $C_7H_{15}NS_2$ requires C, 47·4; H, 8·5; N, 7·9; S, 36·2%).

5-Isopropyldihydro-1,3,5-dithiazine (1c).—Aqueous formaldehyde (35%, 162 ml, 1·89 mol) and isopropylamine (26 ml) and water (40 ml) were mixed and added to aqueous sodium hydrosulphide [0·69 mol; prepared by saturating sodium hydroxide (27·6 g) in water (77 ml) with hydrogen sulphide] at 20°. After stirring for 30 h, the whole was extracted with ether (3 × 50 ml): distillation of the dried (Na_2SO_4) extracts gave the isopropyldithiazine (41 g, 83%), b.p. 113—114°/10 mm, which solidified on cooling and had m.p. 36°. After sublimation at 30°/1 mm the m.p. was 37—38° (lit.,[4] m.p. 42°) (Found: C, 43·3; H, 7·6; N, 8·7; S, 39·6. Calc. for $C_6H_{13}NS_2$: C, 44·1; H, 8·0; N, 8·6; S, 39·3%).

The *5-ethyl analogue* (64%) was prepared similarly as an oil b.p. 107°/10 mm (Found: C, 40·4; H, 7·2; N, 9·8; S, 42·5. $C_5H_{11}NS_2$ requires C, 40·2; H, 7·4; N, 9·4; S, 43·0%). The hydrochloride was prepared in ether and recrystallised from ethanol; it had m.p. 188—192° (decomp.) (lit.,[4] m.p. 201°).

3,5-Dialkyltetrahydro-1,3,5-thiadiazines.—Hydrogen sulphide was passed into aqueous formaldehyde (37%; 253 ml, 3·12 mol) until 0·48 mol (16·3 g) had been absorbed. This solution was gradually added with stirring at 0—5° to the amine (0·96 mol), and the whole kept for 36 h. For the methylamine case only the solution was reduced to 150 ml by evaporation at 50°/15 mm; potassium hydroxide (50 g) was then added. The resulting mixture was extracted with ether (3 × 100 ml), the extracts were dried (Na_2SO_4) and evaporated to give the crude products which were repeatedly fractionated and for the methyl and ethyl compounds purified by preparative t.l.c. on silica gel, and elution with benzene–ether. The compounds were characterised by their n.m.r. spectra (see Table 2): *3,5-dimethyl-* (38% crude), b.p. 72—75/13 mm; *3,5-diethyl-* (88% crude), b.p. 106—107°/15 mm; *3,5-di-isopropyl-tetrahydro-1,3,5-thiadiazine* (90% crude), b.p. 73—76°/1 mm).

1,3-Dithian [14] sublimed at 45°/1 mm, m.p. 53° (lit.,[14] m.p. 53—54°).

2-p-Chlorophenyl-1,3-bistosyloxypropane.—Diethyl *p*-chlorophenylmalonate [15] (14·5 g, 0·053 mol) in ether (90 ml) was added to $LiAlH_4$ (2·5 g, 0·066 mol) under ether (90 ml). The whole was refluxed for 3 h, cooled, and water (2·4 ml) and 4N sodium hydroxide (2·4 ml) were added. Evaporation of the dried (Na_2SO_4) ether layer gave the crude diol (8·5 g, 86%) which was used without further purification.

Toluene-*p*-sulphonyl chloride (17·2 g, 0·09 mol) in dry pyridine (25 ml) was added at 0° to the crude diol (8·5 g) in pyridine (20 ml). After 24 h at 0° and 16 h at 20°, the mixture was poured onto ice and 10N-HCl (50 ml), and extracted with CH_2Cl_2 (3 × 50 ml). The extracts were washed with 3N-HCl and with H_2O and dried (Na_2SO_4). Evaporation left the *ditosylate* (17·4 g, 79%) which crystallised as needles (from ethanol), m.p. 134° (Found: C, 55·4; H, 4·4. $C_{23}H_{23}ClS_2O_6$ requires C, 55·8; H, 4·7%); τ ($CDCl_3$) 2·2—3·0 (m, 12H), 5·8 (d, 4H), 6·8 (m, 1H), and 7·6 (s, 6H).

5-p-Chlorophenyl-1,3-dithian (3).—Potassium (7·8 g) was added to ethanol (50 g) and the product mixed with thioacetic acid (14·2 ml): the potassium salt was precipitated; it was separated by filtration, washed successively with ethanol and ether, and dried. The ditosylate (10·6 g), potassium thioacetate (5·2 g), and dry dimethylformamide (75 ml) were refluxed for 12 h, kept at 20° for 24 h, and poured into water (200 ml). Extraction with chloroform (2 × 50 ml) and evaporation of the dried (Na_2SO_4) extracts gave a product which was refluxed with zinc amalgam (13 g), ethanol (100 ml), and hydrochloric acid (15 ml) for 1·5 h under nitrogen and kept 48 h at 20°. The solution was decanted into previously boiled water at 20° and ether-extracted (2 × 50 ml). The dried (Na_2SO_4) ethereal solution was evaporated to give crude *2-p*-chlorophenylpropane-1,3-dithiol (2·35 g, 51%) as an oil which was characterised by its i.r. and n.m.r. spectra; $\nu_{max.}$ (liquid film) 2930—2960, 2560, 1490, and 830 cm^{-1}; τ (CS_2) 2·8 (m, 4H), 7·2 (m, 5H), and 8·9 (t, 2H).

The dithiol (1·9 g), dry paraformaldehyde (0·26 g), and benzene (100 ml) were refluxed, while dry hydrogen chloride was passed continuously through the solution, in a Dean–Stark apparatus. After 2 h more paraformaldehyde (0·26 g) was added and the solution was refluxed for a further 2 h. The whole was cooled and benzene (100 ml) was added; the mixture was then washed with aqueous sodium hydrogen carbonate. The dried (Na_2SO_4) benzene layer was evaporated to give the *1,3-dithian* (1·1 g, 55%) as needles, m.p. 117—118° (from ethanol 95%) (Found: C, 51·7; H, 4·9; S, 27·3. $C_{10}H_{11}ClS_2$ requires C, 52·0; H, 4·8; S, 27·8%); $\nu_{max.}$ (CCl_4) 2900—2960, 1490, 1410—1430, and 860 cm^{-1}; τ (CCl_4) 2·8 (m, 4H), 5·99 (d, 1H), 6·61 (d, 1H), and 6·8—7·4 (m, 5H).

Dipole Moments.—Dipole moments were calculated by the method of Halverstadt and Kumler [16] from measurements of dielectric constant (ε) and specific volume (*v*) on the solvent (cyclohexane) and four solutions. The specific volumes were measured with an Anton Parr Digital Densimeter model DMA 02 C. Dielectric constants at 25·0° were derived from measurements with a Wayne–Kerr B 641 capacitance bridge, by use of a glass cell.[17] A value for the electronic polarisation was obtained by the summation of bond electronic polarisabilities.[18] No allowance was made for atomic polarisation. As before,[19] the dielectric constant and specific volume for cyclohexane were taken as 2·015

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(ref. 20) and 1·2915 (ref. 21) respectively at 25°. The results are recorded in Tables 3 and 4.

TABLE 3

Measurements of dielectric constants and specific volume at 25° in cyclohexane *

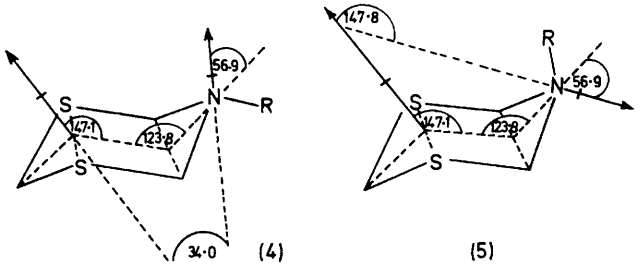
10^6w	$10^6(\varepsilon_{12} - \varepsilon_1)$	$10^6(v_1 - v_{12})$
	1,3-Dithian	
1995	7242	916
2621	9262	1196
2816	9895	1286
2844	10,029	1305
	5-*p*-Chlorophenyl-1,3-dithian	
1429	1230	745
1482	1326	753
1618	1436	844
2339	2119	1225
	5-Methyldihydro-1,3,5-dithiazine	
2458	4115	1128
3689	5998	1700
4690	7628	2176
5660	9229	2634
	5-Ethyldihydro-1,3,5-dithiazine	
3664	5286	1573
5796	8424	2497
5999	8711	2586
6478	9459	2798
	5-Isopropyldihydro-1,3,5-dithiazine	
2188	2778	873
2650	3347	1082
4655	5944	1893
5945	7604	2422
	5-t-Butyldihydro-1,3,5-dithiazine	
3765	7111	1502
4687	8809	1856
5011	9479	1975
6333	8720	1837

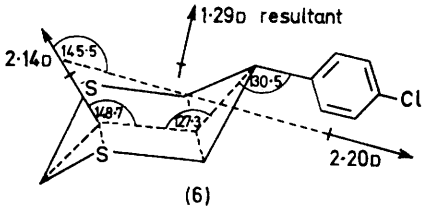
* w = Weight fraction, ε_1 and ε_{12} are the dielectric constants for solvent and solution respectively, and v_1 and v_{12} are the corresponding specific volumes.

RESULTS AND DISCUSSION

Dipole Moments.—The tetrahydrothiadiazines were not sufficiently pure for reliable dipole moment measurements. The total dipole moment of a 5-alkyldihydro-1,3,5-dithiazine is considered as comprising three components, two from the sulphur atoms and their associated C–S bonds and the third from the nitrogen atom and the C–N bonds. We take the resultant moment for the two sulphur components to be 2·14D, the measured moment of 1,3-dithian in cyclohexane (previously reported as 2·09D in benzene [22]). For the nitrogen moiety we use the moment of the corresponding 1-alkylpiperidine [23] (0·77, 0·74, 0·68, and 0·70D for Me, Et, Pr^i, and Bu^t respectively).

The observed moments for the 5-methyl-, 5-ethyl-, and 5-isopropyl-dihydro-1,3,5-dithiazines are all close to the arithmetic difference between the dithian and 1-alkylpiperidine moments. This suggests that these compounds exist essentially entirely in a single conformation with the dithian and 1-alkylpiperidine moments nearly antiparallel. If the ring is in the chair form, the preferred conformation must be that with the *N*-alkyl substituent in the axial position (5).





To calculate the moments expected for the separate conformers [(4) and (5)], we need the angles between the dithian and 1-alkylpiperidine moments. These we have estimated in two separate ways. (*a*) We suppose that the sulphur moments are directed along the bisectors of the C–S–C angle and that the nitrogen moments lie on the pseudo-three fold symmetry axis defined by the three C–N bonds (see ref. 19). We assume the following bond lengths and angles: C–C,[24a] 154; C–S,[25] 181; C–N,[24b] 147 pm; CSC,[25] 100°; SCC, SCS,[25] 115°; CNC,

TABLE 4

Dipole moments in cyclohexane at 25°

Compound	$d\varepsilon/dw$ [a]	$-dv/dw$ [a]	$_TP_{2\infty}$	$_EP$	μ(D) [b]
1,3-Dithian	3·52 ± 0·05	0·458 ± 0·002	127·1	33·3	2·14 ± 0·01
5-*p*-Chlorophenyl-1,3-dithian	0·90 ± 0·02	0·522 ± 0·006	94·9	61·1	1·29 ± 0·02
5-Methyldihydro-1,3,5-dithiazine	1·62 ± 0·01	0·465 ± 0·002	81·1	36·9	1·47 ± 0·01
5-Ethyldihydro-1,3,5-dithiazine	1·457 ± 0·006	0·4316 ± 0·0008	84·8	41·5	1·46 ± 0·01
5-Isopropyldihydro-1,3,5-dithiazine	1·280 ± 0·004	0·408 ± 0·002	86·8	46·1	1·41 ± 0·01
5-t-Butyldihydro-1,3,5-dithiazine	1·885 ± 0·006	0·396 ± 0·001	120·6	50·6	1·85 ± 0·01

[a] ± One standard deviation. [b] ± One standard deviation or 0·01D, whichever is the greater.

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116°. The last value is a little larger than is usually quoted for CNC, but accords with the larger than average CCC angle found [25] in 1,3-dithian; * the results of our calculations are insensitive to small changes in these angles. These calculations, illustrated in (4) and (5), predict angles between the vectors of 34·0 and 147·8° for the *N*-alkyl equatorial and axial conformers respectively. (*b*) As an alternative we have compared in a vector triangle [see (6)] the moments of 1,3-dithian, *p*-chlorophenylcyclohexane [23] (2·20D), and 5-*p*-chlorophenyl-1,3-dithian. We assume the same geometrical parameters as above, and that the 5-*p*-chlorophenylalkyl moment lies along the C_5–C_{Ar} bond direction.[19] We must also assume that the aryl group is almost entirely in the equatorial conformation. Since we have just shown that a 5-alkyl group in 5-alkyldihydro-1,3,5-dithiazines is almost completely axial this assumption requires justification. There are three differences between the dihydrodithiazine and dithian systems which we believe are responsible for the change in conformational preference: (i) the alkyl–equatorial conformers in the dihydrodithiazines are destabilised by lone pair–lone pair repulsions; (ii) the corresponding alkyl–axial conformers are stabilised by easy deformation at nitrogen (see ref. 19); (iii) the aryl–axial conformer in the dithian is destabilised by repulsions between the sulphur lone pairs and the aryl π-system. Our ultimate justification is that the angle between the resultant dithian vector and the S(1)S(3)C(4)C(6) plane calculated this way [see (6)] is virtually identical to that calculated by the first method. Using the calculated vector angles (method 1), with the known dithian and 1-alkylpiperidine moments, we derive the expected moments μ_a and μ_e for the separate conformers with *N*-alkyl groups axial and equatorial respectively (Table 5). From these calculated moments

TABLE 5

Calculated dipole moments and populations of 1-alkyldihydro-1,3,5-dithiazine conformers in cyclohexane solution at 25°

N-Substituent	Calculated moment (D) μ_a	μ_e	N_a
Me	1·54	2·84	1·00
Et	1·56	2·78	1·00
Pr^i	1·60	2·73	1·00
Bu^t	1·59	2·75	0·82

and those observed (μ_o), the proportions N_a of molecules with the 5-alkyl group axial can be derived using equation (1).

$$\mu_o^2 = N_a\mu_a^2 + (1 - N_a)\mu_e^2 \qquad (1)$$

It can be seen from Tables 3 and 4 that, except for the t-butyl compound (1·85D) the observed moments lie outside the range of calculated values. Since the n.m.r. data (below) indicate a consistent molecular structure in the series, and since there is no reason to suppose that the ring is not in the chair form, we need to reconsider the assumptions on which our calculations were based. The one most likely to be in error is that the presence of the *N*-axial substituent in conformers (5) causes no distortion of bond angles. It is very likely that in these conformers the heterocyclic ring and the nitrogen pyramid [19] will be significantly flattened, thus increasing the angle between the dithian and alkyl piperidine vectors and reducing the resultant moment from the calculated value. It may be significant that the discrepancy between μ_o and the calculated value of μ_a increases with increasing bulk of the alkyl group (0·07, 0·10, and 0·19D for Me, Et, and Pr^i respectively).

Hence, we should reconsider the calculated value of N_a for the t-butyl compound. In the extreme, if the distortion were to push the dithian and nitrogen moments completely antiparallel, then μ_e would fall to 1·44D, corresponding to 75% of the conformer (5) with t-butyl axial. The true value is therefore likely to be between 75 and 82%, corresponding to a $\Delta G_{25}°$ value in cyclohexane solution of between 0·65 and 0·90 kcal mol^{-1} in favour of the t-butyl group axial. This is only the second report of such behaviour for an *N*-t-butyl group in a saturated six-membered ring; the other refers to 1,3,5-tri-t-butylhexahydro-1,3,5-triazine,[3] for which $\Delta G_{25}°$ in cyclohexane solution is 0·35 ± 0·12 kcal mol^{-1}. Despite the uncertainty in our value of $\Delta G_{25}°$ for 5-t-butyl-1,3,5-dihydrodithiazine, the larger value in the sulphur heterocycle is not unexpected. The dihydrodithiazine ring is considerably flattened when compared with the hexahydro-1,3,5-triazine ring, and the longer C–S bonds (181 pm compared with 147 pm for C–N) also combine to remove the axial t-butyl group from unfavourable interaction with the sulphur atoms. It is evident from the $\Delta G_{25}°$ values, and from the behaviour of the 5-*p*-chlorophenyl-1,3-dithian, that the change from nitrogen to sulphur in the ring system (involving changes both in separation and electronegativity) has a greater effect in reducing hydrogen-lone pair interactions than in reducing lone pair-lone pair interactions. It is unfortunate that we have not been able to investigate the conformations of the tetrahydrothiadiazines, but by interpolation between these results and those previously reported for the hexahydro-1,3,5-triazines [3] we may suppose that there would be a progressive change from the dimethyl compound in which both the mono- and di-axial conformers will be significantly populated and the diequatorial one only slightly, through to the di-t-butyl compound in which the predominant conformer is expected to be the monoaxial form with a small contribution from the diequatorial.

N.m.r. Spectra.—At room temperature the n.m.r. spectra of the dihydrodithiazines and the tetrahydrothiadiazines (Tables 2 and 1) indicate rapid ring and nitrogen inversion. As the temperature is lowered and the ring inversion slows down the ring methylene protons separate into two AB systems (see *e.g.* Figure 1). Assignments are straightforward. For most of the compounds the upfield doublets of each ring methylene AB system are split (see Figure 1) or at least appreciably broadened; we attribute this to long range W-type

* Some distortion of the CNC angles in the ring is expected in view of the long C–S bonds.

coupling between the equatorial protons on carbon atoms 2, 4, and 6, and accordingly assign the upfield doublets to equatorial protons and downfield ones to axial protons. This is the reverse of the pattern found in cyclohexane [26] but previous work [27,28] has shown that H_a is deshielded relative to H_e for methylene groups adjacent to sulphur in six-membered rings. In the thiadiazines the same pattern is also observed for the methylene group between the two nitrogen atoms (see Figure 2). This long-range coupling is most obvious in the *N*-methyl and *N*-ethyl compounds; probably steric distortion of the rings brought about by the bulkier substituents renders the W-path for coupling less favourable. Low-temperature n.m.r. data are recorded in Tables 6 and 7, together with coalescence data. For all the compounds studied, except the isopropyldithiazine derivative, the two AB quartets from the ring methylene protons coalesced at approximately the same temperature as each other. Values of $\Delta G_c^{\ddagger}$, the free energy of activation for the inversion at the coalescence temperature, were determined from equation (2),[29] in

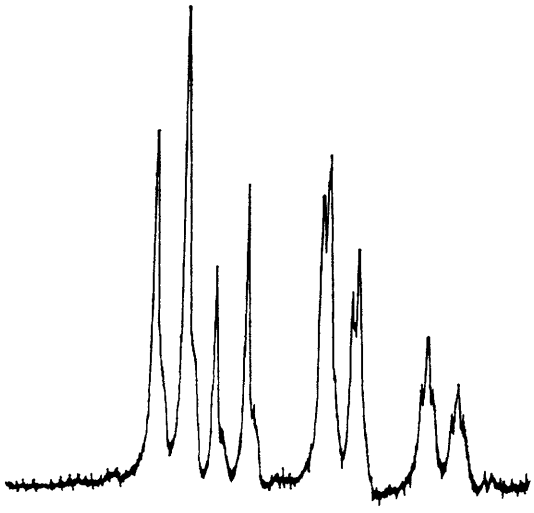

FIGURE 1 100 MHz N.m.r. spectrum of ring protons of 5-ethyldihydro-1,3,5-dithiazine at −80° (expanded scale) in $CDCl_3$–$CFCl_3$ (1 : 1)

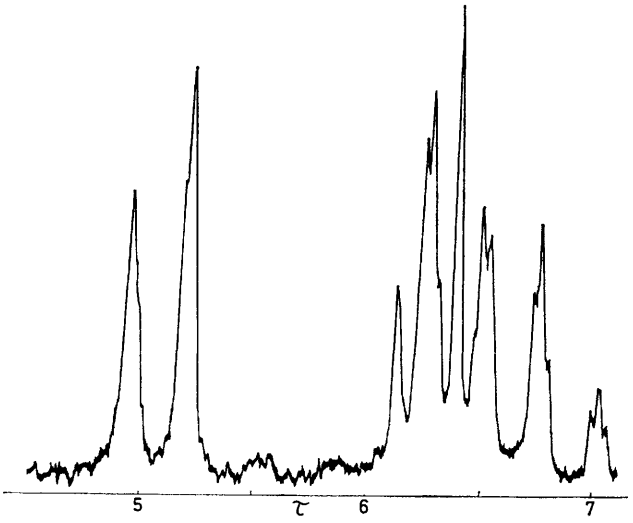

FIGURE 2 100 MHz N.m.r. spectrum of 3,5-dimethyltetrahydro-1,3,5-thiadiazine at −70° in $CDCl_3$–$CFCl_3$ (1 : 1) showing long-range coupling between $H_{2e}/H_{4,6e}$

TABLE 6

Low-temperature n.m.r. spectral data for 3,5-dialkyltetrahydro-1,3,5-thiadiazines (2) *

R	$\delta\nu_{ae(2,6)}$	$J_{ae(2,6)}$	$\delta\nu_{ae(4)}$	$J_{ae(4)}$	T_{min} (K)	T_c (K)	$\Delta G_c^{\ddagger}$ (kcal mol^{-1})
Me	64·0	12·7 [a]	28·5	13·0 [a]	203	248 ± 3	12·1 ± 0·3
Et	58·5	13·0	36·5	13·8	203	248 ± 3	12·0 ± 0·2
Pr^i	~28	12 ± 0·5	⩾50	12 ± 0·5	~173	215 ± 3	10·5 ± 0·4

* All spectra in $CDCl_3$/$CFCl_3$ 1 : 1 at 100 MHz. Chemical shift differences and coupling constants all in Hz.

[a] Long-range coupling $J_{2(6)e,4e} = 1·6$ Hz.

TABLE 7

Low-temperature n.m.r. spectral data for 5-alkyldihydro-1,3,5-dithiazines (1) *

R	$\delta\nu_{ae(4,6)}$	$J_{ae(4,6)}$	$\delta\nu_{ae(2)}$	$J_{ae(2)}$	$T_{min.}$ (K)	T_c (K)	$\Delta G_c^{\ddagger}$ (kcal mol^{-1})
Me	92·0	13·0 [a]	90·0	13·6 [a]	203	232 ± 3	11·0 ± 0·2
Et	73·1	13·0 [b]	92·0	13·6 [b]	193	229 ± 3	10·9 ± 0·2
Pr^i	41·0	14·0	~93	~13·0	183	213 ± 3 [c] 221 ± 3 [d]	10·4 ± 0·2
Bu^t	16·4	14·5	76·0	13·7	~173	193 ± 5	9·3 ± 0·3

* All spectra in $CDCl_3$–$CFCl_3$ 1 : 1 at 100 MHz. Chemical-shift differences and coupling constants in Hz.

[a] Long-range coupling $J_{4(6)e,2e} = 2·3 \pm 0·2$ Hz. [b] Long-range coupling $J_{4(6)e,2e} = 2·7 \pm 0·2$ Hz. [c] T_c for protons 4(6). [d] T_c for protons 2.

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which T_c is the coalescence temperature, $\delta\nu$ the chemical shift between the A and B protons, and J is the AB coupling constant.

This equation is calculated using a transmission coefficient of 1 in the Eyring equation; if a value of $\frac{1}{2}$ were used the resultant $\Delta G_c^{\ddagger}$ values would be 0·3 kcal mol^{-1} smaller.

$$\Delta G_c^{\ddagger} = 4{\cdot}57T_c\left[9{\cdot}97 + \log\left\{\frac{T_c}{(\delta\nu^2 + 6J^2)^{\frac{1}{2}}}\right\}\right] \quad (2)$$

An additional feature of the spectrum of 3,5-diethyltetrahydro-1,3,5-thiadiazine, which we have reported in a preliminary communication [2a] was the appearance at low temperatures of non-equivalence between the methylene protons of the ethyl groups, which at 20° appear as the usual quartet of the A_2X_3 pattern. The reason is that with slow ring inversion the nitrogen atoms can exhibit the fact that they are centres of chirality, regardless of the rate of nitrogen inversion and the relative conformations of the ethyl groups. The value of $\Delta G_c^{\ddagger}$ for the inversion is calculated [2a] from the collapse of the signal from the ethyl methylene groups to be 12·0 kcal mol^{-1}, identical with the value obtained from the coalescence of the ring methylene protons' signals. Similar behaviour was expected for the *C*-methyl groups of 3,5-di-isopropyltetrahydro-1,3,5-thiadiazine, but the chemical shift difference between the two non-equivalent methyl groups is apparently too small.

The inversion barriers for all the compounds studied lie in the range 9·3 to 12·1 kcal mol^{-1}. This accords with similar values found for a large number of saturated six-membered heterocycles, *e.g.* dithians,[30,31] hexahydropyrimidines,[32] and hexahydro-1,3,5-triazines.[32-34] Two trends are discernible within this range of values. In both the tetrahydrothiadiazine and the dihydrodithiazine series the barriers for the *N*-methyl and *N*-ethyl compounds are the same, but as the *N*-alkyl groups increase further in size the inversion barrier is reduced; the fall appears to be largest for the dialkyltetrahydrothiadiazines, but we do not have the di-t-butyl compound to confirm this. The trend is reasonable and accords with many other observations on six-membered rings; presumably it originates in increased steric strain in the ground states with increasingly bulky *N*-substituents. The second trend is that replacement of nitrogen by sulphur lowers the inversion barrier. This too is in agreement with previous observations; thus, the inversion barrier in 1-methylpiperidine is considerably higher than that in tetrahydrothiapyran.[3]

The geminal coupling constants, J_{gem}, between the various axial and equatorial pairs of protons all lie in the range 12·0 to 14·5 Hz. We have previously shown [35] that correlations which had been suggested [36] between J_{gem} and the conformation at the nitrogen atom in oxaza- and thiaza-bicyclononanes cannot usefully be extended to simple six-membered monocyclic systems; the present results confirm this conclusion.

On the other hand there has seemed to be a rough qualitative correlation [35] between Δ_{ae}, the chemical shift difference between geminal axial and equatorial protons, and the conformation of *N*-alkyl groups on adjacent nitrogen atoms, although Riddell and Lehn have cautioned against its use.[37,38] In hexahydropyrimidines, hexahydro-1,3,5-triazines, and tetrahydro-1,3-oxazines the magnitude of Δ_{ae} increases, rather irregularly, with an increasing proportion of axial lone pair (or pairs) on adjacent nitrogen atoms. In those systems the axial proton occurs to higher field, the reverse of what is found in the present series. We might, therefore, expect to find that the differential shielding effect of the nitrogen lone pairs should cause the magnitude of Δ_{ae} to *decrease* with increasing proportion of axial nitrogen lone pair. In the present series of compounds the value of Δ_{ae} for the methylene groups between nitrogen and sulphur atoms, N–CH_2–S (the 2- and 6-protons in the tetrahydrothiadiazines, the 4- and 6-protons in the dihydrodithiazines) does indeed decrease markedly as the size of the *N*-alkyl substituents increases. However, since the dipole moment evidence (above) indicates that for all three of the 5-methyl-, 5-ethyl-, and 5-isopropyl-dihydro-1,3,5-dithiazines the nitrogen lone-pair is effectively 100% equatorial (a conclusion which is likely to apply in $CDCl_3$–$CFCl_3$ as well as in cyclohexane), then it is likely that the change in Δ_{ae} originates in an increasing distortion of the ring with increasing size of the alkyl groups, and/or a differential effect of the change in alkyl group on the two proton shifts. In sharp contrast the Δ_{ae} values for the N–CH_2–N protons of the tetrahydrothiadiazines move in the opposite direction, increasing in magnitude with increasing size of the adjacent *N*-alkyl groups. It is tempting to question our assignment of axial and equatorial signals in this instance, particularly as this methylene group is remote from the anisotropic effect of the C–S bonds, but the long-range coupling (see Figure 2) precludes this possibility. As expected, the value of Δ_{ae} for the S–CH_2–S protons in the dihydrodithiazines is not greatly influenced by the conformation at the nitrogen atoms four bonds away.

For both series of compounds the regularity of the coupling constant and chemical shift changes in the spectra with changing alkyl groups indicates that there is no fundamental variation in ring structure, supporting our assumption that the rings in all the compounds here studied are in the chair form.

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Conclusions.—The *N*-alkyl group in 5-alkyldihydro-1,3,5-dithiazines is predominantly axial, even when it is a t-butyl group. 3,5-Dialkyltetrahydro-1,3,5-thiadiazines probably also exist largely in conformers with one or two axial alkyl groups. Ring-inversion barriers are between 9·3 and 12·1 kcal mol^{-1}; increasing bulk of *N*-alkyl groups and replacement of nitrogen by sulphur lead to values at the lower end of the range. Slow ring inversion leads to observable non-equivalence in the ethyl group methylene protons of 3,5-diethyltetrahydro-1,3,5-thiadiazine. There is no correlation between J_{gem} values for ring methylene protons and the conformation at nitrogen; chemical-shift differences between the geminal protons do change regularly with changes in the size of adjacent *N*-substituents, but the direction of change is different for $N-CH_2-S$ and $N-CH_2-N$ methylene groups.

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