The Conformational Analysis of Saturated Heterocycles. Part LVII.[1,2] Cyclic and Acyclic Tetra-alkylhydrazines

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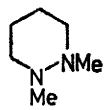
Equilibrium and kinetic processes in acyclic, cyclic, and polycyclic tetra-alkyltetrazines are discussed with reference both to new and to literature data. A consistent overall picture is presented in terms of ' passing ' and ' non-passing ' inversion processes which differ in the magnitude of steric hindrance in the transition state.

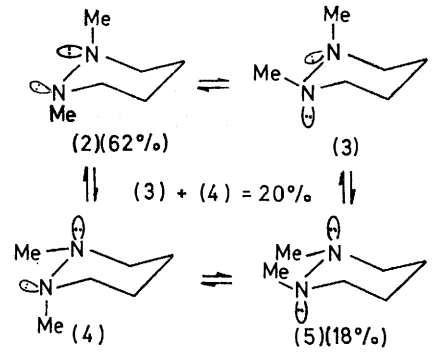
We recently studied [3] 1,2 dimethylhexahydropyridazine (1) and concluded that all three conformations (2), (3) [equivalent to (4)], and (5) were significantly populated. This conclusion disagreed with the literature interpretation [4] of the n.m.r. spectrum of this compound: an investigation of these discrepancies uncovered others and led us to a general study of the kinetic processes involved in the ring and nitrogen inversion and C–N and N–N bond rotations of cyclic and acyclic tetra-alkylhydrazines. We now report our results (see also



(1)

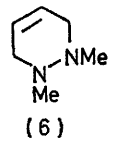
ref. 2) and an explanation in terms of hindered and non-hindered nitrogen inversion which, we believe, satisfactorily accounts for all the known facts.

Anderson [4] (*cf.* ref. 5) from the temperature dependent n.m.r. spectra of several tetra- and hexa-hydropyridazines had concluded that the only conformer of 1,2-dimethyl-1,2,3,6-tetrahydropyridazine (6) present at low temperature possessed one axial and one equatorial group (7), but that the preferred conformation of 1,2-dimethylhexahydropyridazine (1) had diequatorial methyl groups (5). It seemed unlikely that both the



SCHEME 1

tetrahydropyridazine (6) and the hexahydropyridazine (1) would both exist entirely in one conformation, and



(6)

that these would have different configurations about nitrogen, equatorial–axial and diequatorial, respectively.

[1] Part LVI, R. A. Y. Jones, A. R. Katritzky, K. A. F. Record, and R. Scattergood, preceding paper.

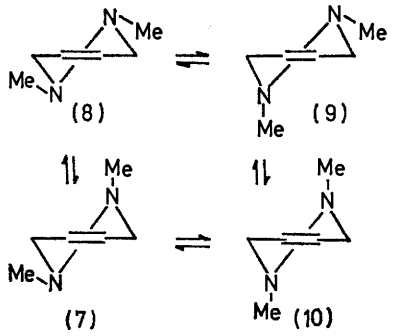
[2] For preliminary communications of part of this work see R. A. Y. Jones, A. R. Katritzky, D. L. Ostercamp, K. A. F. Record, and A. C. Richards, *Chem. Comm.*, 1971, 644; R. A. Y. Jones, A. R. Katritzky, and R. Scattergood, *ibid.*, 1971, 644.

[3] R. A. Y. Jones, A. R. Katritzky, D. L. Ostercamp, K. A. F. Record, and A. C. Richards, *J.C.S. Perkin II*, 1972, 34.

[4] J. E. Anderson, *J. Amer. Chem. Soc.*, 1969, **91**, 6374.

[5] J. E. Anderson and J.-M. Lehn, *Bull. Soc. chim. France*, 1966, 2402.

A study of the various factors influencing the position of the equilibrium and previous work [3] illustrates this point.



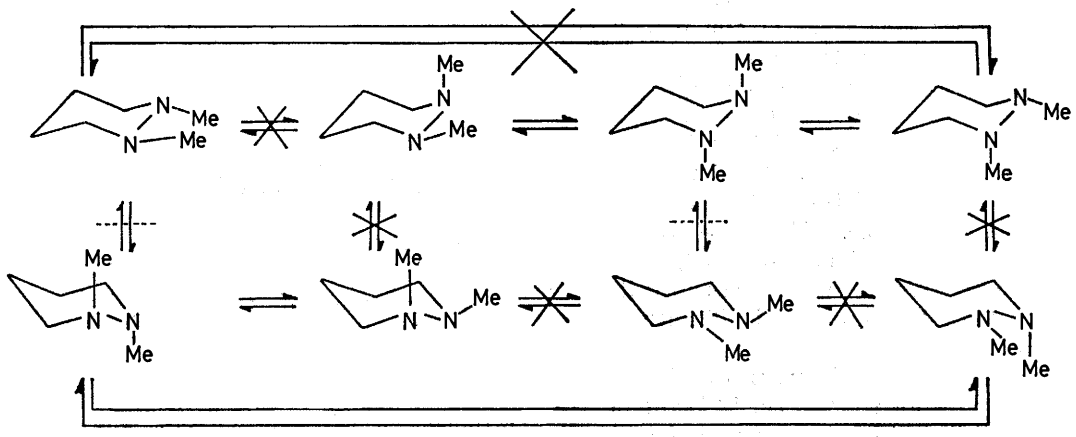
SCHEME 2

Preparation of Compounds.—Tetra- and hexa-hydropyridazines are readily synthesised by a Diels–Alder reaction between the appropriate buta-1,3-diene and diethyl azodicarboxylate. The resulting tetrahydropyridazine can be reduced to the hexahydropyridazine with palladium on charcoal. The ester group was reduced to CH_3 with lithium aluminium hydride.[6]

1,2-*Dimethylhexahydropyridazine* (1).—We have previously [3] suggested that the three conformers of (1) are about equally populated. We offer evidence below which modifies this conclusion. We now believe that at room temperature the diequatorial and doubly degenerate equatorial–axial conformers remain about equally populated, but that the predominant conformer (*ca.* 62%) is the diaxial one. Mole fractions are shown in Scheme 1. These indicate that the diaxial conformer (2) is some 0·7 kcal mol^{-1} more stable that the diequatorial (5), and *ca.* 1·1 kcal mol^{-1} more stable than the equatorial–axial (3) or (4). The diequatorial conformer (5) is destabilised by a *gauche* butane interaction between the methyl groups. Further, recent studies of the barriers in hydrazines [7] indicate that the energy of the *trans*-conformation of lone pairs is 3—4 kcal mol^{-1} above the stable conformation with a dihedral angle between the lone pairs near 90°: this effect considerably destabilises (5).

For the diaxial conformer (2), distortion at the nitrogen atoms will significantly relieve the interactions between the two axial methyl groups and the β-diaxial hydrogen atoms (*cf.* 1-methylpiperidine with a conformational free energy of 0·65 [8] compared with 1·8 kcal mol^{-1} for methylcyclohexane [9]). This *N*-methyl group distortion also increases the dihedral angle between the lone pairs towards 90°.

Conformers (3) and (4) are mirror images with one equatorial and one axial methyl group. The unfavourable interactions due to the axial methyl group and to a *gauche* butane interaction between the methyl groups are unlikely to be relieved by bending the axial



SCHEME 3 The conformers of 1,2-dimethylhexahydropyridazine

methyl group outwards as this decreases the dihedral angle between the lone pairs.

1,2-*Dimethyl*-1,2,3,6-*tetrahydropyridazine* (6).—The relative energies of the conformers of the hexahydropyridazine (1) enable prediction of those for the tetrahydropyridazine (6) conformers of Scheme 2. Substituted cyclohexenes adopt a half-chair conformation [10] with C–H bonds at the 4- and 5-positions which correspond rather closely to the axial and equatorial positions of cyclohexane, but the C–H bonds at the 3- and 6-positions are somewhat altered. Molecular models show that in the tetrahydropyridazine (6) the lone pair positions are slightly different from those in hexahydropyridazines.

In the diaxial methyl conformer (10), the removal of axial–axial interactions allows the methyl groups to be splayed further apart; however, this process is not

[6] H. R. Snyder, jun., and J. G. Michels, *J. Org. Chem.*, 1963, **28**, 1144.

[7] (*a*) R. P. Lattimer and M. D. Harmony, *J. Amer. Chem. Soc.*, 1972, **94**, 351; (*b*) L. Radom, W. J. Hehre, and J. A. Pople, *J. Amer. Chem. Soc.*, 1972, **94**, 2371.

[8] R. A. Y. Jones, A. R. Katritzky, A. C. Richards, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1970, 122.

[9] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Interscience, New York, 1965, p. 43.

[10] R. A. Pasternak, *Acta Cryst.*, 1951, **4**, 316.

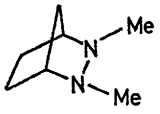
particularly favourable because it decreases the angle between the lone pairs. For the equatorial–axial conformers (7) and (9) the axial methyl group becomes more favoured due to the loss of the β-diaxial CH_3–H interaction; this causes less distortion of the axial methyl group and hence the lone pair–lone pair dihedral angle will tend to increase, to adopt a dihedral angle estimated as 80°, close to the preferred 90°. Introducing a double bond into the 4,5-position of the diequatorial conformer (8) causes unfavourable 1,3- and 1,4-dipolar interactions between the axial lone pairs on nitrogen and the π-orbital of the double bond.

The double bond in (6) thus should increase the proportion of the equatorial–axial conformers (7) and (9) at the expense of the diequatorial (8) and diaxial conformers (10) when compared to the hexahydropyridazine (1).

Dipole Moments.—In the absence of a better estimate we had previously [3] assumed that the moment of the *gauche* hydrazine system was the same in both diaxial and equatorial–axial conformers. This is clearly a crude approximation; distortion of the diaxial conformer towards the favoured 90° between lone pairs is relatively easy, but it is much more difficult to distort the equatorial–axial form. Recent evidence [11] from the dipole moments of hexahydro-1,2,4,5-tetrazines confirms that the diaxial conformer has the lower moment. Values of 1·5 for diaxial and 1·8 D for equatorial-axial conformers seem reasonable. The diequatorial conformer, in which the lone pairs are opposed, has only a very small moment. We previously [3] assumed it to be zero; values up to *ca.* 0·3 D do not significantly change any of our conclusions.

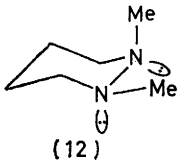
Barrier Magnitudes.—The barriers to nitrogen inversion proposed by Anderson [4] of *ca.* 12 kcal mol^{-1} are difficult to reconcile with those found for acyclic hydrazines [12] of *ca.* 7—8 kcal mol^{-1}. Inclusion in a ring should not of itself substantially raise the barrier to nitrogen inversion as is borne out by considering the data for various acyclic and cyclic amines. The barriers to nitrogen inversion in acyclic amines fall in the range 6·0—7·5 kcal mol^{-1} and those for bridged and unbridged cyclic tertiary amines with five or more atoms in the ring in the range [13] 6·4—8·5 kcal mol^{-1}. At most, there is an increase of 1 kcal mol^{-1} from an acyclic to a cyclic compound.

The Concept of Passing Methyl Groups.—The inversion barriers [14] in 2,3-dimethyl-2,3-diazabicyclo[2.2.1]-heptanes [as (11)] of *ca.* 12—14 kcal mol^{-1} must be nitrogen inversion because the ring system is rigid. The probable explanation of the increase of *ca.* 4—6 kcal mol^{-1} over that for acyclic hydrazines invokes non-bonded interactions and strain energy arising from the need for the methyl groups to pass each other in the transition state.



(11)

This concept of non-bonded interactions due to passing methyl groups applies to unbridged cyclic compounds. The conversion of diequatorial (5) into the equatorial–axial conformer (3) involves eclipsed methyl groups in the transition state (12). Interconversion of the equatorial–axial conformer (3) to the diaxial (2) does not involve methyl groups passing and a lower barrier is expected near the 7—8 kcal mol^{-1} for acyclic hydrazines.



(12)

Ring inversion barriers in saturated rings are also expected to be relatively high. In 1,2-dioxan and 1,2-dithian [15] the barriers are higher than in cyclohexane, probably because the transition states involve eclipsed lone pairs. The ring inversion of the equatorial–axial conformer of 1,2-dimethylhexahydropyridazine likewise involves the nitrogen lone pairs, and the methyl groups, passing each other and the barrier will again probably be higher than in cyclohexane. The ring inversion which interconverts the diaxial and diequatorial conformers does not involve such passings and the barrier is probably comparable with that in cyclohexane,[16] 10·8 kcal mol^{-1}. Non-passing ring inversions for 1,2,3,6-tetrahydropyridazines are expected to have very low barriers; compare cyclohexene,[17] 5·3 kcal mol^{-1}, but if the ring inversion does involve passing (equatorial–axial to axial–equatorial, *cf.* Scheme 4) the barrier should be high.

We thus have three types of barriers in hydrazines: a high energy barrier (*ca.* 12 kcal mol^{-1} or more) relates to nitrogen or ring inversions which involve a crossing of the two nitrogen substituents; an intermediate barrier (10—11 kcal mol^{-1}) for *ee* $\rightleftharpoons$ *aa* ring inversions in saturated systems; and a low energy barrier (*ca.* 8 kcal mol^{-1} or less) relates to nitrogen and unsaturated ring inversions in which no substituent crossing is involved. We have indicated the nature of the barrier in Schemes

[11] R. A. Y. Jones, A. R. Katritzky, A. R. Martin, D. L. Ostercamp, A. C. Richards, and J. M. Sullivan, *J.C.S. Perkin II*, in the press.

[12] (*a*) J. E. Anderson, D. L. Griffith, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1969, **91**, 6371; (*b*) M. J. S. Dewar and W. B. Jennings, *Tetrahedron Letters*, 1970, 339.

[13] J. B. Lambert and W. L. Oliver, jun., *J. Amer. Chem. Soc.*, 1969, **91**, 7774; J.-M. Lehn and J. Wagner, *Chem. Comm.*, 1970, 414.

[14] J. E. Anderson and J.-M. Lehn, *J. Amer. Chem. Soc.*, 1967, **89**, 81.

[15] G. Claeson, G. Androes, and M. Calvin, *J. Amer. Chem. Soc.*, 1961, **83**, 4357.

[16] F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc.*, 1967, **89**, 760.

[17] F. A. L. Anet and M. Z. Haq, *J. Amer. Chem. Soc.*, 1965, **87**, 3147.

3—6 by superimposing on the equilibrium arrows a cross for a high energy barrier and a broken line for an intermediate barrier.

This conclusion differs slightly from that proposed in our preliminary communications,[2] in which we suggested that non-passing ring inversions in saturated rings might also be of low energy.

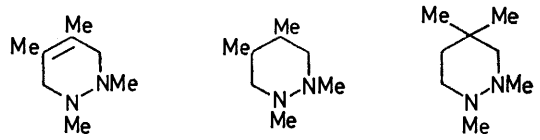
Dipole Moment of 1,2-*Dimethyl*-1,2,3,6-*tetrahydropyridazine* (6).—The diequatorial conformer (8), with a lone-pair angle *ca.* 180°, has a pseudo-centrosymmetric hydrazine system that contributes nothing to the total dipole moment. A small inductive effect towards the nitrogen atoms opposes the double bond moment; thus the moment of conformer (8) should not exceed that of cyclohexene, 0·7 D.[18]

In the diaxial conformer (10) the hydrazine system has a dihedral angle intermediate between the diaxial and equatorial–axial angles of 1,2-dimethylhexahydropyridazine, leading to a predicted moment between 1·5 and 1·8 D. The direction of this moment will be in the same plane as that containing the double bond, and the two moments will be directly opposed giving a total moment of *ca.* 0·9 D.

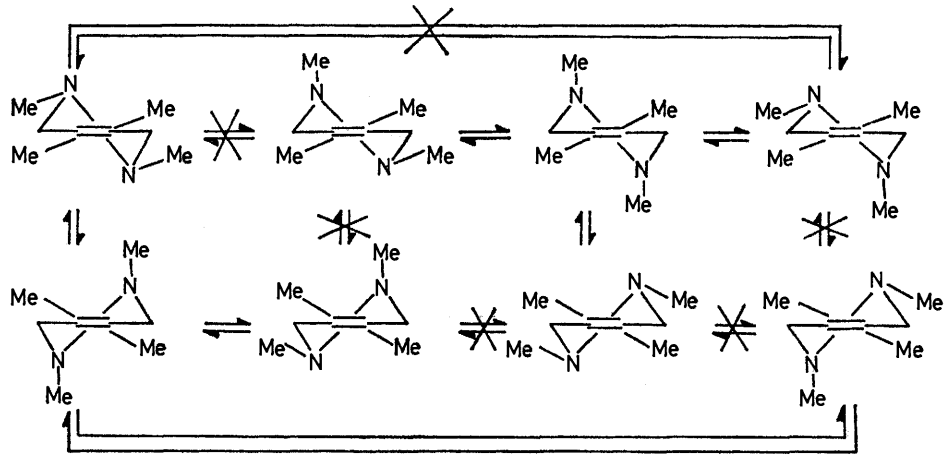
For the equatorial–axial conformers (7) and (9) the angle θ between the hydrazine moment and the double-bond moment must be estimated. In 1,2,4-trimethyl-4-*p*-nitrophenylhexahydropyridazine [3] the angle between the hydrazine moment and the 4-axial bond is 43°. This bond is approximately at right angles to the plane of the ring; we therefore use a similar angle in the present calculation. Molecular models also indicate that the axial lone pair in the tetrahydropyridazine conformers (7) and (9) is at right angles to the plane of the ring. If the hydrazine moment bisects the angle between the lone pairs (*ca.* 80°) it will be at an angle of 40° to the plane perpendicular to the ring. We therefore take θ as 90 + 40 = 130°, whence the moment of the equatorial–axial conformer is calculated by equation (1) to be 1·45 D. If θ is changed by 5° the value of $\mu_{7,9}$ changes by only 0·05 D, which is not significant. Because the dihedral angle between the lone pairs is 80°, the hydrazine moment will in fact be somewhat less than the value of 1·8 D used in equation (1), and the true value for conformers (7) and (9) rather less than 1·45 D.

$$\mu_{7,9}^2 = 1{\cdot}8^2 + 0{\cdot}7^2 + 2 \times 1{\cdot}8 \times 0{\cdot}7 \cos 130° \quad (1)$$

The measured moment of (6), 1·41 D, is in close agreement with that of the equatorial–axial conformer, especially considering the approximations made in the calculations. The dipole moment result thus supports the conclusion that the major conformer is the equatorial–axial one.



1,2,4,5-*Tetramethyl*-1,2,3,6-*tetrahydropyridazine* (13).—The room temperature n.m.r. spectrum shows three singlets of relative areas 3 : 3 : 2. Below −3° the N–CH_2 signal becomes an AB quartet; at −60° the coupling constant is 16 Hz and the separation 0·599 p.p.m. Further cooling broadens the AB quartet and changes occur (Figure 1) until at −123° it resembles two overlapping AB quartets. The N–CH_3 singlet becomes a 1 : 1 doublet below −101°. The spectrum at −123° is shown in Figure 2.



SCHEME 4 The conformers of 1,2,4,5-tetramethyl-1,2,3,6-tetrahydropyridazine

The eight possible conformations of tetrahydropyridazine (13) are shown in Scheme 4. Below the high energy barrier the signal for CH_2 should be an AB quartet, and that for N–CH_3 should be a singlet, in agreement with observation.

At the lowest temperatures, two alternative interpretations are possible. The ring inversion barrier in cyclohexene [17] of 5·3 kcal mol^{-1} is raised in 1,2-bis-ethoxycarbonyl-1,2,3,6-tetrahydropyridazine [19] to 20

[18] A. L. McClellan, ' Tables of Experimental Dipole Moments,' Freeman, San Francisco, 1963, p. 205.

[19] E. W. Bittner and J. T. Gerig, *J. Amer. Chem. Soc.*, 1972, **94**, 913.

kcal mol^{-1} by strong interactions between the nitrogen substituents.[20] By contrast, the N–CH_2 signal of

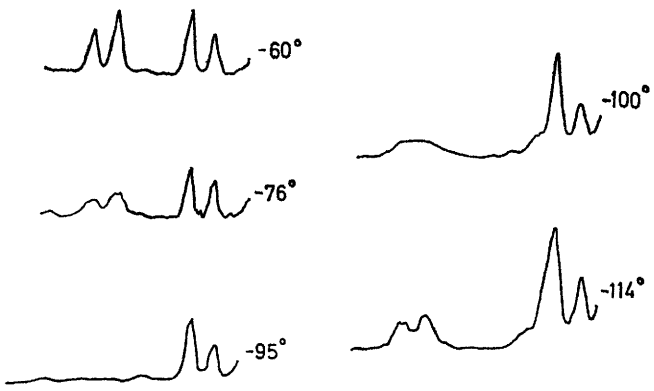


FIGURE 1 N.m.r. spectrum (100 MHz) of 1,2,4,5-tetramethyl-1,2,3,6-tetrahydropyridazine; resonance of N–CH_2 methylene groups

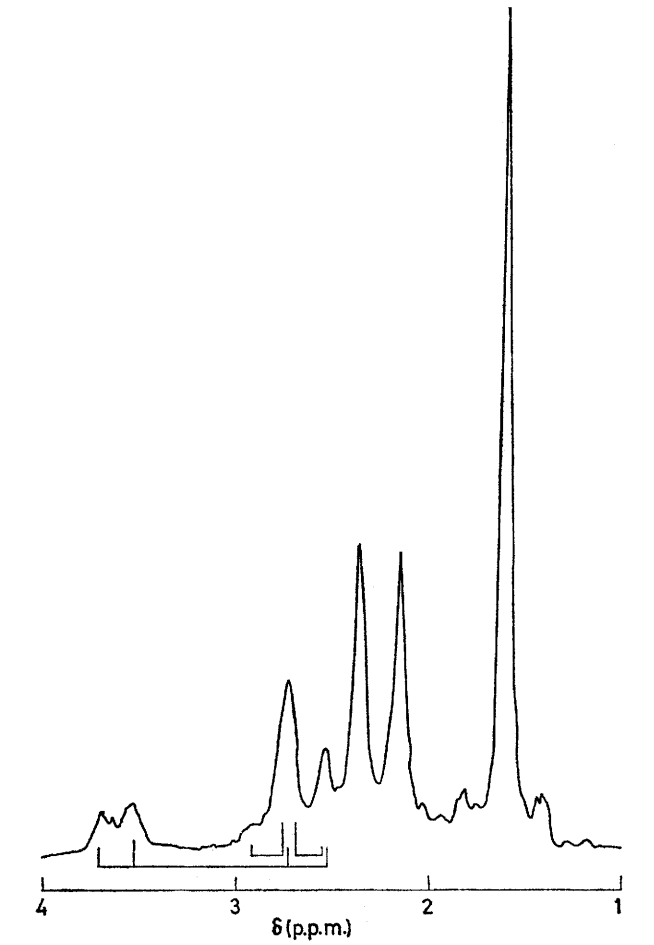
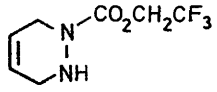


FIGURE 2 N.m.r. spectrum (100 MHz) of 1,2,4,5-tetramethyl-1,2,3,6-tetrahydropyridazine at −123°

1-(2,2,2-trifluoroethoxycarbonyl)-1,2,3,6-tetrahydropyridazine (16) remains [19] as two singlets down to −60°, which indicates that ring inversion is rapid when there is no substituent interaction.

The barrier to ring inversion in the tetrahydropyridazine (13) should therefore be of low energy when the crossing of the methyl groups is not involved, and may not have stopped at −123°. It is therefore necessary to consider two cases. (1) If all processes are slow the three conformations should show four N–CH_3 signals (or two if the configuration at the adjacent nitrogen does not significantly affect the chemical shift) of unequal area. The N–CH_2 protons should occur as four (or two) AB quartets. (2) If nitrogen inversion is slow but non-passing ring inversion fast, the two conformations (equatorial–axial and equilibrating diequatorial–diaxial) should show three N–CH_3 signals and three AB quartets.

Neither of the above two cases fits the observed spectrum if all the conformers are significantly populated. However, the dipole moment of 1,2-dimethyl-1,2,3,6-tetrahydropyridazine (6) indicates a considerable



(16)

predominance of the equatorial–axial conformer at room temperature, which should not be affected by the two methyl groups on the double bond and thus should also apply to (13). At low temperatures the equilibrium will alter to give even less of the high energy conformers. The equatorial–axial conformer should give

TABLE 1

Room temperature n.m.r. spectra [δ (p.p.m.)] measured at 100 MHz [a]

Compound	N–CH_2	N–CH_3	C–CH_3
(1)	2·53br(s)	2·28(s)	
(13)	3·05br(s)	2·38(s)	1·61(s)
(14)	2·5(m)	2·39(s)	0·92(d)
(15) [b]		2·35(s)	1·02(s)
		2·34(s)	

[a] 15% In $CDCl_3$–$CFCl_3$ (3 : 1). [b] 3,3,6,6-Tetradeuterio-derivative.

TABLE 2

N.m.r. spectra at low temperature [δ (p.p.m.)]

Compd.	T/°C	N–CH_2 [a]	N–CH_3	C–CH_3
(13)	−60	3·03 (AB, Δν 59·9 Hz, J 16·0 Hz)	2·41(s)	1·60(s)
(14)	−60	2·58	2·29(2s, Δν 1·2 Hz)	0·95(2d, Δν 7·3 Hz)
(15) [b]	−90		2·51 [c] (2s, Δν 10·6 Hz) 2·45 [d] (2s, Δν 6·4 Hz)	1·15(2s, Δν 13·9 Hz)

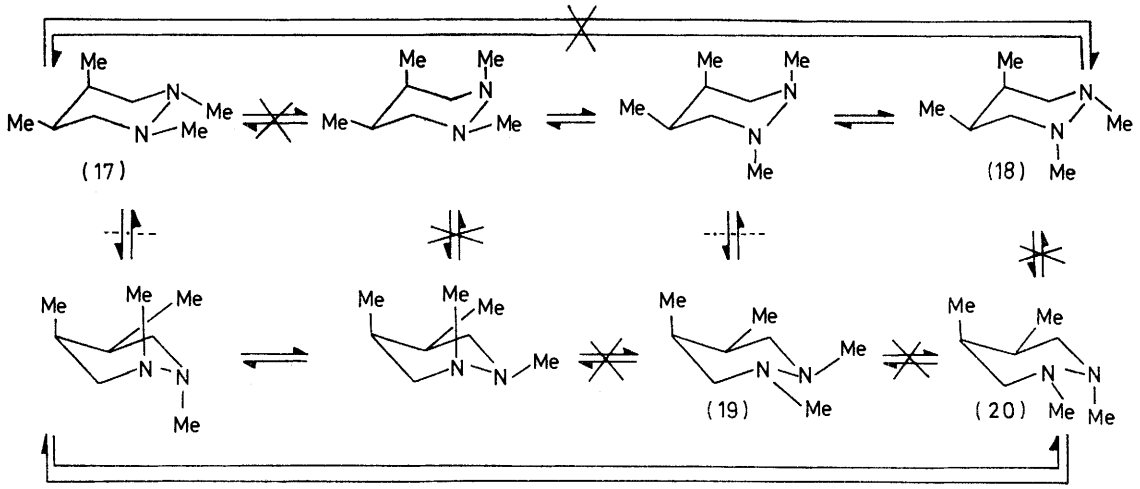
[a] Δν = relative chemical shift; J = coupling constant. [b] 3,3,6,6-Tetradeuterio-derivative. [c] Major peak. [d] Minor peak.

two equal methyl peaks and two AB quartets in agreement with the observed spectrum. It is not possible to

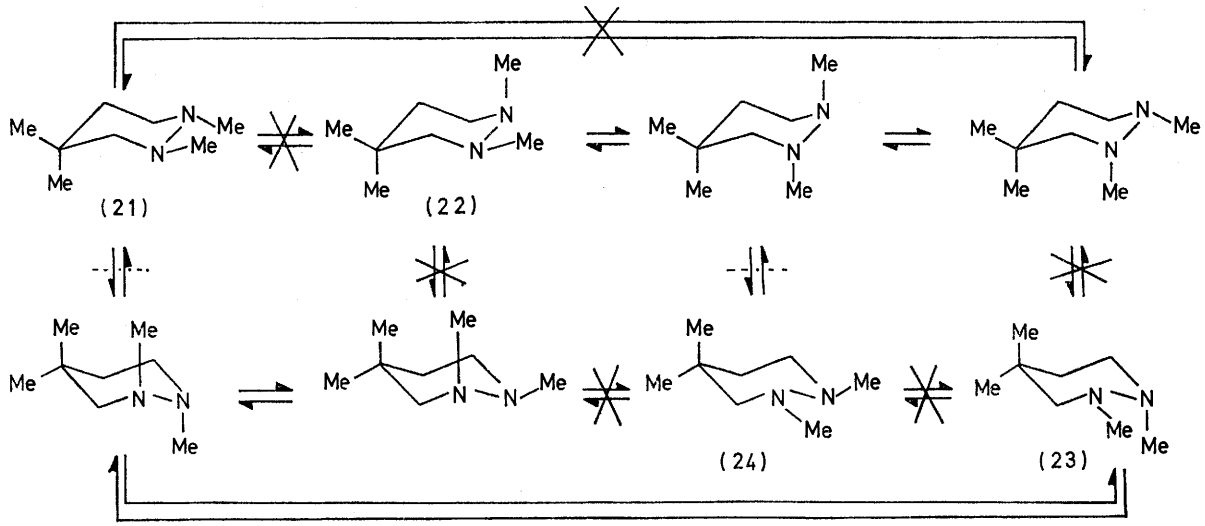
[20] J. C. Breliere and J.-M. Lehn, *Chem. Comm.*, 1965, 426.

decide whether non-passing ring inversions remain fast at the lowest temperatures reached.

cis-1,2,4,5-*Tetramethylhexahydropyridazine* (14).—Four of the conformers (Scheme 5) possess β-diaxial methyl groups and are of high energy. At room temperature the signal for N–CH_3 is a singlet and that for C–CH_3 is a doublet, owing to vicinal coupling. At −60° the C–CH_3 groups appear as two doublets and the N–CH_3 as



SCHEME 5 The conformers of 1,2,4,5-tetramethylhexahydropyridazine



SCHEME 6 The conformers of 1,2,4,4-tetramethylhexahydropyridazine

two singlets of equal area. This indicates that the passing inversions have been frozen, but that the non-passing ring inversions are still equilibrating, (17) with (20) and (18) with (19). This presumably arises because of very small chemical shift differences; the observed separation of the N–CH_3 peaks is only 1·2 Hz. It was not possible to identify further spectral changes at lower temperatures due to the complexity of the spectrum and overlapping of peaks.

1,2,4,4-*Tetramethylhexahydropyridazine* (15).—Four of the conformers (Scheme 6) have β-diaxial methyl groups and thus negligible population. The n.m.r. spectra were simplified by using the 3,3,6,6-tetradeuterio-compound. Below the high energy barrier of 11·5 kcal mol^{-1} (Table 3) conformers (22) and (24) are separated from conformers (21) and (23) and the C–CH_3 singlet splits into two equal peaks whilst the N–CH_3 signal remains as an equal doublet (Table 2) as expected. Further cooling slows the non-passing ring inversion (*ca.* 10 kcal mol^{-1}) and separates the diequatorial conformer (21) and its enantiomer (24) from the equatorial–axial ones [(23) and (22) respectively]. Four N–CH_3 signals were seen, as two pairs of unequal intensity, one pair from each conformer, as expected (Figure 3).

1,2-*Dimethylhexahydropyridazine* (1).—The eight possible conformations of 1,2-dimethylhexahydropyridazine (Scheme 3) are divided into two equivalent sets of four by high energy barriers. Rapid equilibration within each set renders the two *N*-methyl groups equivalent. The N–CH_2 protons are only equivalent if

the two sets are interconverting and hence at low temperatures the $N-CH_2$ singlet should split into an AB *quartet*, as is observed. At still lower temperatures the intermediate ring inversions will be frozen and the diequatorial conformer will be separated from the other three. The observation of splitting of the methyl peaks in the tetramethyl compounds (14) and (15) described above led to the conclusion that at low temperatures it

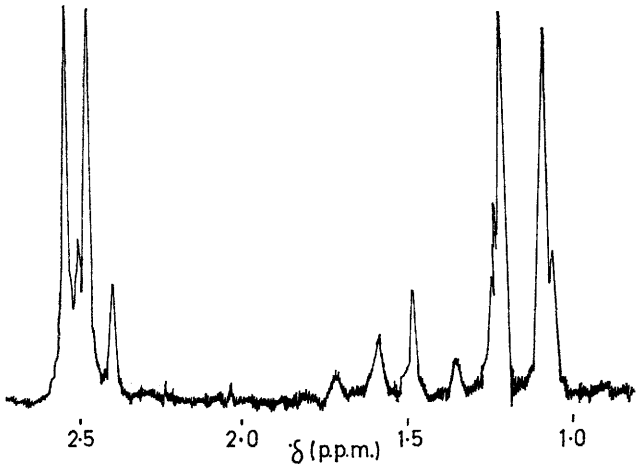


FIGURE 3 N.m.r. spectrum of 3,3,6,6-tetradeuterio-1,2,4,4-tetramethylhexahydropyridazine at −90°

should be possible to resolve separate $N-CH_3$ peaks; previous failures [4] could be due to chemical shift coincidence. In deuteriomethanol solvent interaction enhances differential chemical shifts: the $N-CH_3$ signal occurs as a sharp singlet at room temperature and the $N-CH_2$ protons as a broad singlet which changed on cooling to a broad AB quartet, *cf.* the multiplets previously observed.[4] The $N-CH_3$ singlet broadened as the temperature was lowered and below −73° a minor peak was resolved 0·06 p.p.m. upfield of the major peak. The broad signals caused considerable overlap and the spectrum was further complicated by the presence of the high field part of the $N-CH_2$ AB quartet, but the relative areas are *ca.* 7 : 1.

An approximate calculation of the barrier associated with this separation shows it to be *ca.* 11 ± 1 kcal mol^{-1}. We therefore suggest that the process being stopped is the non-passing ring inversion between diequatorial and diaxial conformers and we therefore assign the minor signal to the diequatorial conformer (5), separated by passing inversions from the remaining three conformers (2)—(4) which are still rapidly equilibrating.

The equilibrium constant [(5)]/[(3)] is likely to be closely similar to [(21)]/[(22)], measured as 2·7 at −90°, equivalent to 2·5 at −73°. The observed 7 : 1 ratio therefore implies that the conformers (2) : (3) + (4) : (5) should exist in the ratios 6·2 : 0·8 : 1 at −73°, corresponding to proportions of 62, 20, and 18% respectively at 25° (assuming that the only entropy factor is that arising from degeneracy).

If we relate these proportions [equation (2)] to the expected dipole moments of the conformers we obtain a calculated value of 1·43 D, in good agreement with the observed value of 1·46 D.

$$\mu^2 \text{ calc} = 0{\cdot}62 \times 1{\cdot}5^2 + 0{\cdot}20 \times 1{\cdot}8^2 + 0{\cdot}18 \times 0{\cdot}2^2 \quad (2)$$

As mentioned above these proportions differ from those previously [3] reported because in the earlier work we were not able to allow for the different dipole moments of conformers (2) and (3) + (4).

Acyclic Hydrazines.—The above treatment can be applied to the processes occurring in acyclic hydrazines ABN·NCD which exist in 24 rotamers possessing *gauche* lone pairs. These 24 rotamers can be divided into two sets of 12 (Scheme 7) which have a mirror image relationship. The 12 rotamers in each set are interconvertible by successive nitrogen inversions in which there are no crossings of substituents. (For convenience the dihedral angle is shown as 60 instead of 90°.)

The barriers in tetrasubstituted hydrazines have previously been interpreted in terms of inversion barriers of *ca.* 8 kcal mol^{-1} and rotation barriers about the nitrogen–nitrogen bond of *ca.* 11 kcal mol^{-1} (see refs. 12*a* and 21). Inversion corresponds to processes of the type shown in Scheme 7. Rotation corresponds to the process shown in Scheme 8. The process (29) ⟶ (31) can also be thought of as two nitrogen inversions, (29) ⟶ (30) ⟶ (31), which involve the passing of substituents. Thus the barrier to the process (29) ⟶

TABLE 3
Coalescence temperatures (T_c) and free energies of activation ($\Delta G_c^{\ddagger}$)

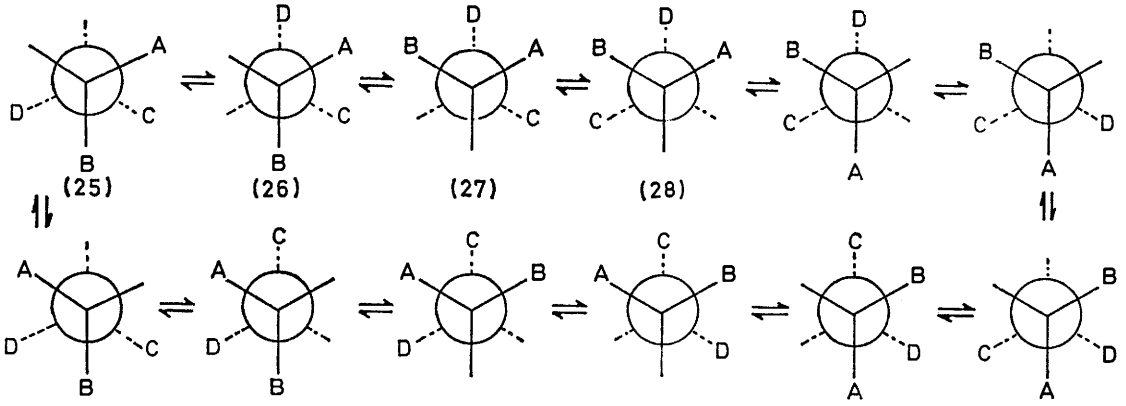
Compound	Solvent	Signal	T_c/°C	$\Delta G^{\ddagger}_c$/kcal mol^{-1}	Lit. $\Delta G^{\ddagger}_c$/ kcal mol^{-1} [a]
(13)	$CDCl_3$–$CFCl_3$ (3 : 1)	$N-CH_2$	−2·5	12·8	12·3
	$CFCl_3$–CS_2 (7 : 3)	$N-CH_3$	−101	8·3	8·2
(14)	$CDCl_3$–$CFCl_3$ (3 : 1)	$N-CH_3$	−42	12·6	12·3
	$CDCl_3$–$CFCl_3$ (3 : 1)	$C-CH_3$	−30·5	12·5	12·4
(15) [b]	$CFCl_3$	$N-CH_3$	*ca.* −50	*ca.* 10	
		$C-CH_3$	−45	11·5	

[a] Ref. 4. [b] 3,3,6,6-Tetradeuterio-derivative.

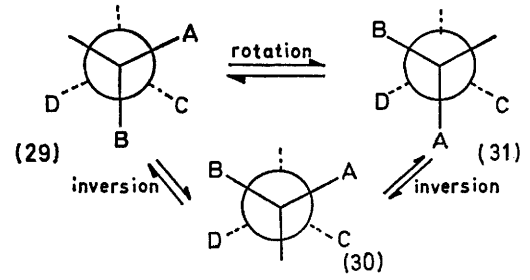
[21] J. R. Fletcher and I. O. Sutherland, *Chem. Comm.*, 1969, 706.

(31) should be of similar magnitude to the barrier between alternative sets in the cyclic hydrazines.

Discussion of Literature Work on Acyclic Hydrazines.—The spectral changes for hydrazines can be predicted by using the two energy barriers. Only conformers (25)—(28) of the set of Scheme 7 need to be used as the remaining eight conformers are identical to these four.

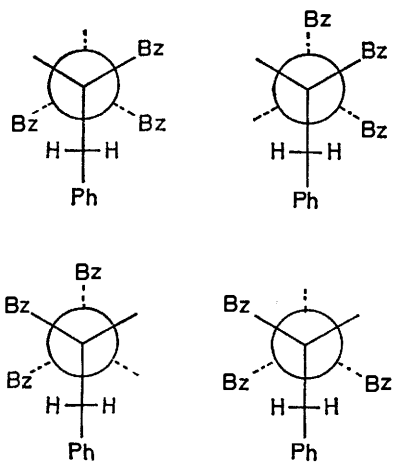


SCHEME 7

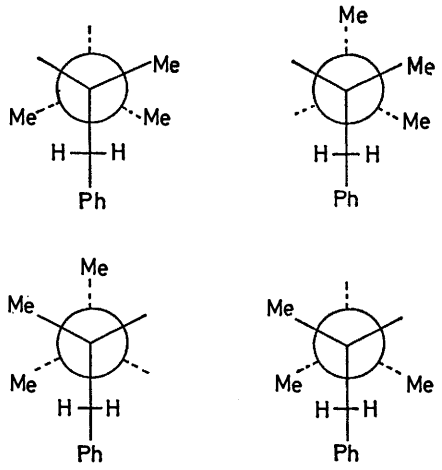


SCHEME 8

For 1,1,2,2-tetrabenzylhydrazine [12b] the CH_2 room temperature singlet split into two AB quartets at −120°, with $\Delta G^{\ddagger}$ 8 kcal mol^{-1}. A sharp singlet for the methylene protons at room temperature is expected, as all the rotamers are interconvertible. Lowering the temperature should separate the two sets but as the four conformers shown in Scheme 9 are still interconvertible, all the CH_2 protons remain equivalent. Further cooling freezes the molecule in one conformation causing nonequivalence both of the benzyl groups and of the CH_2 protons within a single benzyl group, *i.e.*, two AB quartets with a barrier of *ca.* 8 kcal mol^{-1}, in agreement with the observed spectrum.



SCHEME 9

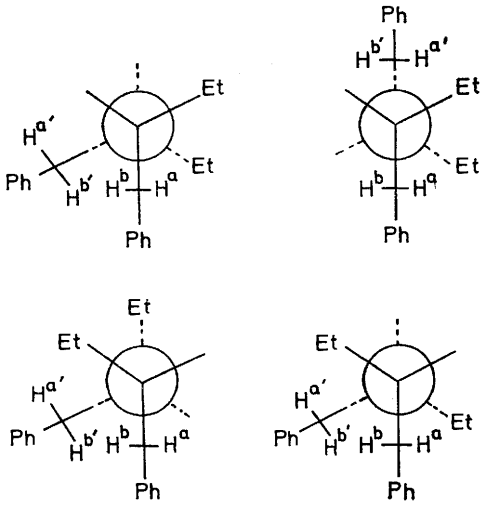


SCHEME 10

1-Benzyl-1,2,2-trimethylhydrazine [12a] displays at room temperature a CH_2 singlet and two singlets in the ratio 2 : 1 for the CH_3 groups. An AB quartet for CH_2 and a single broad peak for the CH_3 groups occur at −130°. The four rotamers to be considered are shown in Scheme 10. Above the low energy barrier the CH_2 protons are equivalent and remain as a singlet. The CH_3 groups of NMe_2 also remain equivalent and no spectral change is associated with the high energy barrier. The broad signals observed mean that small splittings are not detected and there are two explanations: (1) both nitrogens undergo slow inversion, the CH_2 protons will give an AB quartet, and both CH_3 signals will be split

into doublets; (2) fast inversion at NMe_2 gives an AB quartet for CH_2 and a doublet for NMe_2, whilst the H_2CNMe signal will remain a singlet. Benzyl nitrogen inversion must be slow otherwise all the signals remain as singlets.

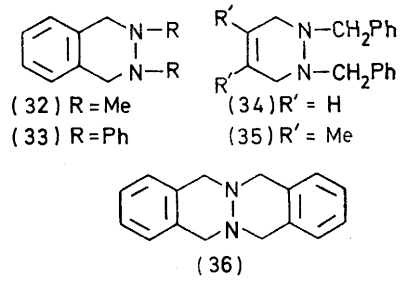
Sutherland [21,22] had studied the high energy barriers in several tetrasubstituted hydrazines. Inversions below the high energy barrier for 1,2-dibenzyl-1,2-diethylhydrazine (Scheme 11) allow the benzyl groups to remain equivalent, but the benzyl CH_2 protons become non-equivalent. The benzyl CH_2 room temperature singlet should thus give one AB quartet on cooling. In



SCHEME 11

the unsymmetrical 1,1,2-tribenzyl-2-ethylhydrazine the predicted changes on cooling are that the $EtNCH_2$ protons should remain a singlet, but the $(PhCH_2)_2N$ protons should give a single AB quartet. These predictions are in complete agreement with experiment.

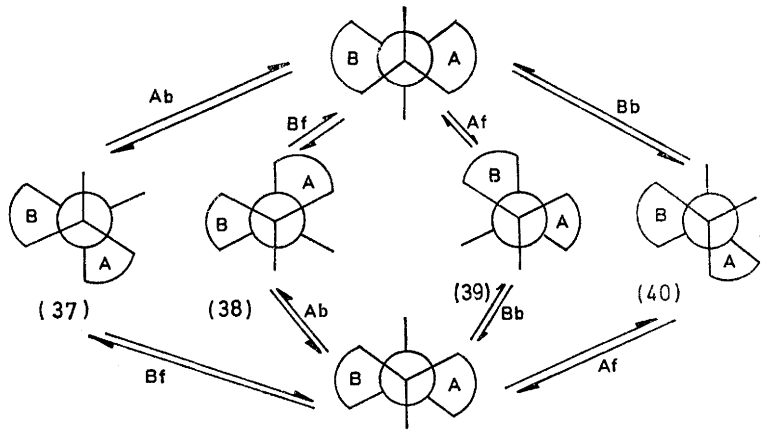
Microwave and far i.r. spectral data for methylhydrazine (in which there can be no passing inversions) have been interpreted [7] in terms of N–N rotation in an otherwise rigid molecule, and indicate a maximum barrier of $8{\cdot}7 \pm 0{\cdot}9$ kcal mol^{-1}. This is in line with the lower (non-passing) barrier for inversion.



(32) R = Me
(33) R = Ph
(34) R′ = H
(35) R′ = Me
(36)

Discussion of Literature Work on Cyclic Hydrazines.—Junge and Staab [23] studied the variable temperature n.m.r. spectra of compounds (32)—(35). In all four compounds the ring methylene protons changed from a singlet to an AB quartet below a high energy barrier of *ca.* 12 kcal mol^{-1}. These spectral changes are analogous to those observed for 1,2,4,5-tetramethyl-1,2,3,6-tetrahydropyridazine (13) and can be interpreted in the same manner.

For 5,7,12,14-tetrahydrophthalazino[2,3-*b*]phthalazine (36) two AB quartets were observed at low temperatures for the CH_2 protons. The fused ring systems restrict the inversion processes to those shown in Scheme 12. Conformers (37) and (38) are mirror images as are (39) and (40). Conformers (37) and (40) are interconvertible by processes analogous to *cis*-decalin inversions. All inversions involve the passing of nitrogen substituents and are thus of high energy. As the preferred conformation of hydrazine [7b] involves a lone pair–lone pair angle of 90° the conformers with *trans* lone pairs will not be substantially populated. As the A and B rings are



SCHEME 12

identical conformers (37) and (39) are identical as are (38) and (40). Thus the n.m.r. spectrum at low temperatures will be due to only one frozen species, (37) or its mirror image. At room temperature a singlet for the

[22] J. R. Fletcher and I. O. Sutherland, *Chem. Comm.*, 1970, 687.
[23] B. Junge and H. A. Staab, *Tetrahedron Letters*, 1967, 709.

methylene protons should be observed which on cooling becomes two equally intense AB quartets.

This spectral change was observed;[23] the two AB quartets had different $\Delta\delta_{AB}$ values of 1·0 and 0·3 p.p.m. The spectrum is similar to that of 1,2,4,5-tetramethyl-1,2,3,6-tetrahydropyridazine (13), where the AB quartets had $\Delta\delta_{AB}$ values of 0·95 and 0·20 p.p.m. (Figure 2). This similarity indicates that the hydrazine moieties have the same conformation. In conformer (37) ring A is substituted equatorially–axially onto ring B and *vice versa*. The similarity of spectra supports the suggestion that the most stable conformer of (13) is equatorial–axial.

General Conclusions.—The above survey demonstrates that the published literature data on cyclic and acyclic hydrazines can be interpreted in terms of the high and low energy barriers.

EXPERIMENTAL

1,2-*Bisethoxycarbonyl*-1,2,3,6-*tetrahydropyridazine.*—Buta-1,3-diene was condensed, using a dry ice–acetone trap, into dimethyl azodicarboxylate (26·2 g) in benzene (15 ml) until the volume had doubled. After 12 h the benzene was removed. Distillation gave the tetrahydropyridazine (30·6 g, 89%) as an oil, b.p. 113° at 0·3 mmHg (lit.,[24] 115° at 0·5 mmHg).

1,3-Dimethylbuta-1,3-diene (15 g) [from pinacol (30 g) and diethyl azodicarboxylate (20 g)] similarly gave 1,2-bisethoxycarbonyl-4,5-dimethyl-1,2,3,6-tetrahydropyridazine (20·1 g, 69%), b.p. 139—141° at 1 mmHg (lit.,[24] 145° at 1 mmHg).

1,2-*Bisethoxycarbonylhexahydropyridazine.*—1,2-Bisethoxycarbonyl-1,2,3,6-tetrahydropyridazine (55·6 g) in EtOH (50 ml) was reduced in a Cook low pressure hydrogenator over Pd–C (10%, 1 g). After filtration, distillation gave the hexahydropyridazine (49·6 g, 89%), b.p. 98° at 0·1 mmHg (lit.,[24] 112—113° at 0·4 mmHg).

1,2-Bisethoxycarbonyl-4,5-dimethyl-1,2,3,6-tetrahydropyridazine similarly gave 1,2-bisethoxycarbonyl-4,5-dimethylhexahydropyridazine as an oil (86%), b.p. 124° at 1 mmHg (lit.,[25] 103—105° at 0·43 mmHg).

1,2-*Dimethyl*-1,2,3,6-*tetrahydropyridazine.*—1,2-Bisethoxycarbonyl-1,2,3,6-tetrahydropyridazine (10 g) in ether (25 ml) was added dropwise to a stirred solution of $LiAlH_4$ (2·5 g) in ether (100 ml). The solution was stirred for 4 h and then water (3 ml), NaOH solution (15%, 3 ml), and water (9 ml) were added. The precipitate was filtered off and extracted with ether (2 × 25 ml). The combined filtrate was dried ($MgSO_4$). The ether was removed and the residue dried over sodium wire for 8 h. Distillation from sodium gave the pure (g.l.c.) tetrahydropyridazine (2·95 g, 60%), b.p. 145° (lit.,[4] 48° at 15 mmHg). Similarly prepared were: 1,2-dimethylhexahydropyridazine from 1,2-bisethoxycarbonylhexahydropyridazine as an oil (63%), b.p. 142° (lit.,[6] 140—141°); 1,2,4,5-tetramethyl-1,2,3,6-tetrahydropyridazine from 1,2-bisethoxycarbonyl-4,5-dimethyl-1,2,3,6-tetrahydropyridazine as an oil (62%), b.p. 184° (lit.,[4] 73—75° at 98 mmHg); and 1,2,4,5-tetramethylhexahydropyridazine from 1,2-bisethoxycarbonyl-4,5-dimethylhexahydropyridazine as an oil (45%), b.p. 173—174° (lit.,[4] 90—91° at 86 mmHg).

N.m.r. Spectra.—The n.m.r. spectra were obtained using a Varian HA100 spectrometer equipped with a V4343 variable temperature attachment. Temperatures were measured by the methanol shift technique.[26] Room temperature data are recorded in Table 1 and low temperature data in Table 2. Dipole moments were measured as in ref. 27 and are shown in Table 4.

TABLE 4

Dipole moment of 1,2-dimethyl-1,2,3,6-tetrahydropyridazine [a]

$10^6 w_2$	$10^6(\varepsilon_{12} - \varepsilon_1)$	$10^6(v_1 - v_{12})$
5608	8849	1025
6550	10,427	1244
6759	10,716	1261
8315	13,246	1583

$d\varepsilon/dw_2$	$-dv/dw_2$	${}_TP_{2\infty}$	${}_EP$	μ/D
1·621 ± 0·015	0·204 ± 0·008	74·56	33·88	1·41 ± 0·01

[a] At 25° in cyclohexane. w = Weight fraction; ε = dielectric constant; v = specific volume. The suffixes 1, 2, and 12 refer to solvent, solute, and solution respectively.

We thank the S.R.C. for studentships (to K. A. F. R. and R. S.) and Dr. J. E. Anderson, University College, London, for helpful discussion, correspondence, and communication of unpublished results. In particular, he kindly informed us of the further changes in the spectra of 1,2-dimethylhexahydropyridazine at very low temperatures.

[3/1096 *Received*, 30*th May*, 1973]

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