The Conformational Analysis of Saturated Heterocycles. Part 76.[1] Ring and Nitrogen Inversion in *cis*- and *trans*-1,4,5,8-Tetramethyldecahydropyrazino[2,3-*b*]pyrazine

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Variable-temperature protonand pulsed proton noise-decoupled carbon-13 Fourier transform n.m.r. have been used to determine the inversion barriers and conformations of *cis*- and *trans*-1,4,5,8-tetramethyldecahydropyrazino[2,3-*b*]-pyrazine. The rate processes causing the spectral changes are discussed.

SIMPLE piperazines are not normally amenable to dynamic n.m.r. studies either because the barriers are low or because the equilibria are highly biased. Consequently, we have now investigated the *trans*- (1) and *cis*- (2) isomers of the bicyclic perhydropyrazinopyrazine, which were expected to possess higher barriers due to '1,3' steric and electronic interactions in the transition state. We recently demonstrated the importance of such steric and electronic interactions in the transition state [1,2] on the free activation energy of inversion at nitrogen. Such interactions raise the free energy of activation of nitrogen inversion in hexahydropyridazines [2] and hexahydropyrimidines.[1]

Two reports of the perhydropyrazinopyrazine ring system have appeared [3,4] but it has not previously been completely characterised. A mixture of the *cis*- and *trans*-isomers of 1,4,5,8-tetramethyldecahydropyrazino-[2,3-*b*]pyrazine (*ca.* 2 : 3 by ^{1}H n.m.r.) was readily obtained from the condensation of *NN'*-dimethylethane-1,2-diamine and glyoxal, and purified by preparative g.l.c. Separation of the isomers was not achieved by distillation or g.l.c.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded on a Varian HA-100 MHz spectrometer. Temperatures (±2 K) were measured with a standard methanol sample [5] above 183 K; below this a platinum resistance thermometer was used. Chemical shifts (±0.01 p.p.m.) were measured in CF_2Cl_2 and $CDCl_3$: $CFCl_3$ (1 : 1) with Me_4Si as internal standard. Natural abundance ^{13}C n.m.r. spectra were measured on a Varian XL-100 spectrometer in pulsed Fourier transform mode using an ICL 1903T computer. The resonance frequency for the ^{13}C nuclei was 25.16 MHz; sealed 12 mm tubes were employed. The D-heteronuclear lock and proton noise decoupling, to ascertain chemical shifts, were used in the experiment.

At low temperatures $CDCl_3$–$CFCl_3$ (1 : 1) or $(CD_3)_2CO$–CF_2Cl_2 (1 : 3) permitted temperatures as low as 133 K to be attained. Temperatures are accurate to at least ±3 K.

1,4,5,8-*Tetramethyldecahydropyrazino*[2,3-b]*pyrazine*.— **To** *NN'*-dimethylethane-1,2-diamine (10 g, 0.11 mol) was added dropwise with stirring at 0 °C aqueous 40% glyoxal (8.6 cm^3, 0.06 mol). The solution was then allowed to attain 20 °C and stirred for a further 1.5 h. Extraction with chloroform (4 × 50 cm^3) and distillation (64 °C at 0.7 mmHg) afforded the *pyrazinopyrazine* as a viscous oil (5.8 g, 52%), purified by preparative g.l.c. on a Perkin-Elmer F21 gas chromatograph (3% SE30 on Chromosorb W) (Found: C, 60.0; H, 11.0; N, 28.1. $C_{10}H_{22}N_4$ requires C, 60.6; H, 11.2; N, 28.3%).

DISCUSSION

In 1,4-dimethylpiperazine both *N*-methyl groups should be predominantly equatorial: their environment is similar to that of the *N*-methyl group in *N*-methylpiperidine which prefers an equatorial environment, ΔG° 2.7 kcal mol^{-1} [6] or *ca.* 1.5 kcal mol^{-1}.[7] However, conformers of 1,4,5,8-tetramethyldecahydropyrazinopyrazine possessing 1,4- or 5,8-equatorial *N*-methyl groups are disfavoured by '*peri*' interactions as well as a generalised '1,3' anomeric effect.

The *trans*-isomer (1) can exist in seven all-chair conformers (Scheme 1), which are interconvertible by nitro-

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[3] H. C. Chitwood and R. W. McNamee, U.S.P. 2,345/237/1944 (*Chem. Abs.*, 1944, **38**, 4274).
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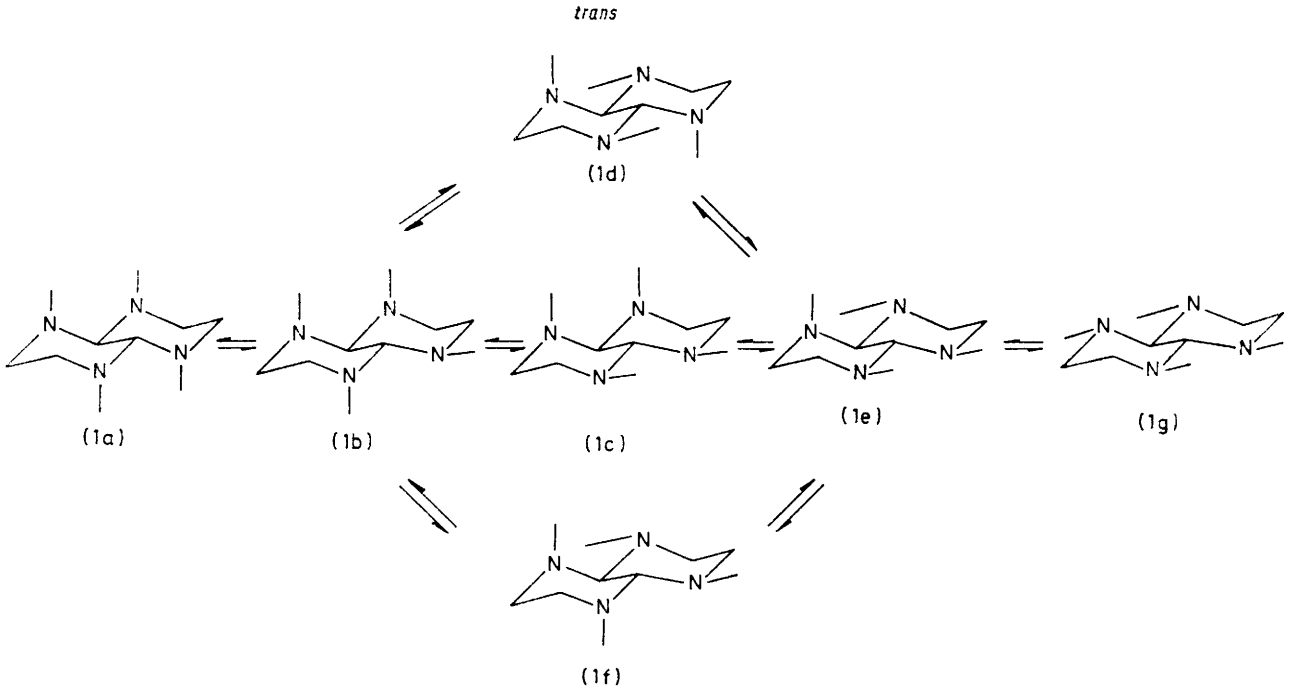
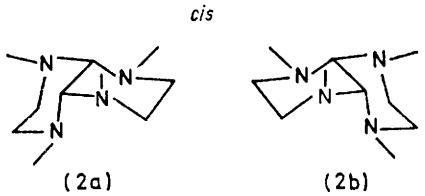
gen inversions. Steric and electronic interactions dictate, on classical energy considerations, that only conformers (1d and f) will be significantly populated; conformer (1e) is next lowest in energy and represents an intermediate between (1d) and (1f). The *trans*-ring fusion prevents ring reversal.

Of the various possible *cis*-conformers only (2a) and (2b), an enantiomeric pair, are appreciably populated; signal remains a sharp singlet. As any ring reversal should possess a higher barrier than *N*-inversion, we assign the preceding set of spectral changes to the slowing of ring reversal between the *cis*-conformers (2a) and (2b). As the temperature is lowered further the *N*-methyl singlet signal of the *trans*-isomer collapses, then separates into two singlets (by 164 K). However, line broadening and overlap result in the interpretation not being totally



SCHEME 1 The all-chair conformers of *trans*-1,4,5,8-tetramethyldecahydro[2,3-*b*]pyrazinopyrazine

the others have much higher ground state energies. Conformers (2a) and (2b) (Scheme 2) are interconvertible



SCHEME 2 The lowest energy conformers of *cis*-1,4,5,8-tetramethyldecahydropyrazino[2,3-*b*]pyrazine

only *via* ring reversal; *N*-inversion is not sufficient for the interconversion of the populated *cis*-conformers and only the slowing of the ring reversal can cause spectral changes.

Spectra at Various Temperatures.—The ^1H n.m.r. spectrum at 307 K (Table 1) is consistent with a mixture of the *cis*- and *trans*-isomers each undergoing fast conformer interconversion; specifically two *N*-methyl singlets are observed, one for the *cis*- and one for the *trans*-isomer. As the temperature is lowered, the low-field *N*-methyl signal broadens, collapses, and then appears as a doublet, while the higher field *N*-methyl unambiguous. That only two *N*-methyl signals are observed, not four, is presumably due to the similarity of the axial environments and the equatorial environments in both conformers.

To confirm our findings and test the applicability of ^{13}C dynamic n.m.r. to conformer elucidation we recorded

TABLE 1

^1H Chemical shifts (p.p.m. from Me_4Si) at 100 MHz for *cis*- and *trans*-1,4,5,8-tetramethyldecahydropyrazino-[2,3-*b*]pyrazine at various temperatures

Isomer	*T*/K	N–CH_3	N–CH–N
cis	307 [a]	2.30	2.64
trans		2.19	2.78
cis	199 [a]	2.46 (*ax*) [c]	2.64
		2.13 (*eq*)	
trans		2.19	2.78
cis	164 [b]	2.46 (*ax*) [c]	2.71 [d]
		2.13 (*eq*)	
trans		2.30 (*ax*)	2.71
		2.09 (*eq*)	

[a] In $CDCl_3$–$CFCl_3$ (1 : 1). [b] In CF_2Cl_2. [c] Assignment is arbitrary and could be reversed. [d] Appears as a broad signal due to line broadening.

the pulsed ^{13}C Fourier transform n.m.r. variable temperature spectra of the isomer mixture. The conformational analysis of saturated heterocycles by ^{13}C dynamic

n.m.r. has received little attention [8] and its accuracy in acyclic systems has been questioned.[9] The proton decoupled spectrum at 304 K [Table 2; Figure (a)] shows six singlets corresponding to methyl, methylene, and methine carbons for each isomer. As the sample is cooled both the *N*-methyl and methylene carbon singlet signals of the *cis*-isomer broaden and collapse and then reappear as doublets which have become well resolved by 233 K; the *N*-methyl and methylene carbon singlet signals of the *trans*-isomer broaden and finally collapse at 153 K. That only two carbon signals are observed for the *N*-methyl groups, arising from the conformers of the *trans*-isomer, instead of four suggests that the environments of the equatorial methyl groups and also the environments of the axial methyl groups are similar in both conformers, differing only in ' 1,4 ' interactions, and thus give rise to insufficient chemical shift differences to be observable. Alternatively, though less likely, there may be a predominance of (1d) over (1f) or *vice versa* and at high temperatures the conformer would be able to undergo interconversion with its mirror image *via* nitrogen inversion.

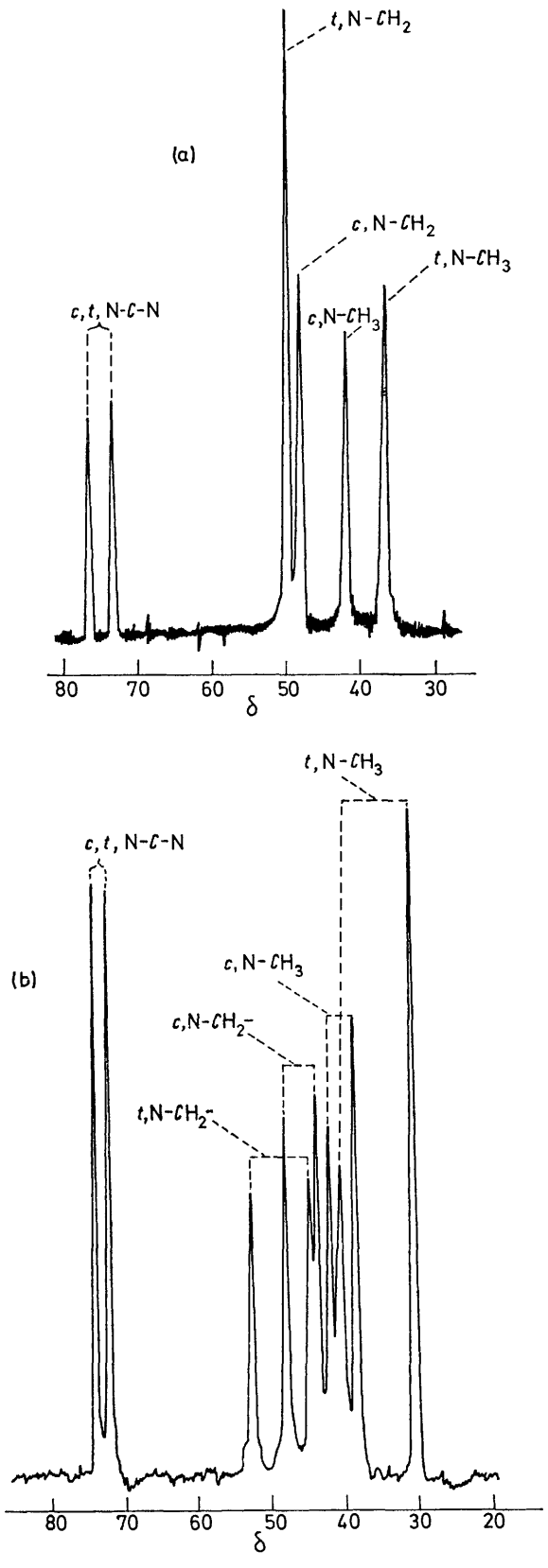
TABLE 2

^{13}C Chemical shifts (p.p.m. from Me_4Si) at 25.16 MHz for *cis*- and *trans*-1,4,5,8-tetramethyldecahydropyrazino-[2,3-*b*]pyrazine at various temperatures

Isomers	*T*/K	N–CH_3	N–CH_2–CH_2	N–CH–N
cis	304 [a]	48.03	41.90	76.28
trans	304 [a]	49.88	36.87	73.09
trans	233 [a]	49.88	36.87	73.09
cis	233 [a]	50.24 (*ax*) [c]	42.80	76.28
cis	233 [a]	45.82 (*eq*)	41.25	76.28
cis	153 [b]	50.24 (*ax*) [c]	42.80	76.28
cis	153 [b]	45.82 (*eq*)	41.25	76.28
trans	153 [b]	53.99 (*ax*) [c]	42.57	73.09
trans	153 [b]	45.77 (*eq*)	31.17	73.09

[a] In $CDCl_3$–$CFCl_3$ (1 : 1). [b] In $(CD_3)_2CO$–CF_2Cl_2 (1 : 3). [c] Although the signal for an axial methyl group normally occurs upfield of an equatorial methyl group, N. K. Wilson and J. B. Stothers (*Topics Stereochem.*, 1974, **8**, 58) have pointed out that the presence of a lone pair *syn* ' 1,3 ' to an axial methyl group may cause a large deshielding. We have observed such deshielding in the low temperature ^{13}C spectrum of 1,3,5-trimethylhexahydro-1,3,5-triazine (to be published), where in fact the axial methyl signal occurs at a lower field than the equatorial methyl signal. The extent of deshielding by the lone pairs in the pyrazinopyrazine is difficult to assess and therefore the assignments of axial and equatorial methyl groups are best considered arbitrary.

Activation Energies for Inversion Processes and the Shape of the Potential Curve.—The temperature-dependent spectra for isomers (1) and (2) yield the activation energies for the rate processes by the Eyring equation [10] (Table 3). The proton spectra give $\Delta G^{\ddagger}$ 11.6 kcal mol^{-1} at 234 K for ring inversion in the *cis*-isomer and $\Delta G^{\ddagger}$ 9.1 kcal mol^{-1} at 183 K for nitrogen inversion in the *trans*-isomer. The ^{13}C spectral parameters give $\Delta G^{\ddagger}$ 11.7 kcal mol^{-1} for ring inversion at 246 K and $\Delta G^{\ddagger}$ 9.1 kcal mol^{-1}



Natural abundance ^{13}C n.m.r. (25.16 MHz) spectra of *cis*- and *trans*-1,4,5,8-tetramethyldecahydropyrazino[2,3-*b*]pyrazine at (a) 304 K, and (b) 153 K; *c*, *cis*-isomer; *t*, *trans*-isomer

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at 202 K. The values derived from ^{13}C spectra are in excellent agreement with the activation parameters obtained from the proton n.m.r. spectra. In calculating the potential energy barrier for *N*-inversion we adopted the widely used value of $f = 1$ for the transmission coefficient [11] corresponding to consecutive *N*-inversions. If conformer (1e) is an intermediate however, the transmission coefficient should be taken as equal to a half, provided the transition states are identical.[12] This would lead to a free activation energy for nitrogen inversion being *ca.* 0.3 kcal mol^{-1} less than the values given in Table 3. As the transition states are not identical, although very similar, we have taken the transmission coefficient to equal one. If (1d) or (1f) were undergoing interconversion with its mirror image a value of one should be taken.

TABLE 3

N.m.r. coalescence data for *cis*- and *trans*-1,4,5,8-tetramethyldecahydropyrazino[2,3-*b*]pyrazine

Isomer	Signal observed	$\Delta\nu$/Hz	T_c/K	$\Delta G^{\ddagger}$/ kcal mol^{-1}
(1) (*trans*)	N–CH_3 [a]	20.5	183	9.1 ± 0.2
	N–CH_3 [b]	259.6	202	9.1 ± 0.3
(2) (*cis*)	N–CH_3 [a]	33.1	234	11.6 ± 0.2
	N–CH_3 [b]	89.82	246	11.7 ± 0.3

[a] From ^1H spectral data. [b] From ^{13}C spectral data.

Of particular interest is the value found for the free energy of activation of *N*-methyl inversion which is appreciably higher (*ca.* 2 kcal mol^{-1}) than in monocyclic analogues such as hexahydro-*s*-triazine [13] and tetrahydro-1,3-oxazine,[1] which also contain β-heteroatoms. The electronic interactions should be similar in all these ring systems, which indicates that the difference in magnitude is essentially steric in nature.

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