The Conformational Analysis of Saturated Heterocycles. Part XLIX.[1] The Conformation of Ring NH-Groups in Piperazines, Hexahydropyrimidines, Tetrahydro-1,3-oxazines, and Tetrahydro-1,3-thiazines

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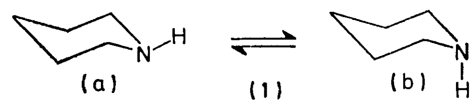
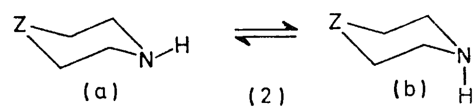
Infrared spectral measurements of the ν_{NH} first overtone and electric dipole moment measurements indicate that N–H in a piperazine ring prefers the equatorial position by about the same amount as in piperidine. However, where another heteroatom is in the β-position, as in tetrahydro-1,3-oxazines, tetrahydro-1,3-thiazines, and hexahydropyrimidines, there is a strong preference for NH to become axial. The reasons for this behaviour are discussed

THE prolonged controversy regarding the conformational equilibrium of piperidine (1a) $\rightleftharpoons$ (1b) now seems to be satisfactorily settled; $\Delta G^\circ = 0{\cdot}4 \pm 0{\cdot}2$ kcal mol^{-1} in favour of the NH-equatorial form for the gas-phase and non-interacting solvents is in agreement with all known facts.[2] This conclusion appears to apply equally to a variety of *C*-substituted piperidines (*cf.* refs. 2—4). The present paper is concerned with the conformational equilibrium of NH-groups in analogues of piperidine in which a ring CH_2-group in the 3- and 4-position has been replaced by O, S, or NR. Such a replacement in the 4-position (2a) $\rightleftharpoons$ (2b) would not be expected to disturb the equilibrium behaviour greatly, for differential steric and electronic effects should be small. The reliable evidence appears to bear this out; the i.r. method has shown [3] morpholine to be similar to piperidine (notwithstanding Kerr constant interpretations to the contrary [5]). Allinger *et al.*[6] reached a similar conclusion regarding *N*-methylpiperazine from dipole-moment evidence, however in this work the conformational preference for the *N*-methyl group was taken as 1·7 kcal mol^{-1} which is now known to be too large.[7] We have therefore reinvestigated this compound, and have also studied *N*-t-butylpiperazine by both the dipole-moment and infrared NH-overtone methods.

Replacement of the 3-position methylene in piperidines by a heteroatom is expected to have considerably greater effect on the NH-equilibrium. Significant changes have already been found for *N*-alkyl equilibria in hexahydropyrimidines [8] and tetrahydro-1,3-oxazines,[9] as compared to *N*-alkylpiperidines. We have now examined 1-methyl- (8) and 1-t-butyl-hexahydropyrimidine (9) and tetrahydro-1,3-oxazine (6) and -thiazine (7). We also examined the 5,5-disubstituted compounds (10) and (11) to see if the β-axial interactions significantly altered the equilibrium. No previous work on the NH-conformation in analogues of piperidine in which a CH_2-group in the 3-position has been replaced by a heteroatom was available when the present study was commenced; recently however Booth and Lemieux examined [10] the low-temperature spectra of (8), (6), and 2-methyl tetrahydro-1,3-oxazine and concluded from the values of the CH–NH coupling

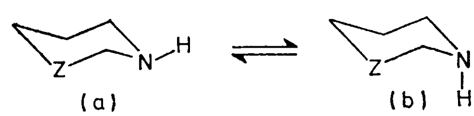


(a) (1) (b)



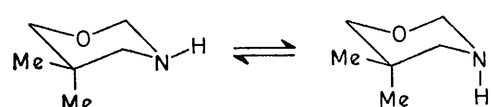
(a) (2) (b)

(3) Z = O; (4) Z = NMe; (5) Z = NBu^t

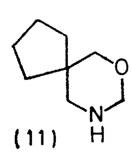


(a) (b)

(6) Z = O; (7) Z = S; (8) Z = NMe; (9) Z = NBu^t



(a) (10) (b)



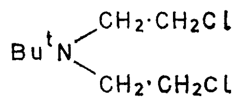
(11)

constants that the N–H axial conformation is strongly favoured in this series.

[1] Part XLVIII, R. A. Y. Jones, A. R. Katritzky, A. C. Richards, S. Saba, A. J. Sparrow, and D. L. Trepanier, *J.C.S. Chem. Comm.*, 1972, 673.
[2] R. A. Y. Jones, A. R. Katritzky, A. C. Richards, R. J. Wyatt, R. J. Bishop, and L. E. Sutton, *J. Chem. Soc.* (*B*), 1970, 127.
[3] R. W. Baldock and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1968, 1470.
[4] F. Moll, *Tetrahedron Letters*, 1968, 5201.
[5] M. J. Aroney, C.-Y. Chen, R. J. W. Le Fèvre, and J. D. Saxby, *J. Chem. Soc.*, 1964, 4269.
[6] N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski, *J. Amer. Chem. Soc.*, 1965, **87**, 1232.
[7] R. A. Y. Jones, A. R. Katritzky, A. C. Richards, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1970, 122.
[8] R. A. Y. Jones, A. R. Katritzky, and M. Snarey, *J. Chem. Soc.* (*B*), 1970, 131.
[9] R. A. Y. Jones, A. R. Katritzky, and D. L. Trepanier, *J. Chem. Soc.* (*B*), 1971, 1300.
[10] H. Booth and R. U. Lemieux, *Canad. J. Chem.*, 1971, **49**, 776.

Preparation of Compounds.—The tetrahydro-1,3-oxazines (10) and (11) were both obtained from the corresponding amino-alcohols, themselves prepared by conventional methods (see Experimental section), and paraformaldehyde. We also prepared the *N*-methyl derivative of (10) for use as a model compound. In fact we did not use it, but we report here the preparative details. The tetrahydro-1,3-thiazine (7) was similarly obtained from the mercaptanol.

1-t-Butylpiperazine (5) was prepared by catalytic debenzylation of the 4-benzyl analogue, itself obtained from the chloro-amine (12) and benzylamine. 1-t-



(12)

Butylhexahydropyrimidine (9) was obtained from *N*-t-butyl-1,3-propanediamine and formaldehyde; the 1-methyl analogue was similarly obtained.

EXPERIMENTAL

Tetrahydro-1,3-oxazine [9] was redistilled before measurement.

5,5-Dimethyltetrahydro-1,3-oxazine.—Ethyl cyanodimethylacetate [11] was reduced by $LiAlH_4$ to 3-amino-2,2-dimethylpropan-1-ol, b.p. 98—100° (30 mm), m.p. 96—98° [lit.,[11a] b.p. 105° (35 mm), m.p. 98—100°]. This aminopropanol (6·3 g), paraformaldehyde (1·83 g), and benzene (100 ml) were heated under reflux in a flask with a Dean–Stark apparatus attached for 3 h. The solvent was then evaporated and the residue distilled to give the *tetrahydro-1,3-oxazine* (1·4 g, 20%) as an oil, b.p. 60° (15 mm) (Found: C, 62·7; H, 11·2; N, 11·9. $C_6H_{11}NO$ requires C, 62·6; H, 11·4; N, 12·2%).

Tetrahydro-1,3-oxazine-5-spirocyclopentane.—Ethyl 1-cyanocyclopentanecarboxylate [12] {38 g; b.p. 111—115° (12 mm) [lit.,[12] b.p. 109—110° (11 mm)]} in THF (150 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (15 g) in THF (300 ml). The mixture was stirred and heated under reflux for 6 h, cooled, and treated with water (15 ml) in THF (100 ml) followed by 10% aqueous NaOH (15 ml) and water (30 ml). The mixture was stirred for 2 h, suction filtered, and the solid washed with isopropyl alcohol. The combined filtrate and isopropyl alcohol wash was distilled *in vacuo* to give *1-aminomethyl-1-hydroxymethylcyclopentane* (19·7 g, 67%) as a viscous oil, b.p. 124—126° (12 mm) (Found: C, 64·9; H, 11·6; N, 10·7. $C_7H_{15}NO$ requires C, 65·1; H, 11·7; N, 10·8%).

1-Aminomethyl-1-hydroxymethylcyclopentane (13 g), paraformaldehyde (3 g), and benzene (100 ml) contained in a flask with a Dean–Stark water separator attached was heated under reflux for 3 h (2·1 ml of water separated). The mixture was distilled *in vacuo* to give *tetrahydro-1,3-oxazine-5-spirocyclopentane*) (8·4 g, 70%) as an oil, b.p. 94° (15 mm) (Found: C, 67·8; H, 10·7; N, 10·2. $C_8H_{15}NO$ requires C, 68·0; H, 10·7; N, 9·9%).

Tetrahydro-1,3-thiazine.—NaOH (0·2 mol) in MeOH (150 ml) was saturated with H_2S during 30 min. 3-Bromopropylamine hydrobromide (22 g, 0·1 mol) in MeOH (100 ml) was added, with stirring, during 30 min. The mixture was stirred and heated at 50—60° for 1 h, cooled, treated with ether (300 ml), and suction filtered under nitrogen. The filtrate was distilled to give 3-aminopropanethiol (9·1 g), b.p. 80° (125 mm), which immediately solidified: it was used directly in the next step. 3-Aminopropanethiol (9·1 g), paraformaldehyde (3·0 g), and benzene (100 ml) were heated under reflux for 3 h with a Dean–Stark water separator attached (2·5 ml water separated). Distillation then gave tetrahydro-1,3-thiazine (4·1 g, 40%), b.p. 62° (22 mm) [lit.,[13] b.p. 65—70° (30 mm)].

1-Methylpiperazine (Eastman) had b.p. 138° (lit.,[14] b.p. 140°).

1-Benzyl-4-t-butylpiperazine.—Bis-(2-chloroethyl)-t-butylamine hydrochloride [15] (91·0 g) and benzylamine (171·0 g) in EtOH (400 ml) were heated under reflux for 2·5 h. Benzylamine hydrochloride was filtered off from the cooled solution which was then made alkaline by addition of 3N-NaOH and extracted with light petroleum (5 × 40 ml). The organic extract was dried (Na_2SO_4) and evaporated. Distillation of the oily residue afforded the *piperazine* (78·0 g) as a colourless liquid, b.p. 128—131° (1·5 mm) (Found: C, 77·5; H, 10·4; N, 12·1. $C_{15}H_{24}N_2$ requires C, 77·6; H, 10·5; N, 12·4%); τ (CCl_4) 2·79 (m, 5H), 6·60 (s, 2H), 7·3—7·8 (m, 4H), and 8·98 (s, 9H).

1-t-Butylpiperazine.—1-Benzyl 4-t-butylpiperazine (13 g) in absolute EtOH (100 ml) was shaken under hydrogen over 10% Pd/C (3·3 g) for 3 days at 4 atm/20°. The catalyst was filtered off and the solution evaporated. Distillation of the residue afforded *1-t-butylpiperazine* as a colourless liquid, b.p. 86° (22 mm), τ (CCl_4) 6·6 (s, 1H), 7·05—7·75 (m, 4H), and 8·98 (s, 9H).

The *methanesulphonamide* separated as needles, m.p. 121—122°, from acetone–light petroleum (Found: C, 49·1; H, 9·15; N, 12·7; S, 14·9. $C_9H_{20}N_2O_2S$ requires C, 49·1; H, 9·15; N, 12·7; S, 14·55%).

1-t-Butylhexahydropyrimidine.—39% Aqueous HCHO (12 ml) was added during 40 min to 1-t-butyl-1,3-propanediamine [16] (21·62 g) in benzene (100 ml). The solution was stirred for 2·5 h, dried (Na_2SO_4), and evaporated. Distillation of the residue through a spinning-band column afforded *1-t-butylhexahydropyrimidine*, b.p. 49° (1 mm) (Found: C, 67·9; H, 12·4; N, 20·0. $C_8H_{18}N_2$ requires C, 67·6; H, 12·7; N, 19·7%); τ (CCl_4) 6·58 (s, 2H), 7·20—7·55 (m, 4H), 8·20—8·75 (m, 5H), and 8·97 (s, 9H).

1-Methylhexahydropyrimidine.—*N*-Methyl-1,3-propanediamine (32·7 g) and paraformaldehyde (11·1 g) in benzene (100 ml) were heated under reflux with azeotropic removal of water for 2 h. Evaporation of the solution and distillation of the residue afforded *N*-methylhexahydropyrimidine as a colourless liquid, b.p. 138—139°; τ (CCl_4) 6·83 (s, 2H), 7·15—7·65 (m, 4H), 7·94 (s, 3H), and 8·20—8·70 (m, 5H).

The *dipicrate* separated from acetone as yellow plates, m.p. 235° (decomp.) (Found: C, 37·0; H, 3·3; N, 19·9. $C_{17}H_{18}N_8O_4$ requires C, 36·6; H, 3·25; N, 20·1%).

[11] (*a*) S. S. Biechler and R. W. Taft, jun., *J. Amer. Chem. Soc.*, 1957, **79**, 4927; (*b*) U.S.P. 2,618,658/1952 (*Chem. Abs.*, 1953, **47**, 9997).

[12] Ch. J. Morel and W. G. Stoll, *Helv. Chim. Acta*, 1952, **35**, 2561.

[13] E. D. Bergmann and A. Kaluszyner, *Rec. Trav. chim.*, 1959, **78**, 327.

[14] F.P. 968,790/1950 (*Chem. Abs.*, 1953, **47**, 617).

[15] J.-L. Imbach, A. R. Katritzky, and R. A. Kolinski, *J. Chem. Soc.* (*B*), 1966, 556.

[16] D. S. Tarbell, N. Shakespeare, C. J. Claus, and J. F. Bunnett, *J. Amer. Chem. Soc.*, 1946, **68**, 1217.

Dipole Moments.—The dipole moments were measured by the method already described.[17] We have previously [2] noted that dipole moment data for NH compounds are unreliable if measured in aromatic or hydrogen-bond accepting solvents and all the present measurements were carried out in cyclohexane; the results are recorded in Tables 1 and 2. 1-t-Butylpiperazine was extremely hygroscopic and was handled in a dry box.

TABLE 1

Dipole moment measurements * in cyclohexane at 25°

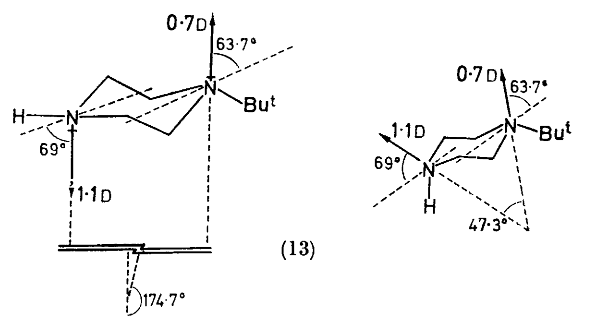
10^6w	$10^6(\varepsilon_{12} - \varepsilon_1)$	$10^6(v_1 - v_{12})$
1-t-Butylhexahydropyrimidine		
1517	1661	216
2136	2341	333
2427	2656	379
3390	3708	529
Tetrahydro-1,3-oxazine		
3062	7294	738
4237	10,097	1025
8070	19,250	1949
8222	19,578	1969
5,5-Dimethyltetrahydro-1,3-oxazine		
4057	5923	714
5290	7723	931
5697	8275	1011
6578	9619	1158
Tetrahydro-1,3-oxazine-5-spirocyclopentane		
3267	4655	930
5423	7728	1543
7740	11,048	2204
8294	11,806	2360
Tetrahydro-1,3-thiazine		
2067	4636	756
3629	8140	1328
4807	10,788	1740
6104	13,683	2260
1-t-Butylpiperazine		
1663	1265	278
2716	2066	454
3690	2800	616
4426	3366	740
Tetrahydropyran		
2962	7029	423
4627	10,980	662
5798	13,760	837
6008	14,258	852
Tetrahydrothiopyran		
2722	7295	792
3770	10,088	1094
3937	10,577	1154
4985	13,362	1451

* w = Weight fraction of solute, ε = dielectric constant, v = specific volume. The suffixes 1 and 12 refer to solvent and solution respectively.

Infrared Spectra.—The i.r. spectra were obtained by the procedures already described,[3] with the addition of a small reflux condenser to the entry tube not occupied by the thermocouple. This was to prevent, as far as possible, the escape of potentially toxic vapours at high temperatures. The details are recorded in Table 3.

RESULTS AND DISCUSSION

Dipole Moments.—The calculation of conformer populations from dipole-moment measurements is, in principle, very simple. The expected dipole moments of two conformers (a) and (b) (μ_a and μ_b respectively) are calculated from the measured moments of appropriate model compounds by assuming that the total moment of a molecule is the vector sum of the moments of its constituent parts. Thus for 1-t-butylpiperazine (5a) $\rightleftharpoons$ (5b) the moments of the two conformations are obtained by vector addition of the moments of piperidine and 1-t-butylpiperidine, the angles between the two constituent moments being obtained from a knowledge of the geometry of the piperazine ring [18] and from assumptions about the directions along which the moments act in piperidine [2] and 1-t-butylpiperidine.[19] These calculations, illustrated in (13), lead to the following expected values for the dipole moments of the two conformers: $\mu_{5a} = 0{\cdot}41$, $\mu_{5b} = 1{\cdot}66$ D. From these values together with the observed moment (1·06 D) of the conformer mixture, (5), we can determine the proportions of the two conformers from the relationship: $\mu_5^2 = N_{5a}\mu_{5a}^2 + (1 - N_{5a})\mu_{5b}^2$, where N is the mole fraction. Thus $N_{5a} = 0{\cdot}63$, corresponding to a conformational equilibrium constant of 1·7, and a standard free-energy difference between the two conformers of 0·32 kcal mol^{-1} in favour of the conformer with the NH equatorial.



(13)

$\mu_{eq} = (0{\cdot}7^2 + 1{\cdot}1^2 + 2 \times 0{\cdot}7 \times 1{\cdot}1 \cos 174{\cdot}7)^{\frac{1}{2}} = 0{\cdot}41$ D

$\mu_{ax} = (0{\cdot}7^2 + 1{\cdot}1^2 + 2 \times 0{\cdot}7 \times 1{\cdot}1 \cos 47{\cdot}3)^{\frac{1}{2}} = 1{\cdot}66$ D

Several assumptions must be made during these calculations. First we assume that the measured values of the dipole moments of the model compounds can be transferred directly to the compounds in question. This implies that there are no inductive interactions between the two constituent parts of the system, an assumption which is quite justified when the two parts are remote, as in the piperazines, and which also appears to be valid for the hexahydropyrimidines.[8] It is more dubious in the tetrahydro-oxazines and -thiazines. Moreover there is, as we have previously discussed,[9] considerable doubt about the value of the oxygen-group moment in these heterocyclic compounds, and the same inconsistency seems to apply to the sulphur compounds as well; the dipole moments of tetrahydrothiopyran and

[17] R. A. Y. Jones, A. R. Katritzky, P. G. Lehman, K. A. F. Record, and B. B. Shapiro, *J. Chem. Soc.* (*B*), 1971, 1302.
[18] M. Davis and O. Hassel, *Acta Chem. Scand.*, 1963, **17**, 1181.
[19] R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones, A. R. Katritzky, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1967, 493.

diethyl sulphide [20] are 1·73 and 1·58 D respectively. In this work we take the oxygen-group moment in the tetrahydro-oxazines to be 1·27 D because this is the value required if we suppose, as is reasonable, that 3-t-butyltetrahydro-1,3-oxazine exists entirely in the one conformation with the t-butyl group equatorial.* This value is closely similar to that of a single oxygen moiety in 1,3-dioxan,[9] and to that of simple aliphatic ethers, but it differs substantially from the moment of tetrahydropyran (1·55 D). We do not have data for 3-t-butyltetrahydro-1,3-thiazine, which we have not yet succeeded in preparing, and so we cannot make the same calculation for this series; we believe the diethyl sulphide value for the sulphur moment will be more reliable than that from tetrahydrothiopyran, but have calculated results using both.†

The second assumption concerns the details of the ring geometry, a knowledge of which is needed for determining the angle between the constituent dipole vectors. Only for the piperazine ring has a detailed analysis been reported.[18] For the hexahydropyrimidines we previously calculated [8] the ring geometry from known bond-lengths and angles. The calculations are less easy for the unsymmetrical tetrahydro-oxazines and thiazines. We have therefore devised a computer program [21] for assessing the ring geometry of six-membered rings which includes an allowance for changes in geometry introduced by minimising the torsional and bond-angle strains.

The third assumption concerns the direction along which the constituent dipole vectors lie. We have taken the C–O–C and C–S–C vectors to lie along the bisector of the C–O–C or C–S–C angle; the direction at N-Bu^t we have previously calculated; [18] and the direction at NH we have taken as before,[2] from the direction in dimethylamine.

Finally we have neglected in all our calculations the contribution of atomic polarisation to the dipole moment. This neglect is most serious for compounds with very small dipole moments, such as the *trans*-conformers of the piperazines, but even here the error is probably not more than 0·05 D in a moment of 0·4 D.

TABLE 2

Dipole moments in cyclohexane at 25°

Compound	$d\varepsilon/dw$	$-dv/dw$	$_{T}P_{2\infty}$	$_{E}P$	μ(D)
1-t-Butylhexahydropyrimidine	1·094 ± 0·001	0·157 ± 0·004	78·20	43·38	1·30 ± 0·01
Tetrahydro-1,3-oxazine	2·383 ± 0·002	0·240 ± 0·001	73·06	23·33	1·56 ± 0·01
3-t-Butyltetrahydro-1,3-oxazine	2·015 ± 0·009	0·223 ± 0·016	107·88		1·80 ± 0·01
5,5-Dimethyltetrahydro-1,3-oxazine	1·459 ± 0·005	0·176 ± 0·001	72·87	32·41	1·41 ± 0·01
Tetrahydro-1,3-oxazine-5-spirocyclopentane	1·425 ± 0·002	0·285 ± 0·001	84·30	39·38	1·48 ± 0 01
Tetrahydro-1,3-thiazine	2·242 ± 0·001	0·368 ± 0·004	79·69	29·19	1·57 ± 0·01
1-t-Butylpiperazine	0·760 ± 0·001	0·167 ± 0·001	66·42	43·38	1·06 ± 0·01
Piperidine					1·10 ± 0·01 [a]
1-t-Butylpiperidine					0·70 ± 0·01 [b]
Tetrahydropyran	2·373 ± 0·001	0·143 ± 0·001	74·13	24·34	1·56 ± 0·01
Tetrahydrothiopyran	2·681 ± 0·004	0·291 ± 0·001	91·70	30·19	1·73 ± 0·01

[a] From ref. 2. [b] From ref. 18.

TABLE 3

Infrared spectral data of piperidine analogues $\overline{CH_2\cdot NH\cdot CH_2\cdot X\cdot Y\cdot Z}$ *

	Compound *			Temp./		*PR*-separation (cm^{-1} ± 1 cm^{-1})					*Q*-Branch absorbance ratio	
							Axial NH		Equatorial NH		Calc. for NH	
	X	Y	Z	K	$\nu_{max.}/cm^{-1}$	Exptl.	B & Z	S-P	B & Z	S-P	axial	Exptl.
(4)	CH_2	NMe	CH_2	430	6579 6486	15 13	14	24	14	18	0·23	0·18 0·24
(5)	CH_2	NBu^t	CH_2	380	6570 6480	10		15		11	0·21	0·19
(6)	CH_2	CH_2	O	380	6538	23	26	26	21	21	0·41	0·40
(7)	CH_2	CH_2	S	380	6534	20	24	23	21	18	0·41	0·32
(8)	CH_2	CH_2	NMe	380	6584 6520	14	12	20	12	16	0·22	0·25
(9)	CH_2	CH_2	NBu^t	400	6505			14		11	0·21	
(10)	CMe_2	CH_2	O	390	6568	15	19	21	15	16	0·26	0·25 ± 0·0
(11)	spiro C_5H_8	CH_2	O	390	6550			15		11	0·21	

* (i) The compounds (5), (9), (11) cannot be treated by Badger and Zumwalt's method because their K values are outside the range dealt with in that paper. (ii) Q-Branch absorbance ratios were calculated by Gerhard and Dennison's method which strictly applies only to parallel bands of symmetric top molecules.

* This value differs slightly from that (1·26 D) used in a previous paper [9] written before we had completed our calculations [21] of ring geometry.

† The literature values [20] for the dipole moments of diethyl sulphide are for benzene solutions; the difference from cyclohexane values is likely to be small; *cf.* 1·73 D for tetrahydrothiopyran in cyclohexane (this work), 1·71 D in benzene.[22]

[20] W. S. Walls and C. P. Smyth, *J. Chem. Phys.*, 1933, **1**, 337; *cf.* E. C. E. Hunter and J. R. Partington, *J. Chem. Soc.*, 1931, 2062.

[21] I. D. Blackburne, R. P. Duke, R. A. Y. Jones, A. R. Katritzky, and K. A. F. Record, following paper.

[22] C. W. N. Cumper and A. I. Vogel, *J. Chem. Soc.*, 1959, 3521.

The results of these calculations are set out in Table 4. They indicate that in all the systems with a heteroatom in the 3-position of the piperidine ring the NH axial conformer is preferred, but in the piperazines the conformational equilibrium is similar to that in piperidine itself with the NH preferentially equatorial.

We expected to find that β-diaxial steric interactions between the axial *N*-hydrogen atom and the axial 5-substituent in the *gem*-disubstituted compounds (10) and (11) would force the equilibrium further towards the NH-equatorial form [as (10*a*)]. The evidence of Table 4 indicates the opposite. In fact the results for these two compounds are probably less reliable than the others because the distortion of valency angles at nitrogen which probably occurs in the NH-axial conformers means that piperidine is not a good model for their nitrogen moments. However, while these results may be quantitatively dubious, they do support the general conclusion that in the tetrahydro-1,3-oxazines the *N*-hydrogen atom is preferentially axial.

TABLE 4

Interpretation of dipole moment measurements

Compound	Calculated moments/ D NH$_{eq}$	Calculated moments/ D NH$_{ax}$	Observed moment/ D	% NH$_{eq}$	K [a]	ΔG° kcal mol^{-1}
1-t-Butylhexahydropyrimidine	1·77	0·98	1·30	34	0·52	0·39
Tetrahydro-1,3-oxazine	2·16	1·03	1·56	38	0·61	0·29
5,5-Dimethyltetrahydro-1,3-oxazine [b]	2·16	1·03	1·41	26	0·35	0·6
Tetrahydro-1,3-oxazine-5-spirocyclopentane	2·16	1·03	1·48	31	0·45	0·5
Tetrahydro-1,3-thiazine [c]	2·46	1·20	1·57	22	0·28	0·75
Tetrahydro-1,3-thiazine [d]	2·59	1·31	1·57	15	0·18	1·0
1-t-Butylpiperazine	0·41	1·66	1·06	63	1·7	−0·32

[a] [NH$_{eq}$]/[NH$_{ax}$]. [b] Less reliable, see text. [c] Calculated using 1·58 D for sulphur moment (see text), probably more reliable than alternative [d] calculation. [d] Calculated using 1·73 D for sulphur moment (see text).

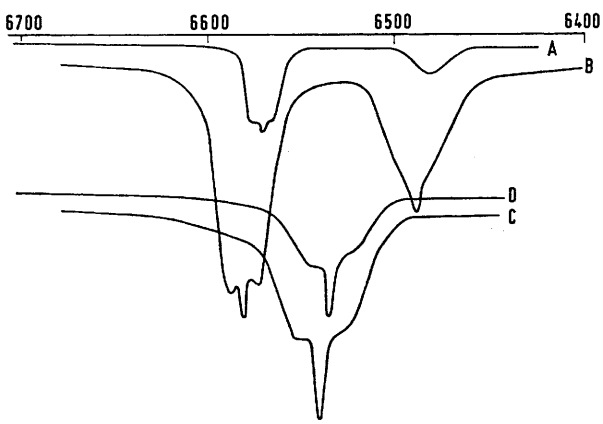


FIGURE 1 Infrared spectra of A, *N*-t-butylpiperazine; B, *N*-methylpiperazine; C, tetrahydro-1,3-oxazine; and D, tetrahydro-1,3-thiazine

Infrared Spectra.—In our studies of piperidine [3] we were able to interpret the temperature variation of the first overtone N–H stretching vibrations in the 6500 cm^{-1} region quantitatively in terms of the NH axial–equatorial equilibrium. This has not been possible in the present series of compounds, largely because they were not sufficiently thermally stable for us to be able to carry out measurements over a wide enough temperature range. We have, however, been able to use the spectra to provide qualitative support for most of the conclusions derived from the dipole-moment measurements.

The i.r. spectra for the first overtone region are shown in Figures 1 and 2: the form varies, some show two well defined bands, others a band and a shoulder. We have attempted to assign the band(s) to individual conformers as before,[3] assuming that only chair forms are significantly populated for all the compounds studied. We have supposed that, because the extinction coefficients of the NH axial and equatorial stretching vibrations are not likely to be greatly different, the more intense band is due to the major conformer.

There are three criteria available for making the assignments: (i) we have observed [3] that in piperidine the NH equatorial vibration is to high frequency of the axial one, following the usual behaviour of ring-substituent bond vibrations in substituted cyclohexanes. There seems no reason why the same principle should not apply in the present compounds. Further criteria are obtained from the band contours: (ii) the separation between the *P* and *R* branches and (iii) by the ratio of *Q*-branch absorbance to the total signal intensity. As the NH-stretching vibration is effectively localised in the NH-bond, the oscillating dipole moment is parallel to the bond axis for overtone as well as fundamental vibrations. The modulation of the vibration by molecular rotation which

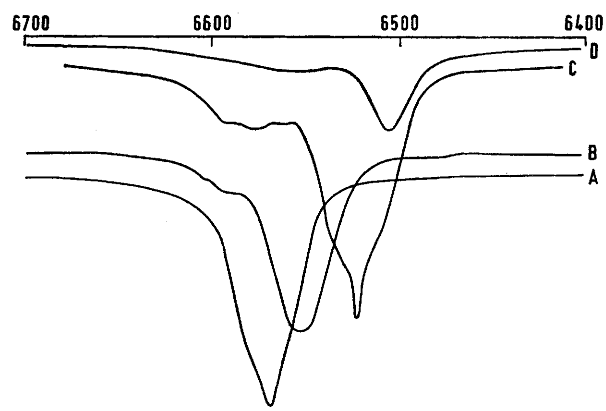


FIGURE 2 Infrared spectra of A, 5,5-dimethyltetrahydro-1,3-oxazine; B, tetrahydro-1,3-oxazine-5-spirocyclopentane; C, *N*-methylhexahydropyrimidine; and D, *N*-t-butylhexahydropyrimidine

determines the band contour, differs for axial and equatorial N–H vibrations. The modulation is related to the moments of inertia, which we have calculated (Table 5) using a program written by R. A. Beaudet and W. R. Pauly and kindly supplied to us by Professor N. Sheppard. The geometry of the systems may be determined with sufficient accuracy from the calculated skeletal geometry [21] with the additional bond lengths and angles detailed in Table 6 chosen from recent measurements. From the moments of inertia about three perpendicular axes the separation between the P and R components of the i.r. band can be calculated. Gerhard and Dennison [23] described a method for this calculation for symmetrical molecules and Badger and Zumwalt [24] extended it to the unsymmetrical rotator but both methods are applicable only to pure A-, B-, or C-type bands. Seth-Paul [25] developed a method for calculating PR separations for 2-dimensional hybrid bands. One or other of these methods may be applied to many of the present molecules, but some of them are 3-dimensional hybrids with significant contributions from A-, B-, and C-modes. For these we have calculated the three 2-dimensional separations (AB, BC, CA) by Seth-Paul's method and taken a weighted mean, weighing the AB component by a factor sin γ, where γ is the angle between the N–H vibration and the C-axis, *etc.* The angles are given in Table 5. This is probably not a very accurate approach, but is adequate for a qualitative distinction between the axial and equatorial bands. In fact, in all such cases we have encountered we have found no overlap between the ranges of PR separations calculated for the 2-dimensional axial vibrations and the ranges for the corresponding equatorial ones, so the exact method of averaging is immaterial. The results of these calculations appear in Table 3. Table 3 also lists the Q-branch absorbance ratios for the NH axial vibrations. These are calculated by the method of Gerhard and Dennison [23] which is strictly applicable only to symmetrical tops; the extension to the NH axial bands of the present series of compounds must be made with caution, and the symmetry of the NH equatorial vibrations is too remote from the ideal model for us to be able to apply the method to them.

1-*t-Butylpiperazine and* 1-*Methylpiperazine*.—These two molecules show spectra (Figure 1; A, B) which are similar to each other, and to the spectra of piperidine, morpholine, and 4-methylpiperidine. For 1-t-butylpiperazine, the assignment is hindered by low volatility and by decomposition at higher temperatures; a satisfactorily intense spectrum could not be obtained and the fine structure could be discerned only for the high-frequency band, for which the measured PR separation agrees with the value calculated by Seth-Paul's method [25] for NH equatorial; that calculated for NH axial is substantially different. The Badger and Zumwalt,[24] and Gerhard and Dennison [23] methods are not applicable.

For 1-methylpiperazine, there is a serious discrepancy between the Badger and Zumwalt and the Seth-Paul methods. Moreover, the values calculated by Seth-Paul's method bear no relation to the experimental values, and the values calculated by Badger and Zumwalt's method do not distinguish between the two assignments. However, the Q-branch absorbance ratios give some support to the assignment of the more intense high-frequency band to NH equatorial.

For both these molecules the assignment of the high-frequency band to the NH equatorial vibration, as in piperidine [3] to which they bear an obvious structural similarity, is likely to hold. Consequently it is likely that the NH equatorial conformer predominates in both cases.

TABLE 5

Moments of inertia (^{16}O a.m.u. Å^2) and angles (°) between NH vector and axes of inertia

Compd.	NH Conform.	I_A	I_B	I_C	α	β	γ
(4)	*a*	110	215	296	88	90	2
	e	109	216	298	22	90	68
(5)	*a*	213	532	615	89	90	1
	e	212	533	617	21	90	69
(6)	*a*	101	113	189	86	85	6
	e	101	114	193	33	65	71
(7)	*a*	124	161	254	86	87	5
	e	125	160	257	72	24	75
(8)	*a*	110	229	311	90	78	12
	e	112	229	315	61	39	67
(9)	*a*	213	550	636	88	78	12
	e	214	551	640	63	38	65
(10)	*a*	162	272	317	89	86	4
	e	163	273	322	54	40	75
(11)	*a*	189	514	538	78	87	12
	e	190	516	544	51	40	82

TABLE 6

Bond lengths (pm) and bond angles (°) used [a]

HNC	112·2	HCO	109·5	N–H	101
HCH	108·5	HCN	109·5	C–H	109
HCC	109·5	HCS	108·7		

[a] See *e.g.* 'Interatomic Distances,' ed. L. E. Sutton, Chemical Society Special Publications No. 11 and No. 18.

Tetrahydro-1,3-*oxazine and Tetrahydro*-1,3-*thiazine*.—These molecules display closely similar spectra (Figure 1; C, D). At moderate temperatures, each shows a single band with a very prominent Q-branch at 6538 cm^{-1} (with a shoulder to high frequency at elevated temperatures) for the oxazine and at 6534 cm^{-1} for the thiazine. The PR separation measured from the oxazine absorbance is intermediate between the calculated PR separations for the axial and for the equatorial NH orientations. Although the measured PR separation for the thiazine is somewhat closer to that calculated for NH equatorial, the difference from the separation calculated for NH axial is small, and no conclusion regarding the orientation is possible from these considerations of PR separation.

These two molecules are asymmetric (the thiazine

[23] S. L. Gerhard and D. M. Dennison, *Phys. Rev.*, 1933, **43**, 197.

[24] R. M. Badger and L. R. Zumwalt, *J. Chem. Phys.*, 1938, **6**, 711.

[25] W. A. Seth-Paul, *J. Mol. Structure*, 1969, **3**, 403.

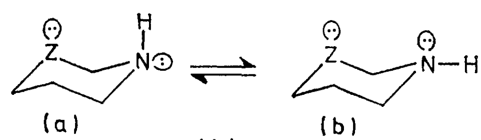
particularly so), and the results from Q-branch absorption ratio calculations must be used with caution. However, for the thiazine, the NH equatorial band is expected to be predominantly (61%) B type (no Q-branch), and the very large value observed for the Q-branch absorbance ratio hence excludes this orientation and strongly indicates a predominant NH-axial conformation. For the oxazine, the situation is less clear cut: the NH axial band is predominantly (87%) C type, and the NH equatorial band is mixed, with 53% A, 27% B, and 20% C type character. However, the large Q-branch absorbance, and the appearance of the shoulder (presumably from the minor conformer) to high frequency lead us to assign the main peak to the NH axial conformer.

5,5-*Dimethyltetrahydro*-1,3-*oxazine and Tetrahydro*-1,3-*oxazine*-5-*spirocyclopentane*.—The *gem*-dimethyl compound shows a single band at 6568 cm^{-1}, almost triangular in shape (Figure 2A), and very similar to the minor band [3] of 3,3-dimethylpiperidine at 6586 cm^{-1}. The measured value for the PR separation is close to those calculated by both Seth-Paul's [25] and Badger and Zumwalt's [24] methods for NH equatorial, but the Q-branch absorbance is compatible with NH axial. The spiro-compound also shows a single band at 6550 cm^{-1} without fine structure; at high temperatures a shoulder appears on the high-frequency side (Figure 2B). The compound approximates to a symmetric top, the spectra of which have been given by Hollas: [26] for a molecule with the symmetry parameters of tetrahydro-1,3-oxazine-5-spirocyclopentane the A (parallel) band has distinct PQR structure whereas the B, C (perpendicular) band forms a Gaussian curve. The latter conclusion is found also in Gerhard and Dennison's paper.[23] The NH axial band is calculated to be only 16% parallel, the NH equatorial 41% parallel; hence the observed shapeless band is probably due to NH axial. This agrees with the minor band as a shoulder at high frequency. If this spiro-oxazine exists predominantly in the NH axial conformation, it seems probable that 5,5-dimethyltetrahydro-1,3-oxazine does also.

N-*t*-*Butylhexahydropyrimidine and* N-*Methylhexahydropyrimidine*.—The t-butyl compound is thermally unstable, and the shapelessness of the spectrum obtained (Figure 2D) effectively prevents analysis. However if, as before, the high-frequency band is NH equatorial, then the high intensity of the other band indicates that NH axial predominates.

The methyl compound (Figure 2C) shows a strong peak at 6520 cm^{-1}; to high frequency is a minor peak which displays a minimum at 6584 cm^{-1}. The shoulder may consist of two peaks one of which is due to an NH vibration in a molecule with an axial methyl group, as the methyl group is not a conformation-fixing substituent. The spectrum of 3-methylpiperidine [3] shows one peak at 6580 cm^{-1} with a central minimum and another at 6504 cm^{-1}. The two methods of calculating PR separations produce different answers. Badger and Zumwalt's [24] figures are both close to the observed value, but do not distinguish between them; Seth-Paul's [25] suggest that the low-frequency band arises from NH equatorial. However, the absence of a strong Q-branch in the high-frequency band indicates that the major conformer is NH axial, which accords with the frequency criterion.

General Conclusions.—The qualitative conclusions of the studies of the infrared overtone spectra in every case support, or are at the least compatible with, the quantitative results obtained by dipole moments. The conformational equilibrium of the NH-group in 1-t-butyl- and 1-methylpiperazine is evidently little influenced by the other heteroatom as it resembles the equilibrium in piperidine. However, the introduction of a further heteroatom β- to the NH group causes the NH-axial conformer to become predominant in all cases, and this conclusion is in close agreement with that of Booth and Lemieux.[10] Two possible explanations for the effect are (i) attractive forces between the lone pair and the NH- in the NH-axial conformer (14a); and (ii) dipolar repulsive forces between the two lone pairs in the NH-equatorial conformer (14b).



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[2/1346 *Received*, 12*th June*, 1972]

[26] J. M. Hollas, *Spectrochim. Acta*, 1966, **22**, 81.