The Conformation of the NH-Groups in Piperazines, Hexahydropyrimidines, Tetrahydro-1,2- and 1,3-oxazine, and Tetrahydro-1,3-thiazine

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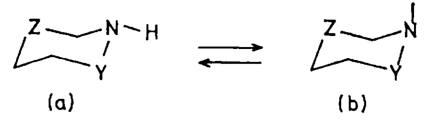
Summary I.r. band shapes and electric dipole moments show that the predominant conformers for tetrahydro-1,3-oxazine, tetrahydro-1,3-thiazine, and 1-t-butylhexahydropyrimidine are those with the NH axial; the predominant conformer for tetrahydro-1,2-oxazine is that with NH equatorial as determined by the same methods.

We recently[1] summarized evidence which shows that the conformational equilibrium in piperidine[2] favours the NH-equatorial (**1a**) by ΔG^0 *ca.* 0·4 kcal mol.$^{-1}$ The NH equilibrium position is not greatly altered by the introduction of an oxygen atom into the 4-position of the piperidine ring, as shown by the similarity of the conformational equilibrium for morpholine.[3] We now consider more generally the effect of hetero-atom substitution in the piperidine ring on the NH-conformational equilibrium of compounds (**2**)–(**5**).



(**1**) $Z = Y = CH_2$
(**3**) $Z = S, Y = CH_2$
(**5**) $Z = CH_2, Y = O$
(**2**) $Z = O, Y = CH_2$
(**4**) $Z = NBu^t, Y = CH_2$

We have applied three criteria to determine the nature of the predominant conformer for the compounds[†] listed in the Table: (i) comparison[3] of the measured *PR*-branch separation in the vapour-phase band-contour of the first overtone NH-stretching frequency with those calculated for the individual conformers by literature methods,[4–6] or an extension of them;[‡] (ii) comparison of the measured *Q*-branch : *PR*-branch absorbance ratios in these same band contours with those calculated by an extension[‡] of the literature procedure;[5] (iii) by comparison of the measured dipole moments with those calculated for the individual conformers by standard methods.[1]

NH-Conformational equilibria for hetero-atom substituted piperidines

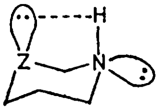
	Predominant conformer from i.r. criteria		Dipole moment
	PR-Separation	*Q*-Absorption	%NH-equatorial
1-Methylpiperazine	inconclusive	NH-*eq*	—
1-t-Butylpiperazine	NH-*eq*	—	63
Tetrahydro-1,3-oxazine	inconclusive	NH-*ax*	38
Tetrahydro-1,3-thiazine	inconclusive	NH-*ax*	22
1-Methylhexahydropyrimidine	inconclusive	NH-*ax*	—
1-t-Butylhexahydropyrimidine	NH-*ax*	NH-*ax*	34
Tetrahydro-1,2-oxazine	NH-*eq*	NH-*eq*	—

The results (Table) show clearly that, whereas the introduction of a hetero-atom at the 4-position has little effect on the piperidine NH- conformational equilibrium, a hetero-atom at the 3-position stabilizes the NH-axial conformation;[7] an oxygen atom at the 2-position considerably stabilizes the NH-equatorial conformation. In each case the qualitative conclusions from the i.r. spectral criteria support the quantitative results obtained by dipole moments.

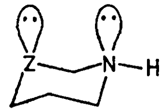
The influence of hetero-atoms β to the NH-group is, we suggest, due to the combined effect of (a) attractive forces between the lone pair and axial NH in the conformer (**6**), and (b) repulsive "rabbit ear" forces[8] between the two axial lone pairs in conformer (**7**).

The stability of the NH-equatorial form for 1,2-oxazine is, we believe, a consequence of the greater lone-pair/lone-pair repulsion in the NH-axial conformer.[8]

The variability of the position of the NH-conformational equilibrium for these compounds clearly demonstrates the inadequacy of the concept of "size" as applied to the comparison of the steric requirements of the NH-group *versus* the lone pair. Clearly the steric requirements of NH and lone pair depend, in a rational manner, on the environment, and their "size" depends on the probe which is used in the measurement.[9]



(6)



(7)

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† All compounds listed were characterised by analysis and/or g.l.c., m.p., as appropriate.

‡ For details see full paper which is in preparation for submission to *J.C.S. Perkin II*.

[1] 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.

[2] A similar value is obtained from calorimetric data, D. W. Scott, *J. Chem. Thermodynamics*, in the press; we thank Dr. Scott for communicating these results to us in advance of publication.

[3] R. W. Baldock and A. R. Katritzky, *Tetrahedron Letters*, 1968, 1159; *J. Chem. Soc.* (*B*), 1968, 1470.

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

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

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

[7] H. Booth and R. U. Lemieux, *Canad. J. Chem.*, 1971, **49**, 777, have concluded from the NH/CH_2 coupling constants in tetrahydro-1,3-oxazine and 1-methylhexahydropyrimidine that these compounds exist predominantly in the NH-axial form.

[8] R. O. Hutchins, L. D. Kopp, and E. L. Eliel, *J. Amer. Chem. Soc.*, 1968, **90**, 7174; (b) R. A. Y. Jones, A. R. Katritzky, and M. Snarey, *J. Chem. Soc.* (*B*), 1970, 131.

[9] For similar conclusions reached from earlier work from this laboratory see, *e.g.*, P. J. Brignell, A. R. Katritzky, and P. L. Russell, *J. Chem. Soc.* (*B*), 1968, 1459; M. D. Brown, M. J. Cook, and A. R. Katritzky, *ibid.*, 1971, 2358; R. A. Y. Jones, A. R. Katritzky, P. G. Lehman, K. A. F. Record, and B. B. Shapiro, *ibid.*, p. 1302.