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The Influence of an Axial 5-Methyl Group on the Chemical Shifts of C2 Methylene Protons in 1,3-Heterosystems

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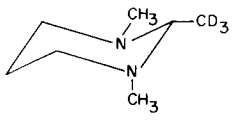
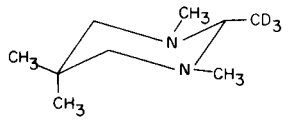
The shielding of a C-2 axial proton by an axial C-5 methyl group in 1,3-heterocyclic systems is described and explained in terms of conformational distortion.

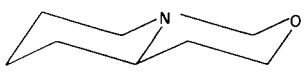
NMR spectral data on 2-alkyl-*N*,*N*′-dimethyl hexahydropyrimidines shows that the introduction of an equatorial methyl group at C-5 causes a small upfield shift (*ca.*, 8Hz) of the H-2 signal whereas an axial C-5 methyl group produces a large upfield shift of *ca.* 36Hz (measured at 60 MHz). This has been taken (2) as evidence for conformations I and II for 2-methyl-*N*,*N*′-dimethylhexahydropyrimidine (δ H-2ax = 2.81) and for the 5,5-dimethyl derivative (δ H-2ax = 2.21) respectively. The higher field chemical shift of H-2ax in II was assumed to be a result of shielding by two *anti*coplanar nitrogen lone pairs of electrons and/or the two equatorial *N*-methyl substituents (3); in I there is only one axial lone pair and one equatorial *N*-methyl group. The influence of the C-5 axial methyl group on the chemical shift of H-2ax was thus considered to be an indirect effect on the *N*-methyl groups,



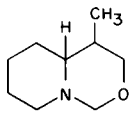
I



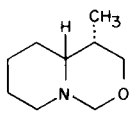
II



III



IV



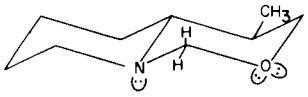
V

both of these being equatorial in II in order to escape *syn* axial Me-Me interactions. If the C-5 axial methyl group is able to influence the chemical shift of H-2ax by a different mechanism, then any quantitative estimates of the position of conformational equilibria in the 5-substituted hexahydropyrimidines and related systems based on the assumption that the H-2ax chemical shift (4) is only a function of the orientation of the nitrogen lone pairs of electrons and of the *N*-substituent will be in error. With this in mind we wish to point out a shielding of C-2 axial protons by similarly placed axial methyl groups in other 1,3-heterosystems which is apparently of a different stereochemical origin. The relevant chemical shifts are given in the Table and in each case these are of the methylene protons situated between the heteroatoms. Introduction of the equatorial methyl group barely affects the chemical shifts of the methylene protons whereas introduction of the axial methyl group results in a very small change in the shift of H-2eq (5) and in a marked upfield chemical shift of H-2ax (0.22-0.28 p.p.m.).

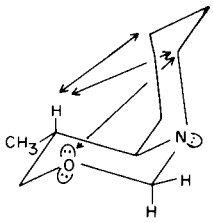
A possible explanation for the upfield shift is to assume that the *trans* 4H, 5H compounds (IV, VI (R = Me, R′ = H), and VII (R = Me, R′ = H) exist as equilibrium mixtures containing appreciable amounts of the *cis* fused ring conformations in equilibrium with the *trans* fused ring conformation and that the *cis* 4H, 5H compounds (V, VI (R′ = Me, R = H), VII (R′ = Me, R = H) exist almost exclusively in the *trans* fused conformation. Taking the specific case of the pyrido-oxazines IV and V, the equilibrium explanation of the chemical shift data would require IV to exist as an equilibrium mixture of IVa and IVb and V to exist as Va. One would then expect C-2Hax to absorb at lower field in IV than in V since in conformation IVb the nitrogen lone pair bisects the C-2 methylene group and the N-CH_2-C is axial with respect to the oxazine ring and in Va the nitrogen lone pair and C-2Hax are *trans*-diaxial and the N-CH_2-C equatorial. On conformational grounds,

TABLE (10)

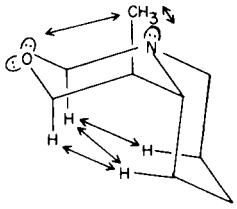
Compound	Solvent	Chemical Shifts (δ ppm) H2eq	H2ax	ΔH2ax H2eq	$J_{2ax\ 2eq}$	Ref.
III	CCl_4	4.18	3.52	0.66	-8.0	6
IV	CCl_4	4.14	3.55	0.59	-7.8	7
V	CCl_4	4.14	3.27	0.87	-7.8	7
VI (R = R′ = H)	$CDCl_3$	3.53	2.38	1.15	-8.4	8
VI (R = Me, R′ = H)	$CDCl_3$	3.53	2.40	1.13	-8.4	8
VI (R = H, R′ = Me)	$CDCl_3$	3.56	2.18	1.38	-8.7	8
VII (R = R′ = H)	$CDCl_3$	3.44	2.44	1.00	-9.0	1
VII (R = Me, R′ = H)	$CDCl_3$	3.45	2.53	0.92	-8.8	1
VII (R = H, R′ = Me)	$CDCl_3$	3.54	2.25	1.28	-8.7	1



IVa



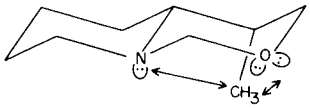
IVb



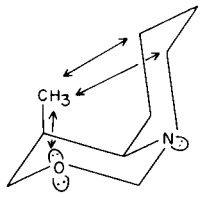
IVc

however, these assumptions are unacceptable since conformation IVb, although relieving the unfavourable dipolar interaction between the heteroatoms present in IVa, does so at the expense of introducing two *gauche*-butane and one *gauche*-propanol interaction into the molecule. Conformations IVc, Vb and Vc likewise suffer either from severe non-bonded interactions or unfavourable dipolar interactions involving the heteroatoms. In addition, conformation IVb should exhibit a J_{gem} for the C-2 methylene group of *ca.* - 10Hz (6) (nitrogen lone pair bisecting the C-6 H-H internuclear axis) whereas J_{gem} for IVa and Va would be *ca.* - 8Hz (nitrogen lone pair and C-6Hax *trans* diaxial). Thus the J_{gem} of a mixture of IVa and IVb in rapid equilibrium would be more negative than that observed for Va. In fact J_{gem} for both IV and V is -7.8Hz.

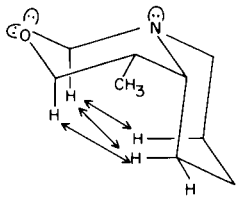
All of the other spectroscopic data including the Bohlmann region of the IR spectra of these and a large number of related systems is in accord with conformations III, IVa, Va, VI and VII being predominant for the compounds discussed. If the shielding is not due to changes in the *cis* or *trans* nature of the ring fusions then it most probably is a result of conformational distortion.



Va

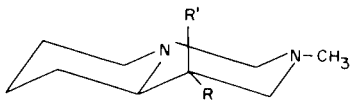


Vb

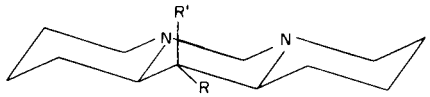


Vc

In monocyclic 1,3-hetero systems deviations from perfect chair geometry occur because the C-O and C-N bond lengths are shorter than the C-C length. This causes flattening of the chair in the C4-C5-C6 region and an axial substituent at this position is expected to be leaning away from the ring (9). This lean away might be expected to be more pronounced in the axially substituted bicyclic and tricyclic compounds V-VII because there is the additional urge to reduce the unfavourable inter-ring *syn* axial Me-H repulsions. Thus in a pair of compounds (*eg.* IVa and Va)



VI



VII

an increased lean away in the latter will alter, among other things, the spatial relationship between the carbon-carbon and carbon-nitrogen bonds and the C-2Hax proton with a resultant change in the shielding of H-2ax. If the effect is indeed a consequence of conformational distortion then its magnitude might be even greater in monocyclic systems such as I and II than in fused systems where distortion of the 1,3-hetero-ring is resisted on the ring fusion side. It seems unlikely, however, that the shielding effect in the hexahydropyrimidines (36 Hz) can all arise from conformational distortion (*cf.* 13-17 Hz in V-VII) and so there is no reason to doubt the existence of conformations I and II for the hexahydropyrimidines, but estimates of the position of conformational equilibrium based on the chemical shift of H-2ax must evidently include consideration of this distortion effect.

These results show that even "remote" groups may have a marked indirect effect on chemical shifts and serve to emphasize Lambert's (3) warning that in experiments aimed at evaluating the relative contributions to shieldings of protons adjacent to nitrogen the choice of model compounds must be made with care.

REFERENCES

(1) Part XIII, T. A. Crabb and P. J. Chivers, *Tetrahedron* (in press).

(2) R. O. Hutchins, L. D. Kopp, and E. L. Eliel, *J. Am. Chem. Soc.*, 90, 7174 (1968).

(3) A recent discussion of the factors contributing to the chemical shifts of protons adjacent to nitrogen has been given by J. B. Lambert and R. G. Keske, *Tetrahedron Letters*, 2023 (1969).

(4) The chemical shifts of H-2ax in 1,3-heterocyclic systems are subject to a variety of influences such as the nature of the *N*-alkyl group, but the present discussion is limited to compounds in which the only major change in structure involves the "remote" C-5 methyl group.

(5) For convenience in comparing chemical shift data all the compounds discussed are numbered as substituted monocyclic 1,3-heterocycles.

(6) T. A. Crabb and R. F. Newton, *Tetrahedron*, 24, 4423 (1968).

(7) T. A. Crabb and E. R. Jones, *ibid.*, 26, 1217 (1970).

(8) T. A. Crabb and R. F. Newton, *ibid.*, 26, 701 (1970).

(9) E. L. Eliel and M. C. Knoeber, *J. Am. Chem. Soc.*, 90, 3444 (1968).

(10) The NMR spectra were recorded as 10% W/V solutions on a Perkin-Elmer R.10 spectrometer using TMS as internal reference. The low field signals of the C-2 methylene AB quartet appeared as doublets or as broad peaks due to long range coupling thus permitting these signals to be assigned to H-2eq.

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