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NMR EFFECTS OF CYCLIC TERTIARY AMINES

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INTRODUCTION: **Bohlmann** reported that quinolizidine derivatives possessing a trans ring juncture exhibit characteristic absorption bands in the infrared (1). These bands appear at 2700-2800 cm^{-1} and are characteristic of hydrogens on carbon atoms adjacent to the nitrogen oriented trans to the lone pair. Several criteria were established and the absorption was considered due to a type of interaction between the lone pair and the trans σ_{C-H} bond. The NMR spectra of quinolizidine (I) and 4-methylquinolizidine (II) were examined in an attempt to determine more precisely the nature of such an interaction, and as models during the course of the investigation of the spectra of Lupin alkaloids.

ASSIGNMENTS: The lowest field signal in quinolizidine (I) appeared as a doublet, τ-7.18, 7.34, corresponding to two protons[*1]. The remainder of the absorption was represented by a broad peak centered near 8.5τ with a distinct shoulder at ca. 8.0τ, roughly correspond-

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[*1] The present chemical shifts are slightly different from those of Katritzky (5) due to the differences in solvent, i.e. $DCCl_3$ vs. CCl_4.

ing to one proton. The area of the lowest field signal excluded assignment to the C_{10}-proton and the shape, the narrow band width of each peak, indicated that the signal is due to equatorially, rather than axially oriented protons. This hypothesis was confirmed independently as follows.

The spectrum of quinolizidine (I), cf. FIG. 1, in TFA (trifluoroacetic acid) exhibited three distinct signals: a doublet with peaks at 6.41 and 6.62τ, similar in appearance to the low field signal of I in $DCCl_3$, roughly corresponding to two protons; a broad diffuse peak near 7.0τ approximately equivalent to three protons and a large peak corresponding to the remaining protons at 8.19τ. Due to the protonation of the quaternary nitrogen, the signals of all

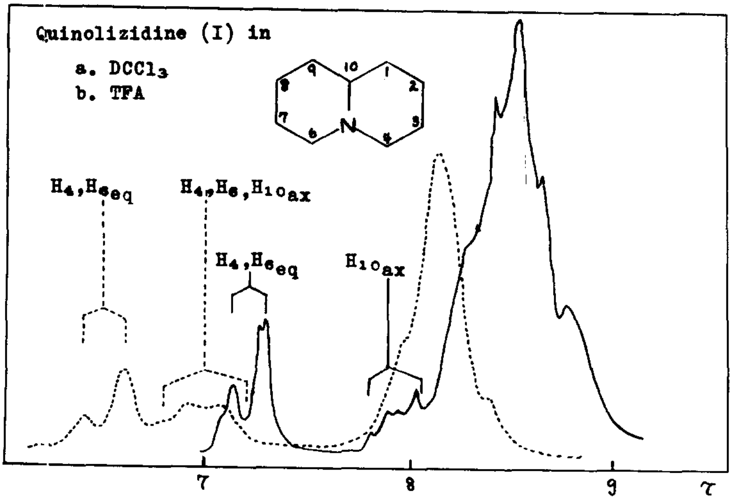

FIGURE 1. NMR of Quinolizidine (I)

hydrogens adjacent to the nitrogen shift to sufficiently low fields so as to be clearly distinguishable. Thus the distinct doublet can be reasonably assigned to the equatorial C_4 and C_6 protons and the broad absorption near 7.0τ to the axial protons at C_4, C_6 and C_{10}. The assignment of the lowest field signal to the equatorial protons parallels the assignments in carbohydrates and in the cyclohexane series (2). Further confirmation of these assignments was obtained from the spectrum of 4-methylquinolizidine (II)[*2] in which the methyl substituent was equatorially oriented. The spectrum exhibited only one low field signal, a diffuse doublet at ca. 6.7τ corresponding to a single proton, which can definitely be assigned to the C_6 equatorial hydrogen. A high field doublet due to the methyl group was observed at 8.87τ, J = 6 cps.

The chemical shift of the axial C_4 and C_6 protons of I in $DCCl_3$ was determined by the decoupling technique which showed these axial protons to absorb at 0.93 ppm[*3] to higher field compared with the equatorial protons.

DISCUSSION: Interestingly, the chemical shift difference of 0.93ppm of H_{ax} versus H_{eq}, although substantially larger than observed in cyclohexane and sugar acetate derivatives (2), is comparable (ca. 0.5ppm) when the nitrogen lone pair is effectively bound as in TFA solutions. Furthermore, the α-proton signals of N-alkylpiperidine

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[*2] The sample of 4-methylquinolizidine was prepared by the procedure described by Katritzky (5). The methyl group is trans to the C_{10} axial proton and the trans ring juncture was confirmed by characteristic bands in the infrared spectrum.

[*3] The band width of irradiation is 5 cps.

derivatives appear near 7.74τ or approximately midway between H_{ax} and H_{eq} signals of quinolizidine (I) (3). Presumably this large shift difference might be observed in piperidine derivatives of fixed chair conformation.

The rationalisation of the phenomena observed in the infrared and NMR will be made in terms of the difference in the electronic bonding character between C_4-H_{eq} and C_4-H_{ax}. Two factors can be deduced from Bohlmann's data which show that the force constant for the C_4-H_{ax} stretching is smaller than for C_4-H_{eq}.

1. The p character of the C_4 atomic orbital in the C_4-H_{ax} direction is larger than in the C_4-H_{eq}.

2. The bonding energy of the axial C_4-H bond is decreased which can be explained by participation of the nitrogen lone pair in an antibonding σ^* orbital between C_4 and the axial hydrogen (cf. Fig 2).

Four possible factors can be considered as causing the observed chemical shift difference between the axial and equatorial C_4 and C_6-hydrogens of quinolizidine.

1. The electron density at the axial hydrogen is greater than at the equatorial hydrogen atom.

2. The atomic magnetic susceptibility of C_4 is more diamagnetic for the axial component than for the equatorial. This can be explained by partial double bond character between C_4-N, thus placing the axial proton perpendicular to this double bond.

3. There is an effect arising from the magnetic anisotropy of nitrogen. However if this were the case, the anisotropic susceptibility in the direction of the lone pair should be diamagnetic since

the chemical shift of H_{ax} is higher than H_{eq}. But previous studies on morphine derivatives show qualitatively that the magnetic susceptibility in this direction is paramagnetic (4).

4. An electric field affects H_{eq} more strongly than H_{ax}. Such an electric field effect would originate from the dipole moment associated with the nitrogen lone pair. However the difference of such an effect on H_{ax} and H_{eq} is rather small and could not account for the observed shift difference.[*4]

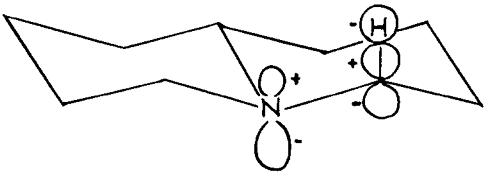

FIGURE 2.

From the above considerations regarding the infrared and NMR the following rationalization is proposed. In saturated cyclic nitrogen compounds in which the direction of the nitrogen lone pair is fixed, partial participation of the lone pair in a σ^{*}C-H_{ax} orbital on the adjacent carbon takes place. The participation of an

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[*4] An electric field at H_{ax} and H_{eq} is represented by : $E = \frac{\sqrt{1 + 3\cos^2\theta}}{R^3}\mu$, where $R = 2\mathring{A}$, the distance from N to H_{ax} or H_{eq} ; $\theta_{ax} = 45°$; $\theta_{eq} = 90°$; $\mu = 1$ D.u., dipole moment of N atom. Then $E_{ax} = \sqrt{5/2} \times 1/8 \times 10^{6}$ e.s.u. and $E_{eq} = 1/8 \times 10^{6}$ e.s.u.. The difference of the chemical shift due to an electric field is ; $\Delta\sigma E = -2 \times 10^{-12} E_z - 10^{-18} E^2$ (6). E_z is almost zero, thus $\Delta\sigma E_{ax} = 0.04 \times 10^{-6}$ and $E_{eq} = 0.014 \times 10^{-6}$. This magnitude could not account for the observed value.

electron in such a $\sigma^* C\text{-}H_{ax}$ orbital allows some overlap between the σ^* and lone pair orbitals generating some double bond character between C_4 and N, and simultaneously increasing the electron density at the C_4 axial proton. Such an interaction can only be expected in the H_{ax} direction since a σ^* $C\text{-}H_{eq}$ orbital lies in a plane perpendicular to the lone pair.

Thus the diamagnetic anisotropic susceptibility of C_4 (and also at the equivalent C_6-position) in the $C_4\text{-}H_{ax}$ direction is larger due to partial C_4-N double bond character[*5] and the increased electron density at H_{4ax} could account for the unusually large shift difference between the axial and equatorial hydrogens at C_4 (and also C_6) in quinolizidine derivatives. This also rationalizes Bohlmann's trans quinolizidine band in the infrared.

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[*5] The magnetic anisotropy of a doubly bonded carbon atom ($\Delta\chi$) is given as -13.5×10^{-30} e.s.m.c.g.s. (cf. ref. 4) and the difference of the chemical shift between H_{ax} and H_{eq} is represented by

$$\Delta\sigma = \left[\frac{(1-3\cos^2\theta_{ax})\Delta\chi}{R^3} - \frac{(1-3\cos^2\theta_{eq})\Delta\chi}{R^3}\right]\alpha$$

Using the values, $R = 1.1\text{Å}$, $\theta_{ax} = 0°$, $\theta_{eq} = 90°$, the chemical shift difference of H_{ax} and H_{eq} is

$$\Delta\sigma = \frac{-3\Delta\chi}{R^3}\alpha = \frac{13.5 \times 10^{-30} \times 3}{1.1^3 \times 10^{-24}}\alpha$$

The value of α (the state density of hyperconjugation) is about 3 % from the observed $\Delta\sigma$(0.93 ppm). This seems to be of the right order of magnitude on the basis of an independent calculation by the second order perterbation method.

REFERENCES

1. F. Bohlmann, Ber., 91, 2157 (1958).
2. L. M. Jackman, Application of Nuclear Magnetic Resonance in Organic Chemistry, P 116, Pergamon Press, London (1959).
3. H. Weitkamp and F. Korte, Ber., 95, 2856 (1962).
4. S. Okuda, N. Nakagawa, and S. Yamaguchi, Chem. Pharm. Bull., 11, 1465 (1963).
5. T. M. Moynhen, K. Shofield, R. A. Y. Jones, A. R. Katritzky, J. Chem. Soc., 1962, 2637.
6. A. D. Buckingham, Canad. J. Chem., 38, 300 (1960).