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THE QUATERNIZATION OF CIS AND TRANS 1-HYDROXYQUINOLIZIDINE

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Abstract- c-1-Hydroxyquinolizidine I gave with MeI a trans-fused quinolizidine methiodide II formerly believed to have a cis-fused structure. The t-1-hydroxyquinolizidine epimer III gave a mixture of two methiodides IV and V having trans and cis-fused quinolizidine structures respectively. Methiodide V exhibits temperature dependent nmr spectra (C-13 and 200 MHz ^{1}H nmr) indicative of a conformational equilibrium.

The quaternization of simple quinolizidines and of quinolizidine-based alkaloids has attracted much attention, mainly directed to the stereochemistry of the reaction. In the particular case of the methiodides of the 1-hydroxyquinolizidine epimers I and III the published data are confusing.

While Möhrle et al. (1) obtained from epimer I a single methiodide to which they assigned a cis-fused structure by analogy with other quinolizidinium salts, other authors (2) have reported, for what should be the same compound, the conformeric cis structure based solely on the N-Me chemical shift.

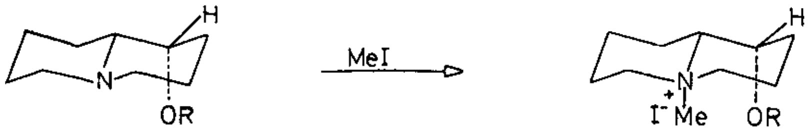
In the N-methylation of epimer III the reports are conflicting too where Möhrle (1) isolated a single trans-fused methiodide, while Sam et al. (2) reported the isolation of two methiodides corresponding to trans- and cis-fused quinolizidine skeletons although only the former was properly characterized.Moreover, the melting points reported for what apparently is the same methiodide from III differ by 30°.

On the other hand, we have found that the N-oxidation of I and III (3), gives one trans-fused N-oxide from epimer I and two N-oxides, one trans and the other cis-fused, from epimer III.

With the aim of clarifying these facts we report here our own findings on the N-methylation of I and III and of their acetates Ia and IIIa prepared as previously described (3).

Brief treatment of I and Ia with MeI (5 min. reflux in acetone) gave in each case a single product, II (m.p. 264-266°) and IIa (m.p. 186-188°), whose nmr spectrum exhibited a singlet for the N-Me protons at δ=3.17 and 3.34 ppm respectively. The multiplet due to H-1 at δ=4.00 and 5.07 ppm, respectively, possessed in both cases a width of W 1/2=12 Hz indicative of an equatorial configuration. The C-13 chemical shifts for the diagnostic carbons N-Me, C4 and C6 (42.8, 63.0, 66.9 and 42.6, 64.1, 66.5 ppm respectively) are characteristic of a trans-fused quinolizidine system (4).

The possibility of a cis-fused structure as claimed in the literature (1-2) can also be eliminated by inspection of the nmr signal due to H-10 easily identified in IIa at δ=4.55 ppm as a poorly resolved doublet of doublets (J=8 and 3 Hz approx.) due to one trans-diaxial and two axial-equatorial couplings (5).



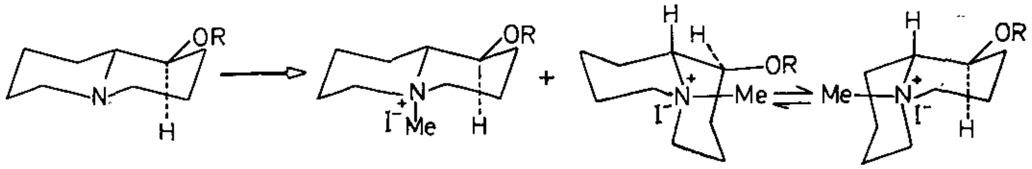
I R=H
Ia R=Ac

II R=H
IIa R=Ac

Epimer III gave, when treated with MeI, a mixture of two methiodides, IV and V in the ratio of 10:1, separated by fractional crystallization from acetone/ethanol. The minor product V (m.p. 295-297°) crystallized first and gave a singlet at δ=3.26 for the N-Me protons and a multiplet at δ=4.18 (W1/2=20Hz) for H-1. Its C-13 nmr spectrum (DMSO,32°) showed an N-Me carbon at δ=51.2 ppm indicative of a cis-quinolizidine methiodide, but it also presented considerable broadening of several signals, particularly for C4 and C6. By increasing the probe temperature to 70° a clear sharpening of these peaks was produced, proving V to be a mixture of cis-quinolizidine conformers in rapid equilibrium whose coalescence temperature lies near room temperature. The C-13 chemical shifts (DMSO at 62°) for the N-Me, C4 and C6 carbons (51.2, 58.2 and 59.2,respectively) correspond to rapid interconversion conditions and are therefore average values.

The H-1 proton band width (W 1/2=20Hz) in the nmr spectrum of methiodide V is accordingly wider than that of an equatorial proton (see II) but still very far away from the well-resolved signal due to an axial configuration such as the one exhibited by IV.

The major product IV (m.p. 219-221°) was isolated from the later crops and showed a singlet at δ=2.98 due to the N-Me protons and a signal for H-1 centered at δ=3.75 and having a well-resolved pattern showing a triplet (J=12Hz) of doublets (J=5.5Hz) due to two trans-diaxial and one axial-equatorial couplings; the C-13 signals for the significant carbons N-Me, C4 and C6 (40.0, 65.6 and 66.9 ppm, respectively) correspond to a trans-fused quinolizidine methiodide.



III R=H
IIIa R=Ac

IV R=H
IVa R=Ac

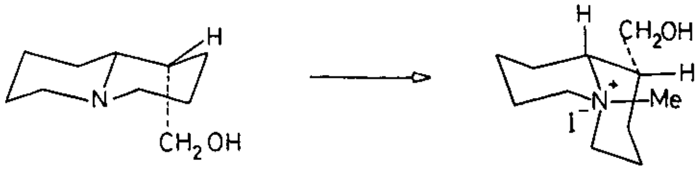
V R=H
Va R=Ac

Similarly IIIa produced a 1:1 mixture of methiodides IVa and Va, which upon fractional crystallization in Me_2CO/EtOH gave in the first crop IVa as prisms (m.p.246-248°) showing in the proton nmr spectrum two singlets at $\delta=3.22$ and 2.08 due to the N-Me and the acetyl protons and a multiplet for H-1 centered at $\delta=4.84$ ppm, the feature being analogous to that of IV. The C-13 chemical shifts for the N-Me, C4 and C6 carbons (40.5, 65.4 and 63.8 ppm, respectively) are also consistent with a trans-fused quinolizidine methiodide.

Methiodide Va (m.p.225-226°) was isolated in the form of fine needles showing in the proton nmr spectrum singlets at $\delta=3.65$ and $\delta=2.12$ (N-Me and acetyl protons) and a non-resolved multiplet for H-1 centered at $\delta=5.11$ ppm (W 1/2=15Hz). The C-13 nmr spectrum showed the same characteristics and temperature behaviour as found in V. The band width value for the H-1 proton (W 1/2=15Hz) and the C-13 chemical shifts (DMSO at 62°) for N-Me, C4 and C6 (51.1, 56.9 and 59.6 ppm, respectively) agree well with an equilibrium mixture of cis-quinolizidine methiodides as shown in the figure. This conformational equilibrium could also be examined through the 200 MHz proton nmr spectra of Va, which showed a sharpening of signals on heating. At 57° H-10 resonates at $\delta=3.85$ as a well-resolved quartet (J=6.3Hz) which collapses to a triplet (J=6.3Hz) upon irradiation of the H-1 signal.

In short, we have found that quaternization of quinolizidine I produces a single trans-fused quinolizidine methiodide II formerly believed to have a cis structure (1,2). Compound III gives a mixture of two methiodides IV and V, which are trans- and cis-quinolizidines respectively, and this also contradicts earlier reports (1) describing a single reaction product. As for the second methiodide mentioned by Sam et al. (2a) in their quaternization of III, we have been unable to detect the presence in the reaction mixture of any compound having the nmr data reported. Furthermore, changing the solvent (6a), reaction time and temperature produced no apparent variation in the nature or ratio (10:1) of the reaction products IV and V, which is markedly different from the IVa-Va ratio (1:1), reflecting perhaps the reduced nucleophilicity of the nitrogen of III in its cis-fused conformation due to the intramolecular hydrogen bond absent in the acetate IIIa.

The stereochemistry of these quaternizations is coincident with what we have observed before for the corresponding N-oxides of I and III (3), but it can not be explained merely on the basis of steric interactions as has been done for a series of methyl quinolizidines (1 and 6b).



VI VII

The report (6-7) describing a single cis-fused quaternary salt VII from the alkaloid lupinine VI serves to indicate the very different influence of carbon and oxygen substituents at C1 on the stereochemistry of quaternization. The great conformational flexibility of V and Va is also interesting in respect that one would not expect such a small energy barrier between two conformers in one of which there is a sizeable 1-3 diaxial interaction, and suggests that the influence of polar effects in determining the stereochemistry of these molecules might be decisive.

ACKNOWLEDGEMENT

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8. All chemicals gave satisfactory mass spectra and elementary analyses. The nmr spectra of methiodides of amino alcohols were run in D_2O with DSS as reference, whereas $CDCl_3$ was used for those of the acetates.

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