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CONCLUSIONS FROM NMR ON THE PREFERRED DIRECTION OF ATTACK DURING QUATERNISATION OF 1-BENZYL-TETRAHYDROISOQUINOLINES

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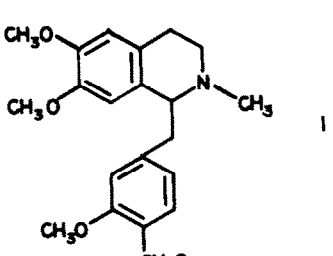
Abstract—For laudanosine, NMR nuclear Overhauser measurements coupled with synthesis using ^{13}C enriched methyl iodide, have shown that quaternisation proceeds as expected for steric reasons from the side of the ring opposite to the 1-benzyl sidechain.

The 1-benzyl tetrahydroisoquinoline moiety is an essential constituent of many natural products used as therapeutic agents and has formed the starting point for a number of synthetic drugs. For example a number of the alkaloids originally extracted from opium[1] have the 1-benzyltetrahydroisoquinoline nucleus as a basic structural element as does the naturally occurring neuromuscular blocking agent tubocurarine chloride. One of the two 1-benzyltetrahydroisoquinoline groups in tubocurarine chloride has a quaternary nitrogen in the form of a quaternary methyl salt[2] but, however, if for other analogues the nitrogen substituents are not identical then *cis*/*trans* isomerism can exist about the C_1–N_2 bond. These isomers may have different biological activities and this fact has implications for any synthetic chemistry used to produce therapeutic analogues. For this reason we have investigated the preferred direction of quaternisation and have used laudanosine, 1 - [(3,4 - dimethoxyphenyl)methyl] - 1,2,3,4 - tetrahydro - 6,7 - dimethoxy isoquinoline (I) as a suitable model.



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It has been shown previously that, among other related substrates, laudanosine can be quaternised with ethyl iodide or benzyl iodide to give mixtures of products with proportions 65:35 and 95:5 respectively.[3] For the N-benzyl products, a higher degree of non-equivalence in the N-benzyl methylene group chemical shifts was observed for the minor component thus indicating a higher potential barrier to rotation and hence the inference that the minor product had the two bulky substituents in a *cis* configuration.[4] If this is true then quaternisation is preferred *trans* with respect to the orientation of the C_1 substituent.

Conformational flexibility of a 1,2 - dimethyl - 1,2,3,4 - tetrahydroisoquinoline ring system was also deduced from the similarity of the N-Me shifts in the quaternary Me salts but for the 1 - phenyl - 2 - Me derivatives it was inferred that the phenyl substituent remained equatorial.[5]

In the quaternary salt with methyl iodide the two Me groups can be distinguished as *cis* or *trans* to the 1-benzyl group and in this communication we present direct evidence to show that quaternisation is preferred via an approach on the side of the ring *trans* to the benzyl group.

EXPERIMENTAL

A Bruker HFX-90 NMR spectrometer with an Instem Datamag data system was used to measure the 90 MHz ^1H spectrum of laudanosine methiodide as shown in Fig. 1. The solvent used was DMSO-d_6 at an operating temp of 80°. The spectrum was measured in the pulse Fourier transform mode with 4096 data points, zero-filled to 16384 before Fourier transformation, and an acquisition time of 1.7 sec.

Most of the assignments are straightforward and are shown in Fig. 1: however in order to assign the N-Me signals unambiguously, nuclear Overhauser enhancement measurements were necessary and this was not possible with the degree of overlap of the resonances as shown.

A careful study of the temp. and solvent dependence of the proton chemical shifts of laudanosine methiodide showed that at 80° a 3:1 mixture of C_6D_6 and DMSO-d_6 gave both N-Me signals well resolved from the O-Me and methylene resonances. It was then possible to selectively irradiate only the resonances of interest (see the left insert in Fig. 1).

Nuclear Overhauser enhancements were measured in the pulse Fourier transform mode by comparing the integral from H_1 with that from H_8 whilst irradiating either N-Me signal. A control measurement was achieved by setting the irradiation frequency at the same power level off resonance by 20 Hz after ensuring that no other resonance came at that point.

The results of duplicate experiments on a degassed solution at 80° are given in the Table.

Irradiation frequency	% Integral enhancement
At high field N-methyl	(i) 17.9
	(ii) 18.3
At low field N-methyl	(i) 9.1
	(ii) 9.7
Off-resonance	0.3

Interpretation of the NOE results. Because nuclear Overhauser enhancements are inversely proportional to the sixth power of the distance between the nucleus

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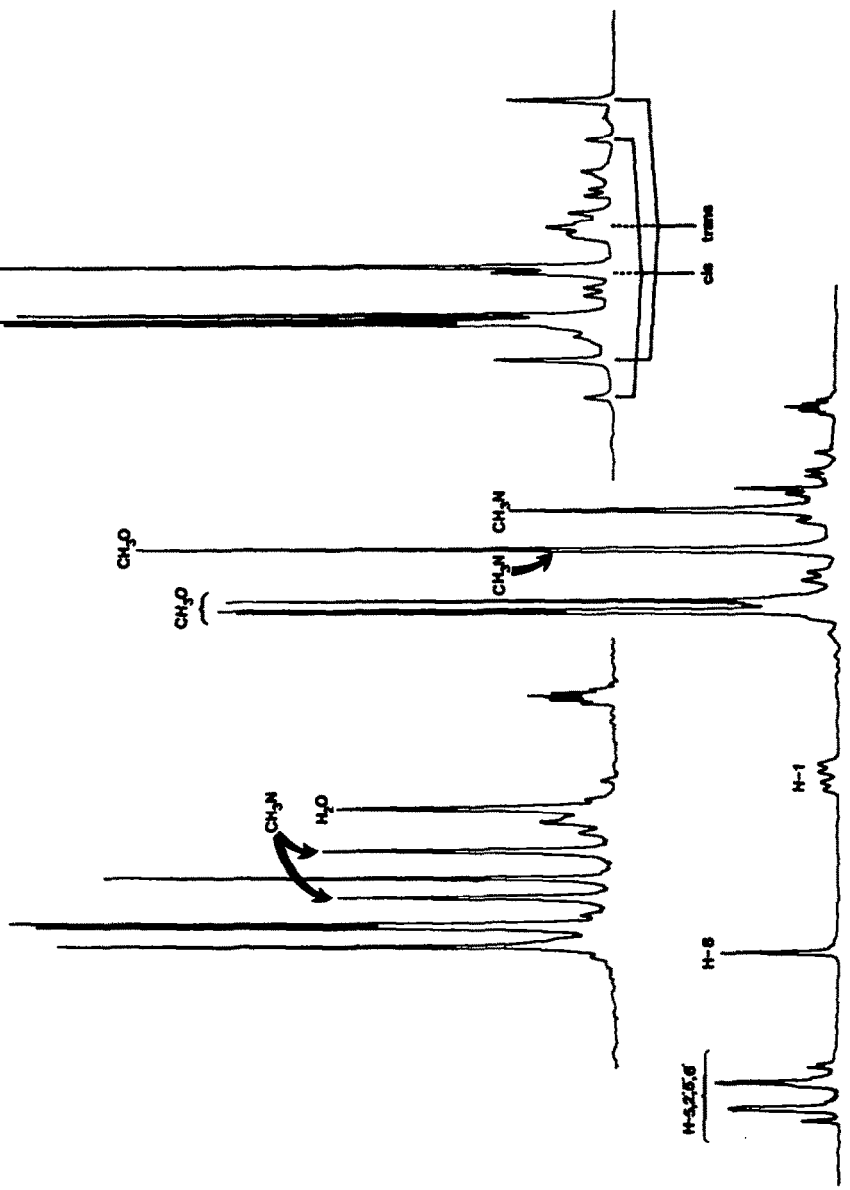
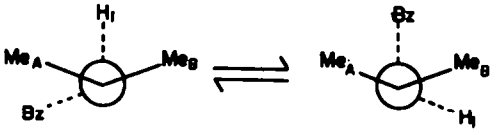


Fig. 1. 90 MHz ^{1}H NMR spectrum of laudanosine methiodide at 80° in DMSO-d_6. The assignments are as marked. The left insert shows the aliphatic region of laudanosine methiodide at 80° in 3:1 C_6D_6 and DMSO-d_6, indicating the separation of the resonances. The right insert shows the ^{1}H NMR spectrum of laudanosine methiodide prepared from ^{13}C enriched methyl iodide, at 130°C in DMSO-d_6. The resonances from the N-methyl groups showing coupling to ^{13}C are marked.

being irradiated and the nucleus whose intensity is being monitored,[6] it is clear that the high field N-Me signal can be assigned as that *trans* to the benzyl group. The average values of 18.1% and 9.4% are almost in the ratio of 2:1 and this can be interpreted in terms of the relative H_1-Me distances.

If we make the reasonable assumption that the two possible twist chair conformations have similar energies and that there is a finite barrier to interconversion then it is only necessary to consider the two individual conformations because the populations of intermediate states will be low.

The situation for these two conformations, if we assume ideal dihedral angles, as viewed along the N_2–C_1 bond is:



where Bz = the 3,4 - dimethoxy benzyl group. The methine hydrogen H_1 remains at the same distance from Me_B in both conformers. In the first conformation, H_1 is also at the same distance from Me_A, but in the second conformation the corresponding distance is much greater. The enhancement drops rapidly as the distance increases[6] and no enhancement will be experienced by H_1 from Me_A in the second conformer. It then follows that if there is fast ring flip between the two conformations, and assuming equal relaxation paths, the Me *cis* to H_1 will provide twice the NOE compared to the Me *trans* to H_1.

Within experimental error, this is observed and thus one explanation is a rapid ring flip between approximately equal energy twist-chair conformations in laudanosine methiodide. Another possibility is that the 1-benzyl group fixes the conformation such that this bulky substituent lies in a pseudo-equatorial position so that the distances between H_1 and the two N-Me groups are different by about 12%, as this would again give an NOE ratio of 2:1. Therefore to summarise the NOE results, the high field N-Me signal in the ^{1}H NMR spectrum of laudanosine methiodide is assigned as trans to the 1-benzyl group.

Quaternisation with $^{13}CH_3I$. If laudanosine base (I) is reacted with ^{13}C enriched methyl iodide the quaternised product has the ^{1}H NMR spectrum shown in Fig. 1 with the major (~80%) ^{13}C enriched N-Me signal to high field and hence quaternisation goes mainly via an approach *trans* to the benzyl group.

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