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THE CONFORMATION OF N-ACYL-1,2,3,4-TETRAHYDROQUINOLINES

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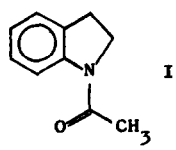
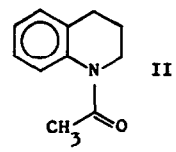
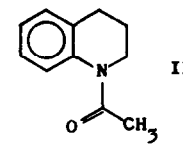
It was reported recently (1) that although N-acetylindoline exists mainly in the endo conformation I, N-acetyl-1,2,3,4-tetrahydroquinoline appears to exist mainly in the exo conformation, II. The evidence in the indoline case was that the proton magnetic resonance (p.m.r.) of the H_7 proton moved 1.77 p.p.m. downfield on acylation of the base, whereas the signal for H_8 in the tetrahydroquinoline series could not be distinguished from those of the other aromatic protons. Additional evidence for the exo conformation II was the 0.73 p.p.m. downfield



I



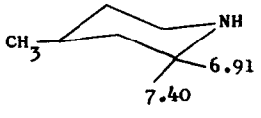
II

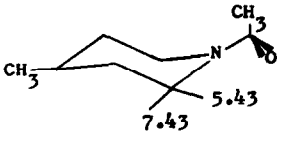


III

shift of the signal for the H_2 protons on acylation. No comment was made, other than the factual statement, that the H_2 protons in the indoline also moved downfield 0.68 p.p.m. on acetylation.

It has been shown that the effect of the magnetic anisotropy of the amide group on the p.m.r. absorption of neighbouring protons is critically dependent on their orientation relative to the plane of the amide group. The chemical shifts (τ, $CDCl_3$) of H_2 and H_6 in N-acetyl-4-methylpiperidine are summarised in Fig. 1 (2).





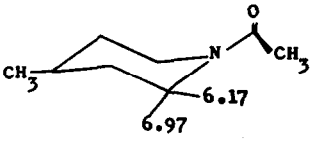
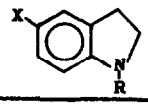
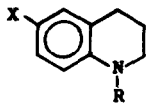


FIG. 1

From these data it can be seen that on acylation of the base, the signal for an equatorial C_2 proton moves downfield ca 1.5 and 0.7 p.p.m. when cis and trans respectively to the carbonyl group, whereas the axial proton signal only moves downfield when trans to the carbonyl

TABLE

P.m.r. Data For Some Benzoheterocycles And Their N-Acyl Derivatives

Compound	X	Chemical Shifts (τ)[a] for Protons ortho[b] to Nitrogen				Conformer Ratio	
		Temp.	R = H	R = $COCH_3$	Δ		
	Br	38°[c]	3.48	1.75[d]	-1.73	Endo	100%
	MeO	38°	3.30	1.73[d]	-1.57	Endo	100%
	Br	38°	3.54	2.56[e]	-1.08		
		-30°		2.23[d]	-1.31	Endo	40%
				2.97[d]	-0.57	Exo	60%
	MeO	38°	3.30	2.68[f]	-0.62		
		62°		2.79[d]			
		-32°		2.20[d]	-1.10	Endo	20%
				2.91[d]	-0.39	Exo	80%
				R = CHO[g]			
	MeO	38°	3.30	1.82[d]	-1.48	Endo	10%
				3.05[d]	-0.25	Exo	90%
		90°		3.10[f]			

[a] Spectra were measured in 10% w/v solutions in $CDCl_3$ on a Varian A60 instrument, with TMS as internal standard. [b] The signal for the ortho proton was readily distinguished by its strong ortho and weak para coupling. [c] The spectra were unchanged at -60°. [d] Essentially a doublet $J_{ortho} \approx 9.5$ Hz. [e] Only a single signal was observed for the three aromatic protons. [f] Broad unresolved signal. [g] In CCl_4.

group. Thus, in a piperidine derivative in which the ring is able to invert fast enough on the p.m.r. time scale for the axial and equatorial protons to become indistinguishable, it can be predicted that if similar proportions of the two chair forms were present at equilibrium then the average chemical shift of the H_2 protons in the base (7.15τ) would become in the acetyl derivative, 6.43τ when cis, and 6.57τ when trans to the carbonyl group. We conclude that the downfield shifts to be expected (ca 0.7 and 0.6 p.p.m.) in interconverting chairs would be insufficiently distinctive to assign structures to cis and trans isomers with any certainty, and thus the chemical shifts of the H_2 protons in N-acyl indolines and tetrahydroquinolines [re ported to be a mixture of rapidly interconverting half-chairs (3)] do not permit reliable assignment of conformation. This deduction demonstrates the inadequacy of lilolidine and compound IX (1) as models for assignment of acyl conformation from p.m.r. data.

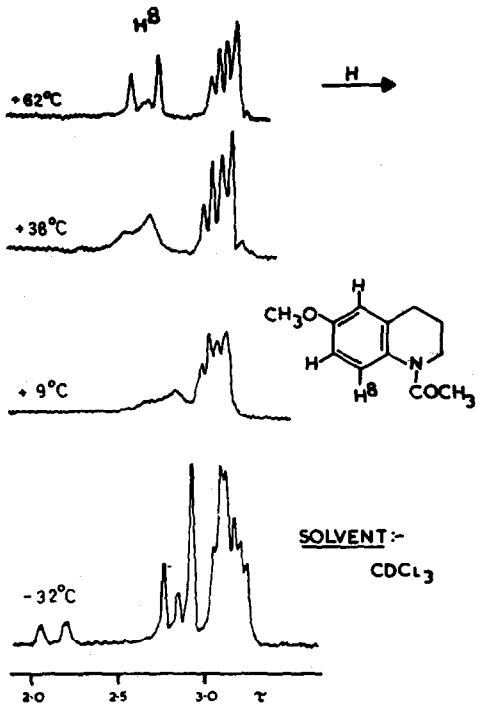


FIG. 2

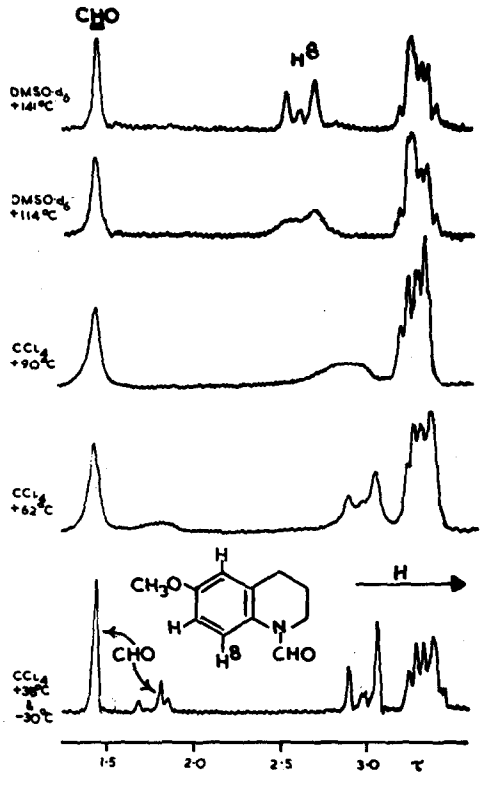


FIG. 3

We have measured the p.m.r. spectra for indoline and tetrahydroquinoline derivatives shown in the Table. It can be seen that on acetylation of the indolines, the ortho proton signal moves downfield by an amount similar to that reported (1) for the unsubstituted parent compound. It is also apparent that at normal probe temperature (38°) an appreciable downfield shift occurs in the tetrahydroquinoline series.* Measurements at different temperatures have revealed that in these latter compounds the single signals observed at 38° for the ortho aromatic proton and the acetyl methyl group, arise from an averaging of signals from the separate conformers. At -30°, the resonances observed for H_8 in the 6-Br and 6-MeO N-acetyl derivatives were each resolved into a pair of doublets; in addition, at this temperature the acetyl methyl groups gave two signals, 6 Hz apart for the 6-MeO derivative and incompletely resolved for the

*Nagarajan et al. (ref. 1) probably did not observe a similar downfield shift for N-acetyl-1,2,3,4-tetrahydroquinoline through the difficulty in first order analysis of the p.m.r. spectrum of the unsubstituted compound.

6-Br derivative. At 62° the broad signal for H_8 in the 6-MeO compound was resolved into a sharp doublet. By comparison with the indoline data (4), the lower field signals are taken to arise from the endo conformation (III), and the proportions of each conformer obtained by integration are shown in the Table.

In the N-formyl derivatives (Fig. 3) two doublets for the ortho aromatic proton (the more intense doublet at higher field) and two signals for the formyl proton (the larger signal at lower field) were apparent at 38°. At 90° the formyl signals coalesced, as did the H_8 doublets, the latter giving a broad singlet, which at 141° (in DMSO-d_6) became a sharp doublet.

We interpret these findings as indicating that in the N-formyl derivatives, the energy barrier ($\Delta G^{\ddagger} \approx 18$ k.cals.) between endo and exo conformations is such that distinct signals are observed for the two forms at normal temperatures, with the exo form predominating. In the N-acetyl derivatives, the exo conformation again predominates, but with a lower energy barrier ($\Delta G^{\ddagger} \approx 14$ k.cals.) existing between the two conformers (cooling to ca -30° is necessary to observe distinct p.m.r. signals for the two forms). This lower barrier to rotation and the smaller deshielding of the ortho proton by the endo acetyl group than by the endo formyl group, or than occurs in the N-acetyl indolines, probably arises from the acetyl group in the tetrahydroquinolines being twisted considerably from the plane of the aromatic ring, probably due, at least in part, to a steric interaction between H_8 and the acetyl group.

We conclude that N-formyl 1,2,3,4-tetrahydroquinolines exist almost entirely in the exo conformation, while in the N-acetyl derivatives both endo and exo conformations are populated to an appreciable extent, but with lower energy barrier to interconversion separating them. Additional evidence supporting this conclusion is available from studies of aromatic solvent-induced shifts and from dipole moment measurements, and this will be published in the full paper.

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2. (a) 4-Methylpiperidine from Varian Associates Spectra Catalog, Vol. 2, Spectrum 479; acetyl derivative from (b) D.M. Lynch and W. Cole, J. Org. Chem., 31, 3337 (1966); and (c) H. Paulsen and K. Todt, Chem. Ber., 100, 3385 (1967).
3. For supporting evidence see H. Booth, J. Chem. Soc., 1841 (1964).
4. K. Nagarajan and M.D. Nair, Tetrahedron, 23, 4493 (1967).