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CONFORMATION OF THE METHYL GROUP AND TETRAHYDROPYRIDINE RING IN N-ACYLTETRAHYDROQUINALDINE DERIVATIVES[a]

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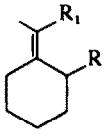
Abstract—NMR spectra of N-acyletrahydro quinaldines **12–19** and of pyridodibenzoxazepines **21–24** show the Me group to be axially oriented with the tetrahydropyridine ring in a half-boat conformation. The aroyl phenyl in both is twisted out of the C=O plane. While the Me group again occupies the axial position in pyridophenanthridones **5** and **7** and pyridooxazinones **8** and **9**, the tetrahydropyridine ring exists as a half-chair.

Allylic strain of the A(1·3) type in system **1** was postulated by Johnson and Malhotra in 1965[1,2] to lead to preferential axial disposition for the R group.[3]

This concept was disputed[4,5] but has been recently vindicated both from NMR[6] and X-ray crystal structure studies of compounds **2** and **3**.[7] Restricted rotation of the amide bond in cyclic amides having the partial structure **4** may be expected to lead to a similar situation.[3] We had encountered this during a study of N-acyltetrahydroquinaldine derivatives published in 1967.[8] This study has been now enlarged and recent results offering definite evidence for A(1·3) strain in system **4** are presented in this communication.



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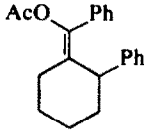

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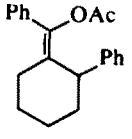

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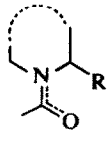

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In the 100 MHz NMR spectrum of pyridophenanthridine **5**[8,9] in $CDCl_3$, the signal due to the starred proton was seen as a complex multiplet at δ 5·5. Irradiation of the Me group reduced it to a triplet with a coupling constant of 3 Hz.† In contrast, in tetrahydroquinaldine **6**, the corresponding C-2 proton was earlier shown to couple with its C-3 neighbours to the extent of 8 and 3 Hz.[8] This signifies that this proton is axial and the Me group equatorial in **6**, *while in* **5**, *the starred proton has to be equatorial and the Me group axial.* The tetrahydropyridine ring has the half-chair conformation in both. Steric repulsion between the O atom and Me group in **5** must then be responsible for the latter taking up the normally thermodynamically less stable axial conformation. X-ray crystal structure study of the bromo-derivative **7** definitely shows that the tetrahydropyridine ring exists as a half-chair with an axial Me group.[10] The carbonyl-equatorial Me group interaction thus appears to be larger than 0·5 K Cal/mole, the value for axial Me and hydrogen interaction.[11]

NMR studies likewise reveal that the Me group in oxazinoquinoline derivatives **8** and **9**[12] takes up the axial conformation with the tetrahydropyridine ring in the half-chair conformation. Thus the methine protons in **8** and **9** are seen as slightly broadened nonuplets in their NMR spectra in $CDCl_3$ at δ 4·85 and 5·02 respectively. After irradiation of the Me group signal in the spectrum of

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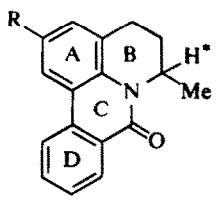
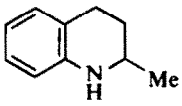
†From the X part of the ABX spectrum, in reality only $J_{AX}+J_{BX}$ is obtained as 6 Hz, but J_{AX} is unlikely to be significantly different from J_{BX} and hence they are assumed to be identical.



5: R = H
7: R = Br



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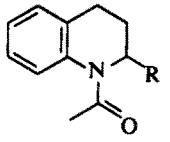
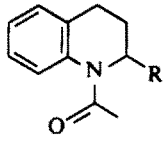
8: R = H
9: R = Br

9, the nonuplet was reduced to a triplet with J = 3·5 Hz;* X-ray crystal structure study of **9** shows the presence of axial Me group in a half-chair tetrahydropyridine ring.[10]

Our earlier analysis[8] of the NMR spectra of N-acyltetrahydroquinolines and N-acyltetrahydroquinaldines at 40° probe temperature indicated that the predominant if not the exclusive configuration of the amide bond in them was *anti* (to benzo ring) as in **10** and not *syn* as in **11** and that the Me group



10: R = H, CH_3



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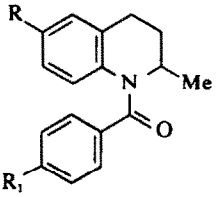
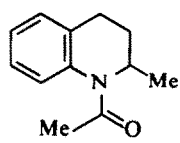
in **10** was axially disposed. Subsequently, Monroe and Sewell[13] have shown by a study of the NMR spectra of 6-bromo- and 6-methoxy-N-acetyl-1,2,3,4-tetrahydroquinolines as a function of temperature that at 38°, these amides were an equilibrium mixture of *anti* (**10**) and *syn* (**11**) forms with the *anti* form predominating and with an energy barrier of about 14 k. calories. We have carefully examined the 100 MHz $CDCl_3$ NMR spectrum of **13** at room temperature and of **14** from −65° to +28°. In both cases only one species appears to be present.† Since the C-2 protons in these molecules have δ 4·85, approximately 1·66 ppm downfield relative to its position in tetrahydroquinaldine, we postulate as we did earlier for **12** and **19** that the C=O group in them is *anti* to the benzo ring as shown with the C-2 proton in an equatorial conformation, coplanar with the C=O group and the Me group in an axial disposition.

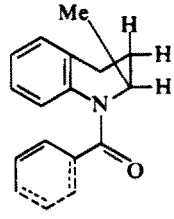
The signal of the C-2 proton in the 60 MHz $CDCl_3$ spectra of N-acyltetrahydroquinaldines **12–19** appears as a sextet with a spacing of about 7 Hz. A first order interpretation would be that the equatorial C-2 proton was coupling to the same extent of 7 Hz with the Me as well as with the C-3 equatorial and axial protons. After irradiation of





12: R = R_1 = H
13: R = Me; R_1 = H
14: R = H; R_1 = Br
15: R = H; R_1 = Cl
16: R = H; R_1 = OMe
17: R = H; R_1 = NO_2
18: R = H; R_1 = NH_2

the Me group in the 100 MHz NMR spectrum of **19**, the sextet was indeed reduced to a triplet of 7 Hz spacing. The apparent equal coupling of the C-2 proton* with the C-3 neighbours to the extent of 7 Hz can be rationalized only if the tetrahydropyridine ring in **12–19** exists as a half-boat as in stereostructure **20**[14] and not as a half-chair as earlier assumed.[8] Dreiding models indicate that slight distortion of the half-boat can give the right dihedral angles for the observed equal and large coupling.



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A second noteworthy feature in the NMR spectrum of **12** and **13** was the slightly broadened singlet type signal for the 5 aromatic protons of the phenyl group at δ 7·3 and not the expected 2 proton low field multiplet centred around δ 7·90 and a 3 proton high field multiplet centred around δ 7·40 characteristic of a benzoyl group.[15] Further the C-8 proton signal present in the NMR spectrum of **6** at δ 6·3 is shifted downfield in the spectra of **12** and **13** by only 0·28 and 0·12 ppm respectively to 6·58 and 6·42. In fact in the entire series **14** to **18**, the chemical shift of the C-8 proton was 6·52 ± 0·07

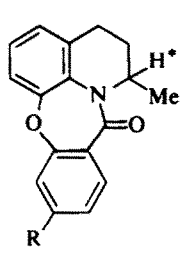
*See footnote † on previous page.

†In DMSO-d_6 again at 40° probe temperature, there was no evidence for two species in the 60 Mc spectra.

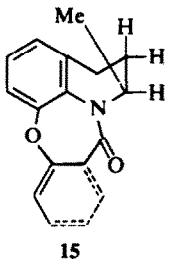
ppm, whereas in the N-acetyl derivative **19**, the signal of this proton was at about 7 ppm. These data require that the aryl group in N-aroyl tetrahydroquinaldines **12** to **18** is noncoplanar with the C=O group and the benzo ring. The latter feature would have been rendered difficult anyhow by interaction between the *ortho* proton of the phenyl ring and C-8 proton. The *para* proton in aniline is reported to be shifted downfield by 0·5 ppm on acetylation.[16,17] In the absence of specific field effects due to C=O or other groups, the deshielding of *ortho* protons in aroyl anilines can be then expected to be around 0·5 ppm. Since the downfield shift of the C-8 proton in aroyl derivatives of tetrahydroquinaldine is less than 0·5 ppm, the aryl groups in **12** to **18** can be expected to be considerably twisted out of the amide carbonyl plane so as to partially shield the C-8 protons. It was further noted that although the C-2 protons in **12** to **18** were deduced to lie in the plane of the aroyl carbonyl group, their chemical shifts were practically the same (4·85 ± 0·017 ppm) for a variety of *para* substituents in the aroyl group such as NO_2, F, Cl, Br, OCH_3 and NH_2. This becomes understandable if the aryl group is not effectively conjugated with the C=O group. Otherwise it would be reasonable to expect that variation in the strength of the C=O group due to electron-releasing and electron-withdrawing substituents would be reflected in its field effect. The above observations then lead to the stereostructure **20** for N-aroyltetrahydroquinaldines in solution. This has been found to be the case in the solid state as indicated by single crystal X-ray analysis of the bromoderivative **14**.[10]

The signals due to the starred proton in the NMR spectra of pyridodibenzoxazepines **21–24**[18] appear as slightly broadened sextets with a spacing of 6·5 Hz, exactly as in **12–19**. It is reasonable to conclude that this proton has the equatorial, and the Me group the axial conformations in the half-boat form of the tetrahydropyridine ring. Dreiding models show that the plane of the substituted aroyl ring deviates considerably from that of the C=O group. Consequently, varying R from NO_2 to NH_2 fails to produce any change in the chemical shift of the starred proton (5·25 ppm in all the derivatives). The stereostructure **25** shown for these compounds has been substantiated by single crystal X-ray analysis of **22**.[10]

The difference in the conformation of the tetrahydropyridine ring in **20** and **25** on the one hand and **5** and **8** on the other deserves comment. Dreiding models indicate that in **20** (and in **25**), the tetrahydropyridine ring goes into the half-boat form readily, whereby the axial Me group at C-2 avoids the 1,3-interaction with a hydrogen which it would face in a half-chair conformation. The half-boat form has no 1,4-flag-pole interaction because the N atom at 1 is part of a planar amide function. On the other hand, the rigidity induced in Dreiding



21: R = H
22: R = Cl
23: R = NO_2
24: R = NH_2



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models by the 6-membered C-rings in **5**, **7**, **8** and **9** appears to constrain the tetrahydropyridine ring to remain in the half-chair form. It would be interesting to study the conformation of this ring in a derivative of **5** carrying an extra Me group in the 4-position of the tetrahydroquinoline moiety *cis* to the one at C-2. This would give relative ideas of steric repulsion between two axial Me groups versus Me and CO groups. The preparation of such a derivative from *cis*-2,4-dimethyl-1,2,3,4-tetrahydroquinoline is under way.

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