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CONFORMATION OF MEDIUM SIZED RING AMINES. NMR STUDIES OF N-ACYL DERIVATIVES.[1]

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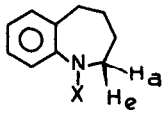
While conformational studies in medium sized rings[2] are complicated by the flexibility exhibited by these compounds, the presence of a double bond as in cycloheptenes simplifies the system to a flexible boat and a reasonably rigid chair conformation.[3] Azacycloheptene (benzazepine) derivatives have been well described from the synthetic point of view and many of them show interesting pharmacological properties.[4] However, in contrast to indolines and tetrahydroquinolines, no detailed nmr and conformational analysis of N-acyltetrahydrobenz[b] azepines has been reported.

We found that N-acyltetrahydrobenzazepines 1b-1d exhibit at room temperature a downfield shift for one of the hydrogens (H_e) of ca. 1.9 ppm with respect to the next lowest CH_2 signal. Although 1b and some derivatives had been reported,[5] no mention of the low field proton absorption at δ 4.66[6] was made. Neither the unsubstituted 7-membered ring 1e nor its N-formyl derivative 1a, nor the 5- and 6-membered ring N-acetyl analogs 2b and 3b exhibit this phenomenon.



1a, X: CH (=O)

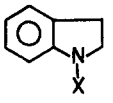
1b, X: C(=O)CH3

1c, X: C(=O)CMe3

1d, X: C(=O)-Ph

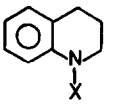
1e, X: H

1f, X: C(=O)-Me, $H_e = H_a$ = D



2a, R: CH (=O)

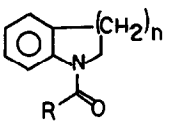
2b, R: CMe (=O)



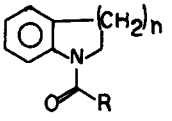
3a, X: CH (=O)

3b, X: CMe (=O)

3c, X: C(=O)CMe3



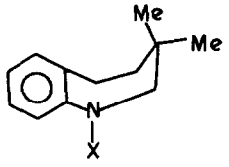
4a



4b

The downfield shift, in 1b can be accounted for by either a boat or a chair conformation of the 7-membered ring in which the amide carbonyl assumes coplanarity with the equatorial hydrogen at C-2. The diamagnetic anisotropic effect of a carbonyl group on properly positioned β-hydrogens[7] and of N-acyl groups on protons in acetamides and formamides is well known.[8] The fact that one is dealing specifically with a C-2 hydrogen in 1b is demonstrated by the spectrum of the d_2-derivative 1f in which the low field absorption vanishes.

In order to shed further light on the conformation of these tetrahydrobenzazepines we prepared a number of specifically substituted derivatives for nmr studies. For instance, the dimethyl derivative 6b, for which the boat conformation 5 can be discounted because of steric crowding, also shows one proton at low field (δ 4.58). Furthermore, the pivaloyl derivatives 1c, 6c, and 7c still exhibit this phenomenon, yet the required coplanarity between a C-2 proton



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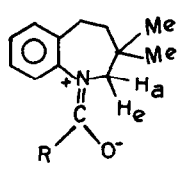
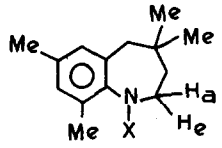


6a, R: H

6b, R: Me

6c, R: CMe_3

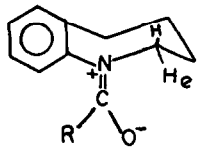


7a, X: CH (=O)

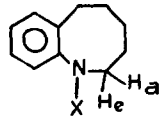
7b, X: CH (=O), $H_a = H_e = D$

7c, X: $CCMe_3$ (=O)

7d: X: H



8



9a, X: CH (=O)

9b, X: CMe (=O)

9c, X: CMe (=O); $H_e = H_a = D$

9d, X: H

and the amide carbonyl would cause inadmissably high steric interactions between the t-butyl group and the peri hydrogen (or methyl group in 7c). These results are best accommodated by a chair conformation with a high degree of exocyclic N=C double bond character in the amide function as shown in 8. Models indicate that in this conformational structure the C-2 equatorial hydrogen (H_e) lies in the plane of the N=C-O system and thus gets highly deshielded.

Furthermore, the $\underset{+}{N}{=}C\overset{O^-}{\underset{R}{<}}$ plane forms a dihedral angle of about 80° with the plane of the benzene ring so that large R groups can be readily accommodated.

In amides 2, one finds from scale models that the $\underset{+}{N}{=}C\overset{O^-}{\underset{R}{<}}$ system is forced to be nearly coplanar with the benzene ring resulting in strong interactions between the R of the amide and the peri hydrogen. Hence, it is not surprising that, whereas the formyl derivative 2a was found to exist mainly (75%) as the exo conformer 4a, the acetyl compound is almost entirely in the endo conformation 4b.[9] In the 6-membered ring derivatives 3 there is less coplanarity between the $\underset{+}{N}{=}C\overset{O^-}{\underset{R}{<}}$ and the benzene ring and indeed one finds that the acetyl compound 3b is able to accommodate the exo conformation (ca. 90%) while the more crowded pivaloyl derivative 3c appears to exist as the endo conformer.[9] We found that compounds 1b-1d exist almost entirely in the exo configuration 4a.[10] The fact that this applies also to the pivaloyl derivative 1c indicates a lack of steric interaction between the t-butyl group and the peri hydrogen and is consistent with our model.

Unlike the seven membered ring exo compounds, neither of the exo conformers of the smaller ring systems (i.e., 2b, 3b) show the dramatic deshielding of a coplanar hydrogen at C-2. We find that in the conformational analysis of these ring systems it is necessary to consider not only the exo-endo equilibration due to restricted rotation about the N-C bond as was discussed by many workers but also ring flipping. In the latter equilibration, the $\underset{+}{N}{=}C\overset{O^-}{\underset{R}{<}}$ moiety has to pass through a conformation in which it becomes coplanar with the aromatic ring and hence interaction with the peri substituent can prevent such a conformational flip.

Examination of scale models indicate that ring flipping should have a lower energy barrier in 2 and 3 than in 1. Hence conformational flipping in the exo isomers of 2 and 3 results in a single absorption of average deshielding (δ 3.8 - 4.1) for both C-2 protons.[11] On the other hand, the C-2 protons of the exo isomers of 1 exhibit two distinct absorptions, one at very low field (∿ δ 4.6) for H_e and one at higher field (δ < 3.0) for H_a. That we are indeed dealing with a rather rigid seven-membered ring with a high barrier to ring flipping is indicated by the following data. In 6b in which H_e is shifted to δ 4.58 the methyl groups at C-3 are nonequivalent. However, in 6a where H_a and H_e appear together at δ 3.8 indicating equilibration via ring flipping, the geminal methyl groups are magnetically equivalent. By placing a methyl substituent in the peri position, we were able to prevent ring flipping so that now even the formyl derivative 7a shows a downfield shift for H_e at δ 4.47 (which vanishes in 7b) and nonequivalent geminal methyl groups. (In the unsubstituted amine 7d these methyl groups appear as a singlet.) Similar results are found for the pivaloyl derivative 7c.

Furthermore the formyl protons for the exo configuration in 1a are more shielded (δ 8.23) than the corresponding protons in the exo configurations of 2a (δ 8.89)[9a] or 3a (δ 8.68)[9a,12] due to the greater divergence between the planes of the amide function and of the aromatic ring. Especially in 7a (exo) where the ring conformation is frozen so that the formyl proton is more under the shielding influence of the aromatic ring, its absorption is found at δ 8.02. In consonance with our conformational assignments is also the fact that the uv spectrum of 1b shows a lack of conjugation between the amide and the aromatic chromophore.[5a]

The phenomenon of deshielding of the equatorial proton H_e is also observed in the N-acetyl

benzazocine 9b but not in compounds 9a and 9d nor in the dideuterated compound 9c. Further work on these medium sized rings is in progress.

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References and Notes

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6. Nmr data obtained in $CDCl_3$.
7. L.M. Jackman and S. Sternhell, Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon Press (1969), p. 88.
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10. A reliable assignment of exo-endo configuration in 2 and 3 is possible from the integration of the signals of the peri hydrogen (ref. 9). This is not feasible in the 7-membered ring analogs because of the large deviation from planarity between the amide and the aromatic ring. However, the percentage of the exo conformer in 1b-1d can be deduced by integrating the signal of H_e. In the case of the formyl derivative 1a which does not exhibit a downfield shift for H_e, the proportions of each conformer can be obtained from the relative intensities of the two distinct signals exhibited by the formyl proton.
11. However, in 4-substituted N-acyl piperidines distinct absorptions for H_e and H_{ax} at C-2 were observed. See for example: D.M. Lynch and W. Cole, J. Org. Chem. 31, 3337 (1966). See also J.B.Hester, J. Org. Chem. 32, 3804 (1967) in azepino-indoles.
12. This shift was reported in chloroform for the mixture of isomers (ref. 9a), however, the compound was shown to be 90% exo. Its formyl proton was reported at δ 8.81 in acetone (ref. 9e).