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BARRIERS TO RING REVERSAL IN DIAZEPAM DERIVATIVES[1]

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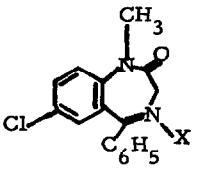
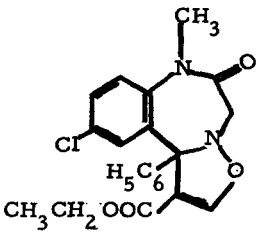
While cycloheptane and other saturated 7-membered rings are quite flexible and exhibit only low barriers to pseudorotation, the incorporation of unsaturation, in cycloheptatriene constrains the system so that only a single conformational energy minimum is of any importance, the boat conformation.[3] The important pharmaceuticals diazepam 1, and chlordiazepoxide represent analogs of cycloheptatriene which adopt boat conformations and



1, X = :

2, X = O

3



4

also,exhibit much higher barriers to ring reversal, 17.7 kcal/mol[4] and 15.2 kcal/mol[5,6] respectively, than that of cycloheptatriene, 7.2 kcal/mol.[3] The large increases are due to the replacement of double bonds by amide or amidine groups[7] and by ring annellation.[8] The N-methyl group in 1 also is involved in a peri-like interaction in the planar or nearly planar transition state which accounts for about 5.6 kcal/mole of the overall barrier.

In contrast with the high barrier observed for 1 and other diazepam derivatives, Sadée has reported that diazepam-N-oxide 2, does not exhibit chemical shift nonequivalence of the ring methylene protons in chloroform solvent and attributed this to rapid ring reversal.[5] He attributed the diminution of the ring reversal barrier attendant upon N-oxidation to stabilization of the planar transition state by conjugation as expressed in canonical structure 3. We have reinvestigated this compound and now report its barrier and that of the related compound 4.[9]

The diastereotopic ring methylene protons of 2 appear as an apparent A_2 singlet in the room temperature nmr spectrum in chloroform-d as reported.[5] However, when the spectrum is measured in toluene-$\underline{d}_8$/acetone-$\underline{d}_6$, the methylene protons exhibit observable chemical-shift nonequivalence (Figure 1). The rate constant at the coalescence point was determined by complete lineshape analysis and used to obtain the free energy of activation for ring reversal: $\Delta\nu$ = 5.6 Hz, T_c = 61° , $\Delta G^{\ddagger}$ = 17.6 kcal/mol. This barrier is unchanged from that in diazepam itself in this solvent: $\Delta\nu$ = 68 Hz, T_c = 89°, $\Delta G^{\ddagger}$ = 17.7 kcal/mol. Thus resonance of the type discussed above need not be postulated. The 1,3-dipolar adduct of 2 with ethyl propiolate exhibits a comparable barrier. Because of the presence of an additional unit of asymmetry in 4 the two boat conformers are diastereomeric,[9] and the nmr spectrum in toluene-$\underline{d}_8$/acetone-$\underline{d}_6$ features two singlets for the two N-methyl groups in a ratio of 3:2. The coalescence of the two N-methyl singlets provided the free energy of activation for conversion of the minor to major isomer: $\Delta\nu$ = 40 Hz, T_c = 79°, $\Delta G^{\ddagger}$ (minor to major isomer) = 17.7 kcal/mol. These results suggest that, contrary to the suggestions of Sadée, the type of substitution at the imino nitrogen does not affect the ring reversal barrier.

However, oxidation at imino nitrogen does effect a striking diminution in the magnitude of the chemical shift difference between the diastereotopic ring methylene protons in diazepam and its N-oxide. The large chemical shift difference in diazepam has been attributed to long range shielding of one of these protons by the anisotropic chlorophenyl ring.[4] The small difference observed in the nitrone casts doubt on this assessment. The major effect has been on the chemical shift of the upfield proton although the boat conformation of the seven-membered ring must remain relatively unaffected by N-oxidation. This suggests that the electronic structure of the imino nitrogen in diazepam is far more important in determining the magnitude of the nonequivalence than has been heretofor realized.

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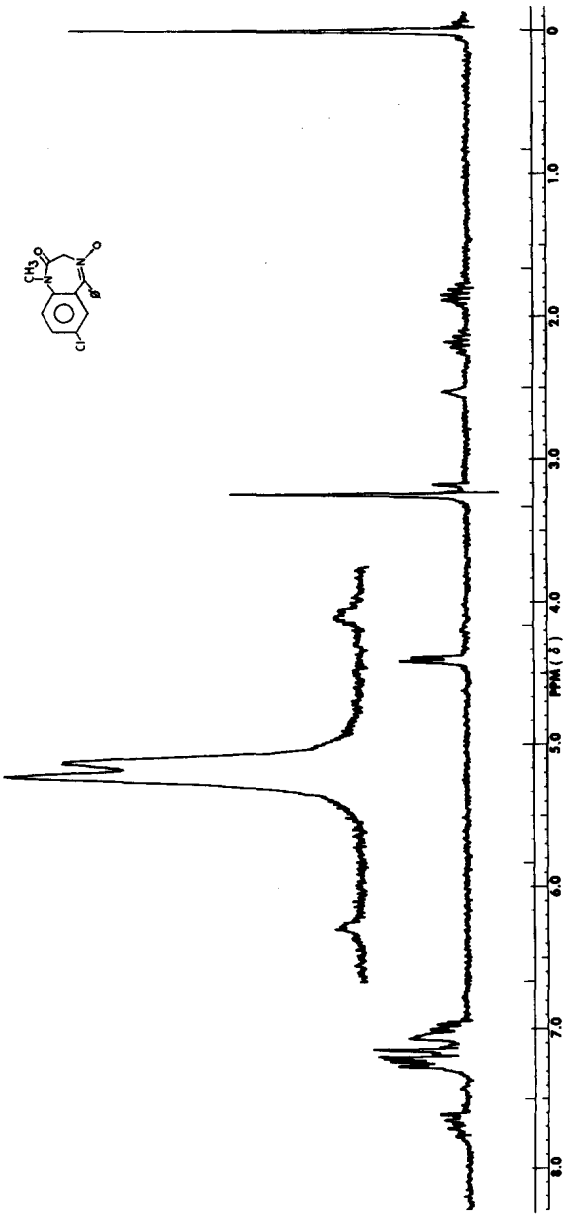
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O
N
N
O
Cl
0
1.0
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