4. SUMMARY

The preferred conformations of twelve N-ethoxycarbonyl-piperidines, three N-ethoxycarbonylhexahydrodiazepines, three N-acylazabicyclononanes, four N-acyltetrahydrobenzodiazepines and four 4-cyano-4-phenylaminopiperidines have been determined using $^1$H & $^{13}$C NMR, COSY (Correlation Spectroscopy), $^1$H-$^{13}$C HETCOR (Heterocorrelation spectroscopy), NOE difference (Nuclear Overhauser Effect), and variable-temperature NMR spectral studies. Dihedral angles between the vicinal protons of these compounds were calculated from the coupling constants by DAERM (Dihedral Angle Estimation by Ratio Method) and these angles were used to determine the preferred conformations of these compounds. In order to know the preferred conformations in the solid state, X-ray crystal structure was determined for six compounds.
1. N-Ethoxycarbonylpiperidines

The preferred conformations of twelve N-ethoxycarbonyl-r-2,6-diphenylpiperidines (28-33 & 36-41) have been determined. The IR, \(^1\text{H} \text{NMR}, \text{\(^{13}\text{C} \text{NMR}}\) and mass spectral data and the calculated dihedral angles indicated that the N-ethoxycarbonyl-r-2,6-diphenylpiperidin-4-one (28), N-ethoxycarbonyl-t-3,5-dimethyl-r-2,6-diphenylpiperidin-4-one (33), N-ethoxycarbonyl-r-2,6-diphenylpiperidine (36) and N-ethoxycarbonyl-t-3-methyl-r-2,6-diphenylpiperidine (37) adopt flattened-boat conformations with N1 and C4 occupying the prow and stern positions while the X-ray crystal structures of 33 and 36 showed a distorted boat conformations with C2 and C5 at the prow and stern positions. The other N-ethoxycarbonyl derivatives (29-32 & 38-41) prefer twist-boat conformations in solution. The preferred conformation of 32 obtained through X-ray crystallography is also a twist-boat with C2 and C5 occupying the prow and stern positions which is similar to the preferred conformation in the solution state. The barriers for the N-CO rotation determined using variable temperature \(^1\text{H} \text{NMR} \) studies for the N-ethoxycarbonyl derivatives 28 & 31 were 47.9 & 50.5 \( \text{kJ mol}^{-1} \), respectively. The lack of splitting even at \(-80^\circ \text{C}\) in the \(^1\text{H} \text{NMR} \) spectra recorded for the N-ethoxycarbonyl-r-2,6-diphenylpiperidine (36) revealed that its energy barrier for N-CO bond rotation is lower than that for the corresponding N-ethoxycarbonylpiperidin-4-one (28). The N-CO rotation barriers for the N-ethoxycarbonylpiperidines (28-33 and 36-41) are lower than those observed for N-NO rotation in
N-nitroso-$\alpha$-2,$\gamma$-6-dimethylpiperidine and N-nitroso-$\alpha$-2,$\gamma$-6-diphenylpiperidines.

2. N-ethoxycarbonyl- & N,N'-diethoxycarbonylhexahydroidiazepines

The preferred conformations of three N-ethoxycarbonyl derivatives of $\alpha$-2,$\gamma$-7-diphenylhexahydro-1,4-diazepin-5-ones 45-47 have been studied using NMR spectral techniques. The $N^1,N^4$-diethoxycarbonyl-$\alpha$-2,$\gamma$-7-diphenylhexahydro-1,4-diazepin-5-ones 45 & 46 were found to prefer flattened boat conformations with fast equilibrium between two N-CO rotamers while the 4-ethoxycarbonyl-$t$-3-isopropyl-$\alpha$-2,$\gamma$-7-diphenylhexahydro-1,4-diazepin-5-one (47) was found to prefer a chair conformation with the N-COOEt group locked in one rotameric state. Dynamic $^1$H NMR studies have been carried out on the $N^1,N^4$-diethoxycarbonyl derivatives 45 & 46 and the barriers for the N-CO rotation were found to be 49.9 & 58.0 kJ mol$^{-1}$, respectively. These barriers are much lower than those observed for N-nitroso- & N-formyl-$\alpha$-2,$\gamma$-7-diphenylhexahydro-1,4-diazepin-5-ones (90.0 & 84.4 kJ mol$^{-1}$, respectively) indicating a fast equilibrium in 45 & 46 at room temperature.

3. N-acetylazabicyclononane and N-acetyl- & N-ethoxycarbonyl-diaza/bicyclononanes

The conformational preferences of N-acetyl-$\alpha$-2,$\gamma$-4-diphenyl-3-azabicyclo[3.3.1]nonane (48) and N-ethoxycarbonyl- & N-acetyl-$\alpha$-2,$\gamma$-4,t-6,t-8-tetraphenyl-3,7-diaza/bicyclo[3.3.1]nonanes (49 & 50, respectively) have been studied using NMR spectral techniques. The N-acetyl-$\alpha$-2,$\gamma$-4-diphenyl-3-azabicyclo[3.3.1]nonane (48) was found to prefer a twin-chair conformation
with a slight flattening at the nitrogen end. In the case of diazabicycles 49 & 50 both the ethoxycarbonylation and acetylation reactions were found to take place only at the boat end of the parent amine (chair-boat) and the preferred conformation was found to be twin-chair with flattening at the C1-C2-N3-C4-C5 part of the ring in both cases. The energy barrier for the N-CO rotation in N-ethoxycarbonyl derivative 49 has been determined from the dynamic $^1$H NMR studies and the barrier for N-CO rotation was found to be 50.8 kJ mol$^{-1}$, much less than that of the N-nitroso analogs.

4. N-acyltetrahydrobenzodiazepines

The 5-benzoyl- & 5-phenylcarbamoyltetrahydro-2,2,4-trimethyl-1H-1,5-benzodiazepines (53 & 54) prefer boat conformations with exo orientation of the acyl groups at N5. The X-ray crystal structure of 54 also showed a boat conformation. The N$^1$,N$^5$-diacetyl derivative 55 prefers to adopt a boat conformation with endo & exo orientations of the acetyl groups at N1 & N5 positions, respectively. The N$^1$,N$^5$-diformyl derivative 56 was found to exist in an equilibrium mixture of major and minor conformers and the orientations of the formyl groups at N1 & N5 positions of both the conformers were endo & exo, respectively. The major conformer prefers a boat conformation while the minor one prefers to adopt a chair conformation. The average energy barrier for the interconversion between the major and minor forms was found to be 79.7 kJ mol$^{-1}$ on the basis of the $^1$H dynamic NMR spectral studies.
5. 4-cyano-4-phenylaminopiperidines

The stereochemistry of four α-(phenylamino)nitriles (57-60) derived from \( \text{R-2,\text{C-6-diphenylpiperidin-4-ones (5a-d) has been determined using NMR spectral techniques. DAERM (Dihedral Angle Estimation by the Ratio Method) calculation was used to estimate the required dihedral angles. The cyano group was found to occupy the axial position with the phenylamino group being in the equatorial orientation. While the C3 unsubstituted aminonitrile 57 appeared to prefer a chair conformation, the presence of alkyl substituents at C3 position in the aminonitriles 58-60 has caused a flattening at C3 end. The predominant formation of one of the two possible isomers has been rationalized by invoking the Cieplak's concept of \( \pi \)-facial diastereoselectivity in which the nucleophilic attack of cyanide over the imine takes place from the axial side. }\)