The Stereochemistry of Some Dihydro-1,3-oxazine Derivatives

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The conformations of one dihydro-1,3-benzoxazine and two dihydro-1,3-naphthoxazines were studied by calculating and measuring their dipole moments.

A "semi-chair" form with a quasi-axial position of the N-substituent was found to be most probable.

In our earlier papers (1, 2), we have reported the results of antitumor screening of a number of dihydro-1,3-oxazine derivatives.

The stereochemistry of the dihydro-1,3-oxazine system fused with an aromatic ring has so far been left unexplored. There are, however, papers concerned with the spatial structure of tetralin derivatives (3, 4, 5). As far as the earlier investigations on some related systems (morpholine (6), 1,3-dioxane (7), tetrahydro-1,5-oxazine (8, 9, 10), 5-nitro-tetrahydro-1,3-oxazine (11), and others) are concerned, it was stated that some ring deformation could take place when substituting one or more carbon atoms by one or more hetero atoms in an alicyclic compound. However, such substitution did not significantly effect the geometry of the molecule. Furthermore, in all the cases examined, the chair conformation as in cyclohexane was observed. It might be expected, therefore, that the structure of dihydro-1,3-oxazines condensed with an aromatic ring should be reasonably close to that of tetralin.

Three compounds were the subject of this investigation: 1,3,4-dihydro-3-cyclohexyl-6-methyl-2H-1,3-benzoxazine (12), II (R = CH₃-), 2,3-dihydro-2-methyl-1H-naphth-[1,2-e]-1,3-oxazine (13), II (R = p-CH₃C₆H₄-), 2,3-dihydro-2-p-tolyl-1H-naphth[1,2-e]1,3-oxazine (14).

The conformation of dihydro-1,3-benzoxazine and naphthoxazine was studied with the aid of Dreiding Stereomodels. Two basic "semi-chair" and "semi-boat" structures A and B, respectively, were distinguished.

Identical forms are possible in the instance of dihydro-1,3-naphthoxazines. Two of them, A²N and B²N, proved to be the most probable on the basis of our experiments and calculations.
The bond lengths and valency angles used in our calculations were those given under (4) and (5) in Table I. The bond moments were taken as follows: C - O, 0.85 D; C - N, 0.40 D; and H - C, 0.30 D. The results of the calculations are tabulated in Table II.

TABLE II

<table>
<thead>
<tr>
<th>Compound</th>
<th>μ/D/ Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1.04</td>
</tr>
<tr>
<td>II</td>
<td>1.03</td>
</tr>
<tr>
<td>III</td>
<td>1.01</td>
</tr>
</tbody>
</table>

As it may be seen, the experimental values fall fairly close to those calculated for A² and B¹ conformations.

Atoms (1) and (10) have no hydrogen substituents. Subsequently they cannot influence in any way the N-substituent (i.e. in position 3) through 1,3-interaction. This would support form A². In form B¹, the N-substituent is almost eclipsing the hydrogen attached to C₄ and this again supports conformation A². Nevertheless the possibility of a A² ⇌ B¹ equilibrium should also be taken into consideration.

It is hoped that further research, which is now in progress, will bring an unequivocal answer to this question.

**EXPERIMENTAL**

The dipole moment measurements were carried out by the heterodyne-beat method in a benzene solution at 20° with the aid of "DMO1 Dipol-meter" (Wissenschaftliche Technische Werkstätte, Weilheim).

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**REFERENCES**


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