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

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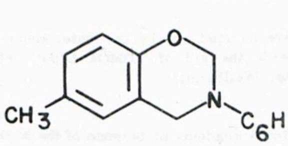
The conformations of one dihydro-1,3-benzoxazine and two dihydro-1,3-naphthoxazines were studied by calculating and measuring their dipole moments.

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

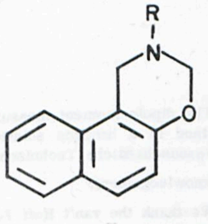
In our earlier papers (1, 2), we have reported the results of antitumor screening of a number of dihydro-1, 3-oxazine derivatives.

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, 3-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: I, 3,4-dihydro-3-cyclohexyl-6-methyl-2H-1,3-benzoxazine (12), II (R = CH_3-), 2,3-dihydro-2-methyl-1H-naphth-[1,2-e]-1,3-oxazine (13), II (R = p-$CH_3C_6H_4$-), 2,3-dihydro-2-p-tolyl-1H-naphth[1,2-e]1,3-oxazine (14).

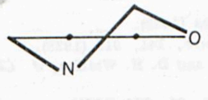


I

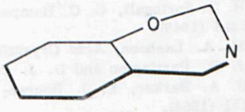


II

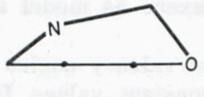
The conformation of dihydro-1,3-benzoxazine and naphthoxazine was studied with the aid of Dreiding Stereomodels. Two basic "semi-chair" and "semiboat" structures A and B, respectively, were distinguished.



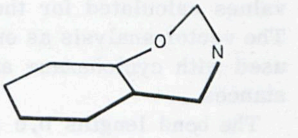
SIDE VIEW



A

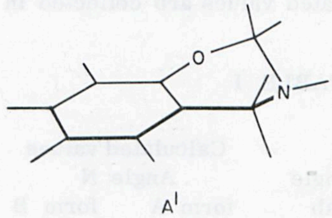


SIDE VIEW

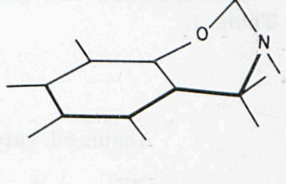


B

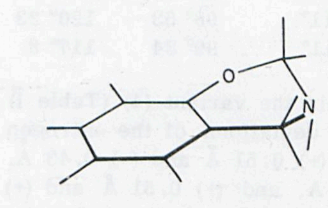
Each of them can theoretically exist in two forms depending on the position of the substituent at the nitrogen atom. Hence, four conformations, A^1, A^2, B^1 and B^2, respectively, may be expected in dihydro-1,3-oxazines condensed with aromatic rings in the positions five and six.



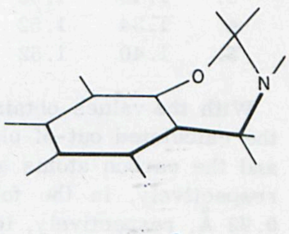
A^1



B^1

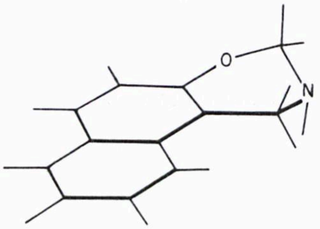


A^2

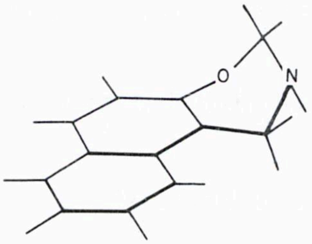


B^2

Identical forms are possible in the instance of dihydro-1,3-naphthoxazines. Two of them, A^2N and B^1N, proved to be the most probable on the basis of our experiments and calculations.



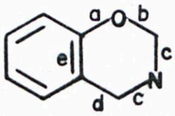
A²N



B¹N

In order to establish the actual conformation of the compounds under investigation, we have measured their dipole moments and compared them with the theoretical values calculated for the four possible conformations. The vector analysis as outlined by Corey (15) have been used with cyclohexane and cyclohexene as model substances.

The bond lengths b, c and e, and valency angles ea, ed, bc, and cd were taken as constant values from the literature (16).



b = 1.43 Å   angle ea = ed = 120°
c = 1.47 Å   angle bc = cd = 109° 28
e = 1.40 Å

With regard to the bond lengths a and d and valency angles ab, various values existing in the literature (16) were used and enabled us to calculate the values of the angle at N-atom *i.e.* cc.

The assumed and calculated values are collected in Table I.

TABLE I

	Assumed values			Calculated values	
			Angle	Angle N	
Variant	a Å	d Å	ab	form A	form B
1.	1.40	1.50	111°	100° 32	122° 57
2.	1.40	1.52	108°	97° 58	120° 27
3.	1.40	1.52	114°	104° 42	124° 42
4.	1.34	1.52	111°	98° 53	120° 23
5.	1.40	1.52	111°	99° 34	117° 8

With the values obtained in the variant (4) (Table I) the calculated out-of-plane deviations of the nitrogen and the carbon atoms are (+) 0.51 Å and (-) 0.43 Å, respectively, in the form A, and (+) 0.51 Å and (+) 0.92 Å, respectively, in the form B. Analogously, the corresponding values based on the data of the variant (5) (Table I) are: (+) 0.52; (-) 0.40; (+) 0.52 and (+) 0.91 Å, respectively.

As can be seen, the nitrogen valency angles depart rather considerably from the usual values.

In several compounds, however, such deviations are known to be even much greater (4, 17).

Consequently, we have calculated the theoretical values of the dipole moments for I, II and III, which proved to be identical.

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

μ/D/ Calculated

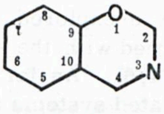
Reference to Table I	form A^1	form A^2	form B^1	form B^2
4.	1.59	1.03	1.09	1.25
5.	1.33	1.11	0.92	1.35

The experimental values are presented in Table III.

TABLE III

μ/D/ Measured

Compound	μ/D/
I	1.04
II	1.03
III	1.01



As it may be seen, the experimental values fall fairly close to those calculated for A^2 and B^1 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 A^2. In form B^1, the N-substituent is almost eclipsing the hydrogen attached to C_4 and this again supports conformation A^2 Nevertheless the possibility of a $A^2 \rightleftarrows B^1$ 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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