

Institute of Organic Synthesis, Polish Academy of Sciences

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

J. B. Chylińska and T. Urbąński

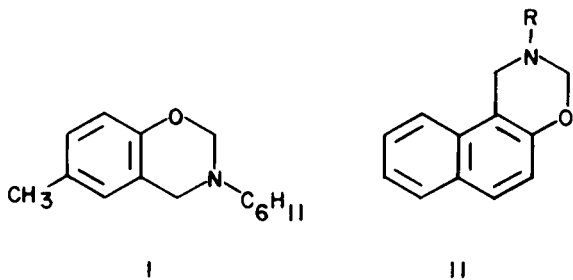
The conformations of one dihydro-1,3-benzoxazine and two dihydro-1,3-naphthoxazines were studied by calculating and measuring their dipole moments.

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.

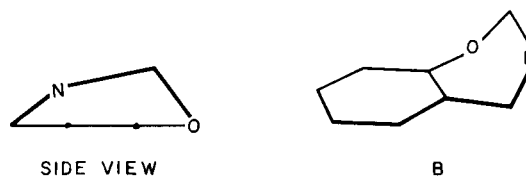
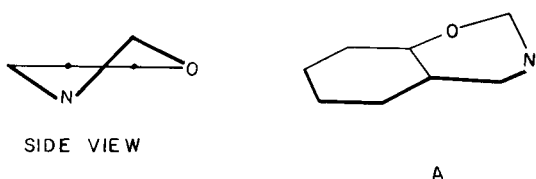
The stereochemistry of the dihydro-1,3-oxazine system fused with an aromatic ring has so far been left unexplored. There are, however, papers concerned with the spatial structure of tetralin derivatives (3,4,5). As far as the earlier investigations on some related systems (morpholine (6), 1,3-dioxane (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 = CH₃-), 2,3-dihydro-2-methyl-1H-naphth-[1,2-e]-1,3-oxazine (13), II (R = *p*-CH₃C₆H₄-),

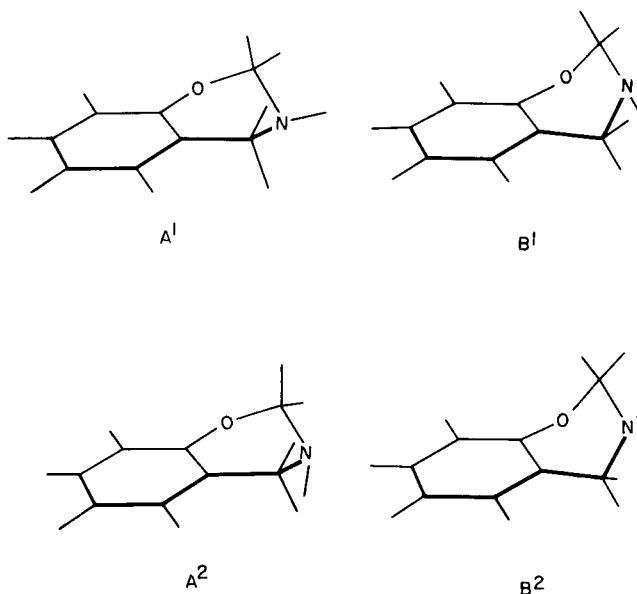


2,3-dihydro-2-*p*-tolyl-1H-naphth[1,2-e]1,3-oxazine (14).

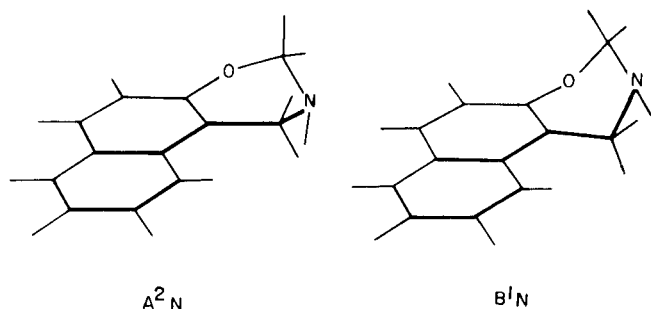
The conformation of dihydro-1,3-benzoxazine and naphthoxazine was studied with the aid of Dreiding Stereomodels. Two basic "semi-chair" and "semi-boat" structures A and B, respectively, were distinguished.



Each of them can theoretically exist in two forms depending on the position of the substituent at the nitrogen atom. Hence, four conformations, A¹, A², B¹ and B², respectively, may be expected in dihydro-1,3-oxazines condensed with aromatic rings in the positions five and six.

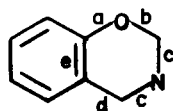


Identical forms are possible in the instance of dihydro-1,3-naphthoxazines. Two of them, A²N and B¹N, proved to be the most probable on the basis of our experiments and calculations.



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).



$$\begin{aligned} b &= 1.43 \text{ \AA} \\ c &= 1.47 \text{ \AA} \\ e &= 1.40 \text{ \AA} \end{aligned}$$

$$\begin{aligned} \text{angle } ea &= ed = 120^\circ \\ \text{angle } bc &= cd = 109^\circ 28' \end{aligned}$$

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

Variant	Assumed values			Calculated values	
	a \AA	d \AA	Angle 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 \AA and (-) 0.43 \AA, respectively, in the form A, and (+) 0.51 \AA and (+) 0.92 \AA, 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 \AA, 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.

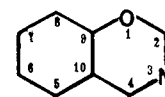
TABLE II

Reference form to Table I	μ/D / Calculated			
	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

Compound	μ/D / Measured
I	1.04
II	1.03
III	1.01



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 \rightleftharpoons 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 Werkstatt, Weilheim).

Acknowledgement.

We thank the van't Hoff Foundation, Royal Academy of Science of the Netherlands for the gift of Dreiding Stereomodels.

We also wish to thank Mr. Jerzy Norwa, M.S., for his assistance in the dipole-moment calculations.

REFERENCES

- (1) J. B. Chylińska and T. Urbański, *Bull. acad. polon. sci. Sér. sci. Chim., géol. et géograph.*, **7**, 635 (1959).
- (2) J. B. Chylińska, T. Urbański and M. Mordarski, *J. Med. Chem.*, **6**, 484 (1963).
- (3) A. Kossiakof and H. D. Springall, *J. Am. Chem. Soc.*, **63**, 2223 (1941).
- (4) H. D. Springall, G. C. Hampson, C. G. May and H. Spedding, *J. Chem. Soc.*, 1524 (1949).
- (5) M. A. Lasheen, *Acta Crystallogr.*, **5**, 593 (1952).
- (6) J. R. Partington and D. J. Comber, *Nature*, **141**, 918 (1938).
- (7) S. A. Barker, E. J. Bourne, M. Stacey and D. H. Whiffen, *J. Chem. Soc.*, 171 (1954).
- (8) W. Stfthmer and W. Heinrich, *Chem. Ber.*, **84**, 224 (1951).
- (9) N. L. Wendler, *Experientia*, **9**, 412 (1953).
- (10) R. Lukes, K. Blaha and Y. Kovar, *Chem. listy*, **51**, 927 (1957).

- (11) D. Gürne and T. Urbafski, *J. Chem. Soc.*, 1912 (1959).
- (12) T. Urbafski and D. Gürne, Z. Eckstein and S. Slopek, *Bull. acad. polon. sci.*, Classe (III), 7, 397 (1955).
- (13) W. J. Burke, M. J. Kolbezen and S. C. Wayne, *J. Am. Chem. Soc.*, 74, 3601 (1952).
- (14) W. J. Burke, K. C. Mudrock and G. Ec, *ibid.*, 76, 1677 (1954).
- (15) E. J. Corey and R. A. Sneek, *ibid.*, 77, 2505 (1955).
- (16) L. E. Sutton, Ed., "Tables of Interatomic Distances and Configurations in Molecules and Ions", The Chemical Society, London, 1958.
- (17) M. Aroney, L. H. L. Chia and J. W. Le Fevre, *J. Chem. Soc.*, 4144 (1961).

Received December 19, 1963

Warsaw, Poland