SPATIAL STRUCTURE OF SOME 6-ALKYL-6-PHENYL-TETRAHYDRO-1,3-OXAZINES

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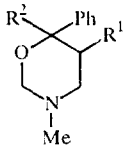
It is shown from ^{13}C NMR spectra and molecular mechanical calculations that 5,6-dialkyl-(or 6-alkyl-)-3-methyl-6-phenyltetrahydro-1,3-oxazines exist in a conformation with the phenyl group orientated axially. The relative configuration of the substituents on the $C_{(5)}$ and $C_{(6)}$ atoms of 5,6-dialkyl-3-methyl-6-phenyltetrahydro-1,3-oxazines is established.

In order to study the possibility of using substituted tetrahydro-1,3-oxazines in the preparation of biologically active materials, we made 5,6-dialkyl-(or 6-alkyl)-3-methyl-6-phenyltetrahydro-1,3-oxazines I-IV starting from the corresponding γ-aminoalcohols. The synthesis and spatial structure of compounds I-IV were described previously in [1]. Data from PMR spectroscopy allowed the authors of that paper to show from the values of the vicinal SSCC (spin−spin coupling constants) of the $H_2C_{(4)}$ and $H-C_{(5)}$ protons that the methyl group on $C_{(5)}$ of the oxazine ring has an axial orientation. However, the conclusion concerning the equatorial orientation of the phenyl group on $C_{(6)}$, drawn from the effect of the "aromatic solvent influence," does not appear to be completely unambiguous. In the present work, we have succeeded in answering the question of the orientation of substituents on $C_{(6)}$ with the aid of ^{13}C NMR.



I-IV

I $R^1 = H$, $R^2 = Me$; II $R^1 = R^2 = Me$; III $R^1 = H$, $R^2 = Et$; IV $R^1 = Me$; $R^2 = Et$

The chemical shift (CS) for the methyl group on $C_{(6)}$ in compound I (31.3 ppm) (Table 1) shows the group to be in an equatorial position. In fact, the expected value of the CS for an axially oriented methyl group in this case is ~25 ppm (in the model compound, 1,1,3-trimethylcyclohexane, the CS of the axial methyl group on $C_{(1)}$ is 24.86 ppm [2]). Replacement of the corresponding carbon atoms of the model with oxygen and nitrogen (β and δ effect of a heteroatom) cannot increase the CS of the atom under consideration by 6.8 ppm ($\delta_{exp} - \delta_{calc} = 31.3 - 24.5 = 6.8$ ppm). Thus, despite the greater bulk, the phenyl group in compound I occupies a predominantly axial position. The lower energy of conformer Ia compared to conformer Ib (Table 2) is predicted by a molecular mechanical calculation using strong field MM2P [4].

It follows from a comparison of the CS of the methyl groups on $C_{(6)}$ in compounds I and II that the appearance of a methyl group on $C_{(5)}$ causes a 6.8 ppm strong field shift in the signal of the CH_3 group on $C_{(6)}$. This strong field shift is caused by the γ effect [2, 3] and, in agreement with the stereochemical requirements necessary for the appearance of a γ effect, is only possible with a skewed arrangement of the vicinal methyl groups on $C_{(5)}$ and $C_{(6)}$ (with a transoid arrangement, this effect vanishes). In view of the axial arrangement of the methyl group on $C_{(5)}$ (from PMR data, Table 3) one can conclude that $CH_3C_{(6)}$ occupies an equatorial position. Thus, compound II is 3,5r,6-trimethyl-6t-phenyltetrahydro-1,3-oxazine and exists predominantly in conformation IIa.

M. V. Lomonosov Institute of Fine Chemical Technology, Moscow 117571. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 246-249, February, 1993. Original article submitted July 15, 1992.

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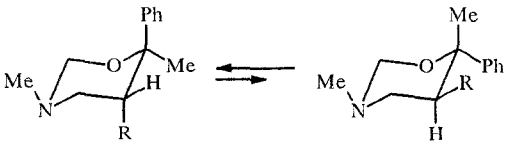
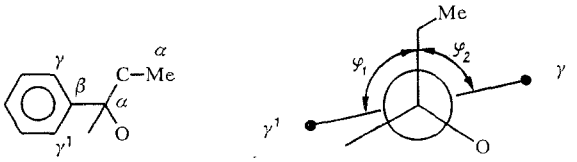


I, II a I, II b

I R=H, II R=Me

A lower energy for conformer IIa compared to IIb is also shown by a molecular mechanical calculation (Table 2).

Analysis of the ^{13}C NMR spectra of tetrahydrooxazines III-IV carried out in similar fashion to the foregoing leads to the conclusion that the ethyl groups in these compounds are arranged equatorially, which agrees with calculations. It should be noted that the difference in the CS of the methylene carbons of the ethyl groups ($\Delta\delta$ = 9.1 ppm) in oxazines III and IV exceed the expected value of the γ effect from a methyl substituent on $C_{(5)}$ by ~3 ppm. This "excess" difference in the CS may be due to a dissimilar orientation in oxazines III and IV of the methyl groups bound to the atoms under discussion (different α effects [2, 3]) and also to the conformational position of the phenyl substituent (dependence on angles φ_1 and φ_2, i.e., a γ effect from the ortho atoms).



Thus, despite the conclusions drawn in [1] on the basis of the effect of the "aromatic solvent influence" concerning the conformational position and relative configuration of substituents on $C_{(6)}$ in oxazines I-IV, the results of the analysis of ^{13}C NMR spectra and molecular calculations allow us to assert that the phenyl group in compounds I-IV has a predominantly axial orientation and, in oxazines II-IV, occupies a position to the methyl group on $C_{(5)}$.

TABLE 1. ^{13}C NMR Parameters of Tetrahydro-1,3-oxazines I-IV

Compound	Oxazine ring C atoms				Axial substituent C atoms				Phenyl group C atoms			
	$C_{(2)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	N—CH_3	$C_{(5)}$—CH_3	$C_{(6)}$—R		ortho	meta	para	quat
I	80,4	48,4	30,0	74,9	38,9	—	31,3	—	127,9	125,2	126,1	144,4
II	80,5	56,3	36,6	76,7	40,4	16,3	25,1	—	127,6	124,9	125,8	146,3
III	80,6	48,6	28,2	77,9	39,1	—	36,6	7,0	127,9	126,3	126,3	142,5
IV	80,3	56,6	36,1	79,0	40,5	16,7	27,5	6,5	127,5	125,3	125,6	144,3

TABLE 2. Energy Characteristics of Conformers I-III (a, b) and Their Occupancies, Calculated by Molecular Mechanics

Conformer	Ia	Ib	IIa	IIb	IIIa	IIIb
Heat of formation, kJ/mole	-140,33	-128,37	-164,93	-149,29	-159,20	-154,26
Steric energy, kJ/mole	55,94	96,23	61,42	77,32	61,13	66,11
Occupancy, %	99,2	0,8	99,8	0,2	88,0	12,0

TABLE 3. PMR Data for Tetrahydro-1,3-oxazines I-IV

Compound	Chemical shifts, δ, ppm	SSCC of ring protons, J, Hz
I	1,42 (3H, s, 6-CH_3); 2,88 (1H, m, 5*a*-H); 2,65 (1H, m, 5*e*-H); 2,38 (3H, s, N—CH_3); 2,13 (1H, m, 4*a*-H); 2,19 (1H, m, 4*e*-H); 4,04 (1H, d, 2*a*-H); 4,22 (1H, d.d, 2*e*-H); 5,88 6,00 (1H 4H, m, C_6H_5)	J_{2a2e} = 9,5; J_{2e4e} = 1,7; J_{4a4e} = 12,7; J_{4a5a} = 10,2; J_{4a5e} = 3,9; J_{4e5e} = 4,4; J_{4e5a} = 4,4; J_{5a5e} = 13,9
II	0,88 (3H, d, ^3J = 7,1 Hz, 5-CH_3); 1,58 (3H, s, 6-CH_3); 2,06 (1H, m, 5*e*-H); 2,25 (3H, s, N—CH_3); 2,68 (1H, m, 4*e*-H); 2,75 (1H, broadd, 4*a*-H); 4,07 (1H, d, 2*a*-H); 4,31 (1H, d d 2*e*-H); 7,20, 7,31 & 7,40 (1H, 2H & 2H, *p*-H, *m*-H, *o*-H arom	J_{2a2e} = 8,4; J_{2e4e} = 1,2; J_{4a4e} = 11,7; J_{4a5e} = 3,4; J_{4e5e} = 4,1
III	0,65, 1,68 =, 1,78 (3H, t, 1H, d.q, 1H, d.q, ABX$_3$, J_{AB} = 13,4, J_{AX} = J_{BX} = 7,6 Hz 6-CH_2CH_3); 2,07 (1H, m, 5*a*-H); 2,15 (1H, m, 5*e*-H); 2,36 (3H, s, N—CH_3); 2,62 (1H, m, 4*a*-H); 2,82 (1H, m 4*e*-H); 4,04 (1H, d, 2*a*-H); 4,19 (1H, d d, 2*e*-H); 7,25 &7,35 (1H & 4H, m C_6H_5)	J_{2a2e} = 9,4; J_{2e4e} = 1,7; J_{4a4e} = 12,7; J_{4a5a} = 9,5; J_{4a5e} = 5,1; J_{4e5a} = 4,2; J_{4e5e} = 4,2; J_{5a5e} = 14,2
IV	0,55, 1,55 & 2,58 (3H, t; 1H d.q 1H, d.q, ABX$_3$, J_{AB} = 14,9; J_{AX} = J_{BX} = 7,3 Hz 6-CH_2CH_3); 0,82 (3H, d ^3J = 7,1 Hz, 5-CH_3); 1,96 (1H, m, 5*e*-H); 2,22 (3H, s, N—CH_3); 2,65 (1H, m, 4*e*-H); 2,79 (1H, broad dd, 4*a*-H); 3,92 (1H, d, 2*a*-H); 4,34 (1H, d.d 2*e*-H); 7,15 & 7,31 (1H 4H, m, C_6H_5)	J_{2a2e} = 8,3; J_{2e4e} = 1,5; J_{4a4e} = 11,5; J_{4a5e} = 3,4; J_{4e5e} = 3,2

EXPERIMENTAL

The NMR spectra were taken on a Bruker WM-250 spectrometer with a working frequency of 250.13 MHz for ^1H and 62.89 MHz for ^{13}C. Solvent, $CDCl_3$; standard, HMDS. Monoresonance spectra were used in assigning the ^{13}C signals.

Tetrahydro-1,3-oxazines I-IV were prepared by the reaction of substituted 1,3-aminoalcohols with formaldehyde, as described in [1]. The constants of synthesized compounds I-IV corresponded to the literature data, where the initial 1,3-aminoalcohols and tetrahydro-1,3-oxazines are described as individual isomers.

REFERENCES

1. Yu. E. Kazantsev, I. P. Boiko, Yu. F. Malina, O. I. Zhuk, Yu. Yu. Samitov, and V. V. Unkovskii, Zh. Org. Khim., **9**, 2597 (1973).
2. D. K. Dalling and D. M. Grant, J. Am. Chem. Soc., **89**, 6612 (1967).
3. H. Günther, NMR Spectroscopy. An Introduction to Proton NMR and Its Application to Chemistry, Thieme, Stuttgart (1983).
4. U. Burkert and N. Allinger, Molecular Mechanics, American Chemical Society, Washington, D.C. (1982).