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Structure of Substituted 5-Chloromethyloxazolidines

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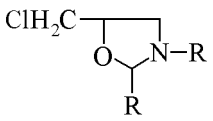
Abstract—By means of ^{1}H NMR spectroscopy isomerism was demonstrated in N-alkyl substituted 5-chloromethyl-1,3-oxazolidines due to relative *cis-trans* orientation of substituents in 2 and 5 positions of the ring. The preferred configuration in 2,3-diaryl-5-chloromethyl-1,3-oxazolidines, *cis*-(2R,5R), was proved by quantum-chemical calculations.

Substituted 5-chloromethyl-1,3-oxazolidines are polyfunctional compounds possessing versatile physiological and biological activity and important technical properties [1, 2]. Besides they attract more and more attention as object of theoretical studies on conformational analysis [3] and on relations between the structure of compound and its reactivity [4, 5].

We reported formerly [6] on the synthesis of substituted 5-chloromethyl-1,3-oxazolidines **I–VII**.



I–**VII**

I, R = Ph, R' = Me; **II**, R = Ph, R' = Ph; **III**, R = 4-$MeOC_6H_4$, R' = Me; **IV**, R = 4-$MeOC_6H_4$, R' = Et; **V**, R = 4-$MeOC_6H_4$, R' = Ph; **VI**, R = 4-ClC_6H_4, R' = Ph; **VII**, R = 2,4-$(MeO)_2C_6H_3$, R' = Ph.

Compounds **I, III, IV** with alkyl substituents attached to nitrogen were obtained as mixtures of two stereoisomers in 1 : 1 ratio, and *N*-phenyl substituted 1,3-oxazolidines **II, V–VII** were isolated as single diastereomers.

The present study was carried out in continuation of investigation on this class compounds performed with the use of ^{1}H NMR spectroscopy. As characteristic signals in the ^{1}H NMR spectra (see table) are regarded a singlet from proton in *2* position (4.49–6.23 ppm) and resonance of the proton in *5* position appearing in the region 3.96–4.62 ppm. The signal of proton in *5*-position that is surrounded by four vicinal protons appears as an asymmetrical quintet indicating that all the coupling constants are different. The multiplets in 1.82–3.79 ppm region correspond to protons in *4*-position of the ring and to those of the chloromethyl group. The resonances of protons from phenyl substituents are observed in the 6.18–7.50 ppm region, and those of alkyl protons at 0.92–3.77 ppm.

The comparison of ^{1}H NMR spectra of the N-alkyl and N-phenyl substituted 1,3-oxazolidines shows that the phenyl substituent operates as electron-acceptor as evidences the downfield shift of signals from the protons in positions *2*, *4*, and *5* by 1.3, 1.0–0.6, and 0.2 ppm respectively. This significant downfield shift can be attributed to *cis*-orientation of these protons with respect to the N-phenyl substituent, and, consequently, to *trans*-orientation of the N-phenyl group with respect to the other substituents.

The prevailing conformation of 1,3-oxazolidine rings turned out to be that where the unshared electron pairs of oxygen and nitrogen are of axial orientation [7–9]. Therefore the substituent at the nitrogen occurs in pseudoequatorial position [10].

In all the oxazolidines studied the protons of CH_2Cl group appear as multiplets, and each proton has a separate signal. The comparison of ^{1}H NMR spectra of compounds **II, V** with the spectra of the corresponding 1,3-oxazolidines with no substituents in *5*-position [11] evidenced the acceptor properties of the CH_2Cl group. In 5-chloromethyl-1,3-oxazolidines **II, V** the signal from the proton in *2*-position is displaced by 0.15 ppm downfield as compared to the unsubstituted 1,3-oxazolidines, and the signal of the proton in *5*-position is shifted downfield by 0.5 ppm. Apparently in the *5*-position the negative inductive effect of the chlorine atom is transferred through bonds, and the through-space interaction of

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Table 1. ^{1}H NMR spectra, δ, ppm (*J*, Hz) of substituted 5-chloromethyl-1,3-oxazolidines

Compd. no.	C^2H, s (1H)	C^4H, m	C^5H, m (1H)	R'	R	CH_2Cl, m (2H)
I[a]	4.49, 4.62	2.12–2.76 (2H)	4.04–4.42	7.16–7.44 m (5H)	2.06 s (3H)	3.48–3.70
II	5.85	3.24–3.44 (1H), 3.59–3.72 (1H)	4.30–4.62	7.21–7.50 m (5H)	6.42 d (2H, H^o, ^3J 7.6), 6.72 t (1H, H^p, ^3J 7.6), 7.10 t (2H, H^m, ^3J 7.6)	3.32–3.72
III[a]	4.52, 4.65	2.20–3.00 (2H)	4.02–4.47	7.00 d (2H, H^o, ^3J 8.4), 7.50 d (2H, H^m, ^3J 8.4), 3.67 s (3H, CH_3O)	2.07 © (3H)	3.60–3.72
IV[a]	4.56, 4.66	1.82–2.66[b] (4H)	3.96–4.46	6.80 d (2H, H^o, ^3J 8.4), 7.28 d (2H, H^m, ^3J 8.4), 3.68 s (3H, CH_3O)	0.92 t (3H, CH_3 ^2J 7.2)	3.46–3.62
V	5.84	3.28–3.48 (1H), 3.68–3.90 (1H)	4.22–4.60	6.76 d (2H, H^o, ^3J 8.4), 7.24 d (2H, H^m, ^3J 8.4), 3.64 s (3H, CH_3O)	6.38 d (2H, H^o, ^3J 7.6), 6.72 t (1H, H^p, ^3J 7.6), 7.04 t (2H, H^m, ^3J 7.6)	3.34–3.56
VI	5.85	3.22–3.48 (1H), 3.69–3.90 (1H)	4.24–4.54	6.20–7.40 m (4H)	6.20–7.40 m (5H)	3.48–3.69
VII	6.23	3.16–3.44 (1H), 3.70–4.00 (1H)	4.29–4.60	6.18–7.24 (3H), 3.64 s (3H, CH_3O), 3.77 s (3H, CH_3O)	6.18–7.24 m (5H)	3.55–3.79

[a] Stereoisomers mixture in $(CD_3)_2CO$.

[b] Proton signals of CH_2 group from R substituent at nitrogen and protons at C^4 atom are overlapped.

the chloromethyl group with the unshared electron pairs of oxygen and nitrogen results in the corresponding redistribution of the electron density on the second carbon atom.

The X-ray diffraction study carried out on a single crystal of 5-chloromethyl-1,3-oxazolidin-2-one showed [12] that CH_2Cl group was located in a pseudoaxial position. Thus it is presumable that in compounds **I–VII** the preferred orientation of the chloromethyl group is *cis* with respect to the unshared electron pairs of the oxygen and nitrogen atoms. This position provides a possibility of their through-space interaction.

Compounds **I, III, IV** with alkyl substituents at nitrogen are mixtures of two stereoisomers in 1 : 1 ratio. The presence of two diastereomers in N-alkyl substituted 5-chloromethyl-1,3-oxazolidines is revealed by more complicated ^{1}H NMR spectra and by appearance of two singlets from the proton in *2*-position.

It was reported [13–15] that N-alkyl- and N-aryl-1,3-oxazolidines exist as a single or predominantly one isomer with *cis*-configuration of the substituents in positions *2*, *4*, and *5*. Taking into account that the diastereomers of compounds **I**, **III**, **IV** arise under conditions favoring isomerization they may be considered equally stable thermodynamically. Besides the isomers ratio observed in the ^{1}H NMR spectra is not affected by the use of solvents with different polarity [16].

The stability of a molecule is defined by combined effect of electronic and steric factors. With *N*-alkyl-1,3-oxazolidines the steric strain is small, therefore the substituents in positions *2* and *3* may be both in *cis* and *trans* mutual orientation. Thus taking into account both electronic and steric factors the isomerism of 2-aryl-3-alkyl-5-chloromethyl-1,3-oxazolidines originates from the reciprocal orientation of substituents in positions *2* and *5*, and the *cis*- and *trans*-orientation of these substituents may be regarded as equally probable (Fig. 1).

According to ^{1}H NMR data N-phenyl-1,3-oxazolidines **II, V–VII** were separated as single isomers. The analysis of reaction mixtures by ^{1}H NMR spectroscopy revealed a presence in a small amount of the other diastereomer. Under the synthesis conditions the isomerization might occur via ring opening [17]; therefore we believe that the isolated diastereomer is thermodynamically more stable.

Presumably in the *N*-phenyl-1,3-oxazolidines alongside the electronic factor operates also the steric one. A steric strain arises at the *cis*-orientation of bulky substituents attached to positions *2* and *3*. Consequently the stable configuration has the aryl substituents in the *trans*-orientation. Taking into account electronic and steric factors the preferred configuration of 2,3-diaryl-5-chloromethyl-1,3-oxazolidines should be *cis*-(2*R*,5*R*) (Fig. 1).

Further data on the steric structure of 2,3-diphenyl-5-chloromethyl-1,3-oxazolidine were obtained from the ^{1}H NMR spectrum registered at 300 MHz. At this resolution we were able to assign the multiplets corresponding to protons in *4*-position of the ring and to those in the chloromethyl substituent (Fig. 2). Eight lines in 3.61–3.77 region by location and overall intensity correspond to the CH_2Cl group. The protons of the chloromethyl group appear as signals of a complicated AB-system at 3.66 and 3.73 ppm. The geminal coupling constant is $^2J_{12}$ 11.27 Hz, the vicinal constants are $^3J_{13}$ 4.61 and $^3J_{23}$ 6.68 Hz.

Introduction into the ethane fragment of an electronegative substituent, an oxygen atom, results in a change in the vicinal coupling constant, and therewith the steric orientation of substituents in the fragment is significant. The maximal effect on the vicinal coupling constant is observed at the *trans*-position of the substituent with respect to one of the protons of the neighbor CH_2Cl group. The smaller coupling constant corresponds to this proton [18]. Considering the above and also the Newman projection along the

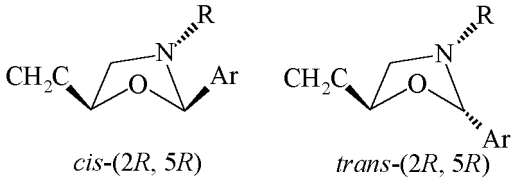

Fig. 1. Configuration of 2-aryl-3R-5-chloromethyl-1,3-oxazolidines.

C^5–CH_2Cl bond (Fig. 3, *a*) it is possible to conclude that the vicinal constant $^3J_{13}$ 4.61 Hz corresponds to the coupling between protons H^1 and H^3, since the H^1 proton is located *trans* with respect to the more electronegative atom, oxygen. Consequently the downfield part of the AB-system belongs to the H^1 proton.

The doublet of doublets at δ 3.96 ppm corresponds to the H^5 proton. It is coupled with the H^4 proton with the geminal constant $^2J_{45}$ 8.61 Hz and the vicinal constant J_{53} 5.88 Hz. The H^4 proton gives rise to a triplet at δ 3.49 ppm for the vicinal constant $^3J_{43}$ 8.01 Hz is close in its value to the geminal constant (Fig. 2).

The assignment of signals from H^4 and H^5 protons was done with accounting for the acceptor effect of the phenyl substituent attached to the nitrogen. The orientation of these protons is illustrated on Newman projection (Fig. 3, *b*). The H^5 proton is actually more affected by the influence of the phenyl group bound to nitrogen. Therefore the corresponding doublet of doublets is located in a weaker field.

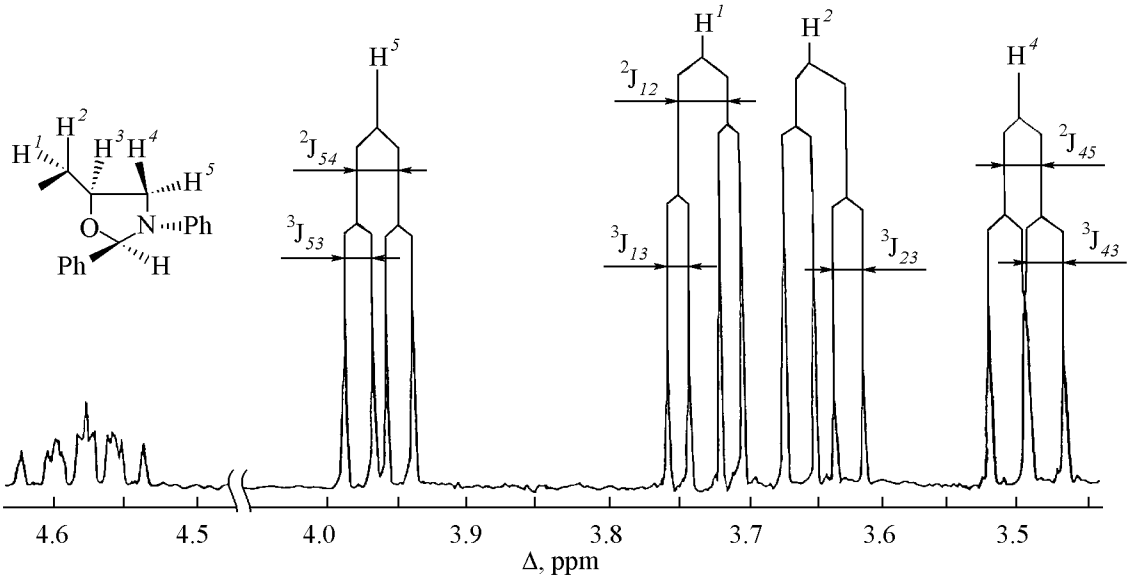

Fig. 2. Part of the ^{1}H NMR spectrum of 2,3-diphenyl-5-chloromethyl-1,3-oxazolidine (300 MHz).

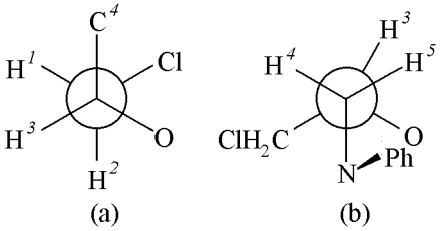

Fig. 3. Newman projections: (*a*) along C^5–CH_2Cl bond; (*b*) along C^4-C^5 bond.

We supported the conclusions on the configuration of 2,3-diphenyl-5-chloromethyl-1,3-oxazolidine by calculation of the preferred conformations of the molecule with the use of OUP Molecular Modelling software [19]. The preferred conformation is evaluated by the minimal energy of a molecule (E_{min}) that includes the bond energies, bond angles, torsion angles, and van der Waals interactions.

The calculation established that for 2,3-diphenyl-5-chloromethyl-1,3-oxazolidine the *cis*-configuration is energetically more feasible since the minimal energy for this form (3.73 kJ mol^{-1}) is notably less than that for the *trans*-isomer (9.63 kJ mol^{-1}). The bond angles H^1CH^2 and H^4CH^5 equal respectively to 109.2 and 110.7 deg, and the torsional angles H^1CCH^3, H^2CCH^3, H^4CCH^3 and H^5CCH^3 are 56.4, 62.9, 58.6 and 2.2 deg. For 2-(4-methoxyphenyl)-3-(4-tolyl)-5-chloromethyl-1,3-oxazolidine the *cis*-configuration also is more preferable than *trans* (E_{min} 4.45 and 11.53 kJ mol^{-1} respectively).

EXPERIMENTAL

^1H NMR spectra were registered on spectrometers Tesla BS-497 and Bruker AM-300 (operating frequency 100 and 300 MHz respectively) at 18–20°C.

The samples were prepared in standard NMR tubes of 5 mm diameter, 10 vol% solutions in deuterochloroform or deuteroacetone, internal reference HMDS.

Substituted 5-chloromethyl-1,3-oxazolidines **I–VII** were obtained from 1-chloro-2,3-epoxypropane and Schiff bases in carbon tetrachloride in the presence of $SnCl_4$ at 5-10°C along procedure described in [6].

REFERENCES

1. Rakhmankulov, D.L., Latypova, F.N., and Zlotskii, S.S., *Sintez i biologicheskaya aktivnost' 1,3-digeterotsikloalkanov* (Synthesis and Biolocal Activity of 1,3-Diheterocycloalkanes), Moscow: NIITEKhim., 1985.
2. Rakhmankulov, D.L., Zorin, V.V., Latypova, F.N., Musavirov, R.S., and Siraeva, I.N., *Metody sinteza 1,3-digeteroanalogov tsikloalkanov* (Methods of Synthesis of 1,3-Diheterocycloalkanes), Ufa: GINTL "Reaktiv", Nova Science Publ., 1998.
3. Rakhmankulov, D.L., Karakhanov, R.A., Zlotskii, S.S., Kantor, E.A., Imashev, U.B., and Syrkin, A.M., *Itogi Nauki i Tekhniki, Ser. Tekhnol. Organ. Veshchestv*, Moscow: VINITI, 1979, vol. 5, p. 287.
4. Rakhmankulov, D.L., Zorin, V.V., Kuramshin, E.M., and Zlotskii, S.S., *Konstanty skorosti gomoliticheskikh zhidkofaznykh reaktsii 1,3-digeteroanalogov tsikloalkanov i rodstvennykh soedinenii* (Rate Constants of Homolytic Reactions in the Liquid Phase for 1,3-Diheteroanalogs of Cycloalkanes and Their Derivatives), Ufa: GINTL "Reaktiv", 1999.
5. Rakhmankulov, D.L., Zorin, V.V., Kuramshin, E.M., Zlotskii, S.S., Zorina, L.N., Sergeeva, L.G., and Sherepovets, V.V., *Metody issledovaniya reaktsionnoi sposobnosti organicheskikh soedinenii* (Methods of Investigation of Reactivity of Organic Compounds), Ufa: GINTL "Reaktiv", 1999.
6. Bulatova, O.F., Romanov, N.A., Chalova, O.B., and Rakhmankulov, D.L., *Zh. Org. Khim.*, 1994, vol. 30, no. 1, pp. 55–58.
7. Kirby, A., *Anomeric Effect and Related Stereoelectronic Effects in Oxygen*, Springer Verlag, 1982.
8. Potapov, V.M., *Stereokhimiya* (Stereochemistry), Moscow: Khimiya, 1976.
9. Deslongchamps, P., *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, 1983, 375 p.
10. Crabb, T., Hall, M., and Willimans, R., *Tetrahedron*, 1973, vol. 29, pp. 3389–3398.
11. Alimirzoev, F.A., Lapshova, A.A., Zorin, V.V., Stepanyants, A.U., Lezina, V.P., Lapotova, F.N., Zlotskii, S.S., and Rakhmankulov, D.L., *Zh. Prikl. Khim.*, 1980, vol. 53, no. 4, pp. 911–914.
12. Just, G., Potvin, P., Uggowitzer, P., and Bird, P., *J. Org. Chem.*, 1983, vol. 48, pp. 2923–2924.
13. Beckett, A. and Jones, G., *Tetrahedron*, 1977, vol. 33, no. 24, pp. 3313–3316.
14. Irivin, W.J. and Wheeler, D.L., *J. Chem. Soc. C* 1971, vol. 19, pp. 3166–3167.
15. Tarahasku, A., Suzuki, Y., and Kametani, T., *Heterocycles*, 1983, vol. 20, no. 4, pp. 607–610.
16. Agami, C. and Rizk, T., *Tetrahedron*, 1985, vol. 41, no. 3, pp. 537–540.
17. Rakhmankulov, D.L., Chalova, O.B., Kiladze, T.K., and Kantorm E.A., *Khim. Geterotsikl. Soed.*, 1984, no. 3, pp. 291–306.
18. Gunther, H., *NMR Spectroscopy*, Chichester: Wiley.
19. Winter, J., Davis, A., and Saunders, M., *J. Comput. Aided Molecular Design I*, 1987, pp. 31–51.