ISSN 1070-4280, Russian Journal of Organic Chemistry, 2011, Vol. 47, No. 12, pp. 1832–1840. © Pleiades Publishing, Ltd., 2011.
Original Russian Text © N.A. Keiko, E.A. Funtikova, N.V. Vchislo, L.I. Larina, Yu.L. Frolov, 2011, published in Zhurnal Organicheskoi Khimii, 2011, Vol. 47, No. 12, pp. 1794–1802.

Dedicated to Full Member of the Russian Academy of Sciences M.G. Voronkov on his 90th anniversary

Regioselectivity of the Hydrolysis of 2-(1-Alkoxyvinyl)-Substituted Imidazolidines, 1,3-Thiazolidines, and 1,3-Oxazolidines

N. A. Keiko[a], E. A. Funtikova[b], N. V. Vchislo[a], L. I. Larina[a], and Yu. L. Frolov[†]

[a] *Favorskii Irkutsk Institute of Chemistry, Siberian Division, Russian Academy of Sciences, ul. Favorskogo 1, Irkutsk, 664033 Russia*
e-mail: keiko@irioch.irk.ru

[b] *Irkutsk National State Research Technical University, Irkutsk, Russia*

Received January 15, 2011

Abstract—2-(1-Alkoxyvinyl)-1,3-thiazolidines reacted with H_2O or D_2O in the presence of 105 mol % of *p*-toluenesulfonic acid or trifluoroacetic acid (20°C, 1 h) to give 2-acetyl-1,3-thiazolidine in quantitative yield. 2-(1-Alkoxyvinyl)-3,5-diphenylimidazolidines underwent hydrolysis in the presence of 20 mol % of an acid (20°C, 24 h) at the vinyloxy group with high regioselectivity yielding 2-acetylimidazolidines. Hydrolysis of 2-(1-alkoxyvinyl)-3-phenyl-1,3-oxazolidines in the presence of 10 mol % of *p*-toluenesulfonic acid (20°C, 5 days) takes two pathways, one of which involves the endocyclic C–O bond with ring opening and the other involves the vinyloxy group to produce 2-acetyl-3-phenyl-1,3-oxazolidine. Unlike phenyl-substituted 1,3-thiazolidines and imidazolidines, hydrolysis of their 3-methyl- and 3,5-dimethyl-substituted analogs in acid medium occurs mainly via ring opening. The observed hydrolysis pathways were interpreted in terms of B3PW91/6-311G(*d*,*p*) quantum-chemical calculations.

DOI: 10.1134/S1070428011120098

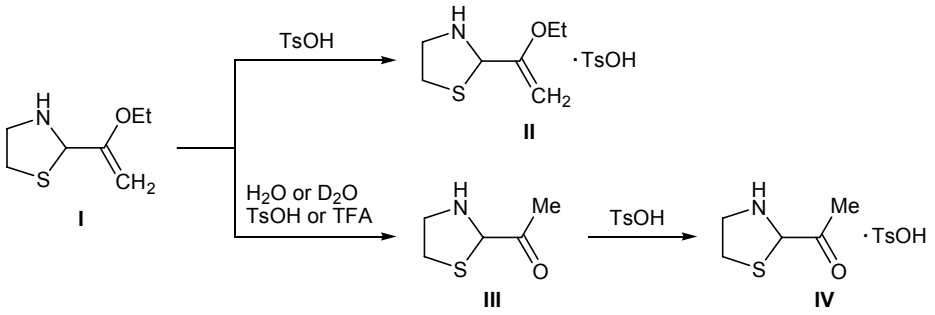
Interest in the chemistry of 2-alkyl- [1] and 2-acyl-1,3-oxazolidines [2], 2-alkyl- [3] and 2-acetyl-1,3-thiazolidines [4], 2-alkylimidazolidines [5], and 2-acetylimidazolidines [6] is related to the presence of the corresponding fragments as structural units of many medical agents and natural compounds, as well as to their use as starting compounds for the synthesis of pharmaceuticals and fragrant substances. In particular, some 2-acyloxazolidines are convenient precursors in the synthesis of alkaloids [7]. 2-Alkylthiazolidines exhibit radioprotective, antimutagenic, antibacterial, and antiviral activity [3, 8]. Compounds of the thiazolidine series are important as models for studying biochemical transformations of their complex analogs involved in natural processes [9].

Hydrolytic stability of the above listed heterocyclic compounds is an important factor determining their application as therapeutic agents which undergo cleavage of the heteroring *in vivo* [10, 11]. It is known that L-cysteine responsible for intracellular level of glutathione could be introduced at a required dose as appropriate prodrugs, 2-alkylthiazolidines [10, 11]. The nitrogen-containing heteroring *in vivo* undergoes nonenzymatic hydrolysis to release amino acid and the corresponding aldehyde. The mechanism of acid hydrolysis of some 1,3-thiazolidines was studied *in vitro* [12]. The results of kinetic studies on hydrolytic ring opening in 2-aryl-*N*-methyl(phenyl)oxazolidines showed that the rate of hydrolysis and optimal pH value often strongly depend on the nature and/or stereochemistry of substituents in the oxazolidine ring [13].

We previously found that 2-alkoxypropenals readily react with 2-aminoalkanols [14], 2-aminoethanethiol [15], and ethane-1,2-diamines [16] to give the corresponding 2-(1-alkoxyvinyl)-1,3-oxazolidines, -1,3-thiazolidines, and -imidazolidines as mixtures with their open-chain tautomers. The fraction of the cyclic structure decreases as the solvent polarity rises [15, 16],

[†] Deceased.

Scheme 1.

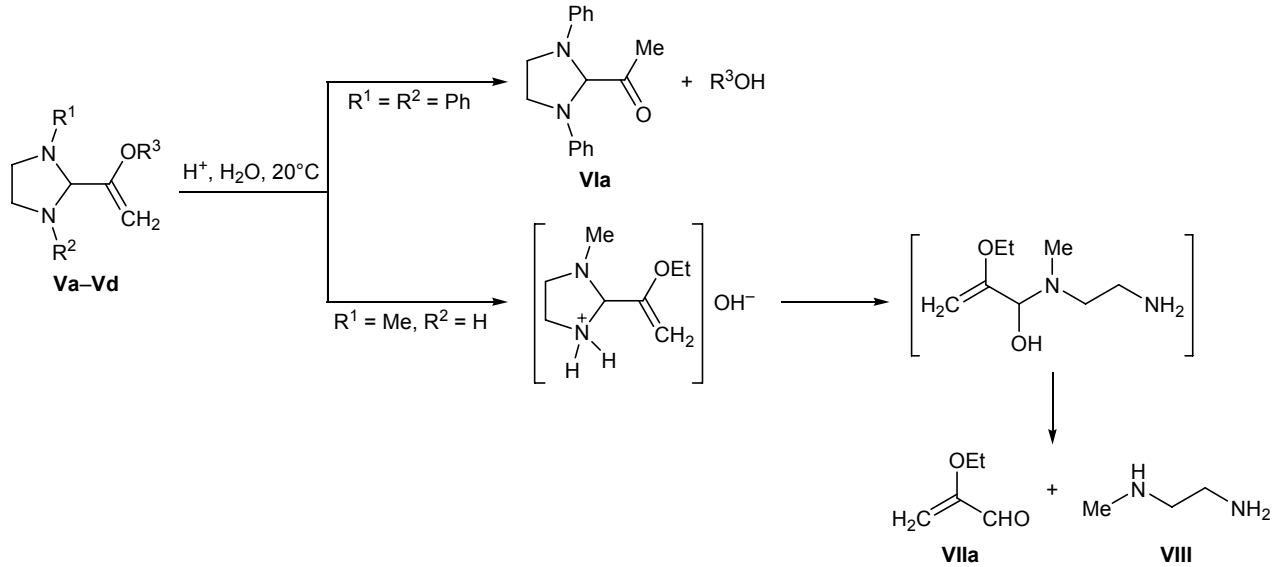


while introduction of substituents into oxazolidine [14] or imidazolidine ring [16] increases the stability of the cyclic structure. Selectivity of acid hydrolysis of 2-(1-alkoxyvinyl)-substituted 1,3-oxazolidines, 1,3-thiazolidines, and imidazolidines having two competing reaction centers was not studied previously.

The goal of the present study was to elucidate regioselectivity of hydrolysis of 2-(1-alkoxyvinyl)-substituted imidazolidines, 1,3-thiazolidines, and 1,3-oxazolidines in acid medium with a view to find conditions ensuring predominant hydrolysis at the vinyloxy group and formation of 2-acetyl-1,3-heteroazolidines as cyclic S,N- or O,N- acetals or aminals of methylglyoxal. The latter is an important metabolite acting *in vivo* as mediator in Parkinson's and Alzheimer's diseases and as low-molecular cell division regulator [17].

We previously found that the nitrogen atom in 2-(1-ethoxyvinyl)thiazolidine (**I**) is strongly basic. Therefore, addition to compound **I** of an equimolar amount of an acid (H_2CO_3, CF_3SO_2OH) leads to quantitative formation of the corresponding ammonium salts, which is reflected in the ^{1}H NMR spectra by downfield shift of almost all proton signals by 0.1–0.15 ppm [15]. The reaction of thiazolidine **I** with *p*-toluenesulfonic acid also yields thiazolidinium *p*-toluenesulfonate **II**. However in the presence of an equimolar or slightly higher (105–107%) amount of TsOH or trifluoroacetic acid (TFA) in excess H_2O or D_2O compound **I** readily undergoes strictly regioselective hydrolysis at the alkoxyvinyl group with formation of 2-acetyl-1,3-thiazolidine (**III**) (Scheme 1). In the reaction of **I** with TFA at 20°C in D_2O the conversion was 60% in 1 h and 100% in 24 h (according to the ^{1}H NMR data). The subsequent neutralization of the reaction mixture and evaporation afforded pure 2-acetylthiazolidine (**III**) which did not require additional purification. The reaction in D_2O at 45°C was complete in 1 h in the presence of both TsOH and TFA. No opening of the heteroring was observed under these

Scheme 2.



$R^1 = R^2 = Ph$, $R^3 = Et$ (**a**); $R^1 = R^2 = Ph$, $R^3 = Me$ (**b**); $R^1 = Me$, $R^2 = H$, $R^3 = Et$ (**c**); $R^1 = Me$, $R^2 = H$, $R^3 = Me$ (**d**).

conditions. The hydrolysis in a large excess (84-fold) of distilled water in the presence of 1 equiv of TsOH at 20°C in 7 days at pH 5 gave acetylthiazolidine **III** in 80% yield (isolated compound). By evaporation of the reaction mixture without neutralization we succeeded in isolating up to 70% of 2-acetyl-1,3-thiazolidinium *p*-toluenesulfonate (**IV**). The formation of salt **IV** indicates stability of the cyclic structure of **III** and its fairly high basicity. Acetylthiazolidine **III** was synthesized previously from cysteamine and methylglyoxal, but in this case compound **III** was formed as a mixture with two other products [18].

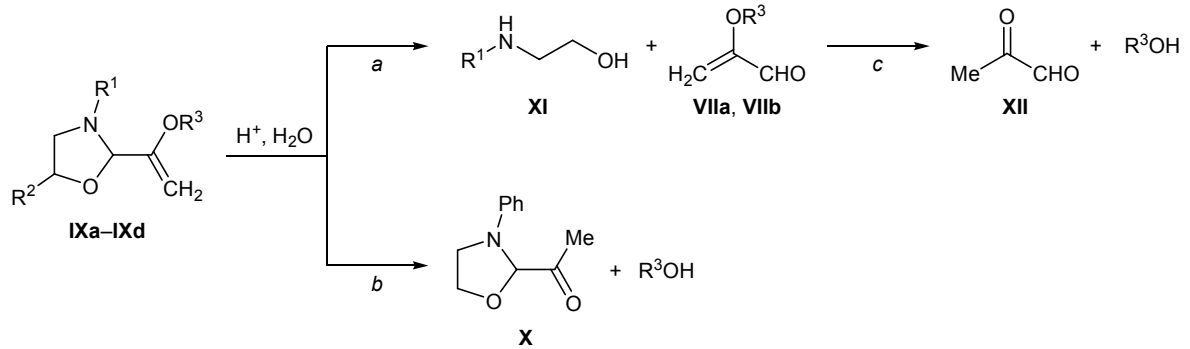
Reduction of basicity of the nitrogen atoms in 1,3-diphenyl-2-(1-alkoxyvinyl)imidazolidines **Va** and **Vb** due to electronic effect of the aryl groups facilitates their hydrolysis at the vinyloxy group. The reaction in chloroform at 20°C (24 h) in the presence of 20 mol % of TsOH gives 2-acetyl-1,3-diphenylimidazolidine (**VIa**) in 78–100% yield (according to the ^{1}H NMR data; 40% after recrystallization; Scheme 2).

Imidazolidines **Va** and **Vb** are insoluble in excess water in the absence of a homogenizing solvent, and their hydrolysis catalyzed by 20 mol % of TsOH occurs at a low rate: the yield of acetyl derivative **VI** is 10% in 24 h. Unlike *N*-phenyl derivatives **Va** and **Vb**, *N*-methyl-2-(1-alkoxyvinyl)imidazolidines **Vc** and **Vd** reacted with water in the presence of 20 to 70 mol % of TsOH or TFA very slowly both in heterogeneous medium (in the absence of a solvent) and in chloroform or acetone solution. Small amounts of the corresponding alkanol and/or 2-alkoxyprop-2-enal appeared in the reaction mixture only after 2–6 days. The conversion of 2-(1-ethoxyvinyl)-1-methylimidazolidine (**Vc**) in the reaction with excess water in the presence of 105 mol % of TFA in acetonitrile at room temperature was 45% in 18 h, and 2-ethoxyprop-2-enal (**VII**) was formed in 35% yield (according to the ^{1}H NMR data). The same conversion and yield of hydrolysis products were attained in 3 h at 45°C in the presence of TsOH (105 mol %).

Unlike thiazolidine **I** and 1,3-diphenylimidazolidines **Va** and **Vb**, their oxygen-containing analogs, 2-(1-alkoxyvinyl)-3-phenyl-1,3-oxazolidines **IX** in acid aqueous medium readily undergo protonation at the endocyclic oxygen atom with subsequent opening of the heteroring. Hydrolysis of 2-(1-ethoxyvinyl)-3-phenyl-1,3-oxazolidine (**IXa**) in the presence of 10–15 mol % of TsOH in chloroform at 20°C takes two pathways involving the vinyloxy group and the endocyclic C–O bond (Scheme 3). According to the ^{1}H NMR data, the reaction mixture after 24 h contained compounds **IX**, **VII**, and **X** at a ratio of 4:2:1; after five days, the product ratio changed to 1:1:2; the conversion of initial oxazolidine **IXa** reached 100% in 13 days, while 2-ethoxyprop-2-enal (**VIIa**) disappeared, presumably as a result of hydrolysis (reaction *c*). Hydrolysis of 2-(1-methoxyvinyl)-3-phenyl-1,3-oxazolidine (**IXb**) in the presence of 20 mol % of TsOH afforded 40% of 2-acetyl derivative **X** in 3 days (^{1}H NMR data), so that the rate of hydrolysis of **IXb** is comparable with the rate of hydrolysis of ethoxyvinyl derivative **IXa**.

The yields of 2-acetyl derivatives **III** and **VI** in the hydrolysis of thiazolidine **I** and imidazolidines **V**, which occurs only at the alkoxyvinyl group, can be calculated on the basis of ^{1}H NMR spectra from the amount of reacted initial compound. If the process is accompanied by hydrolytic opening of the heteroring, the depth of hydrolysis along pathway *a* cannot be monitored by the amount of 2-alkoxypropenal **VII**, for it depends on the time of sample withdrawal. Aldehyde **VII** in acid aqueous medium is gradually converted

Scheme 3.



IX, R^1 = Ph, R^2 = H, R^3 = Et (**a**); R^1 = Ph, R^2 = H, R^3 = Me (**b**); R^1 = Me, R^2 = H, R^3 = Et (**c**); R^1 = R^2 = Me, R^3 = Et (**d**); **VII**, R^3 = Et (**a**), Me (**b**).

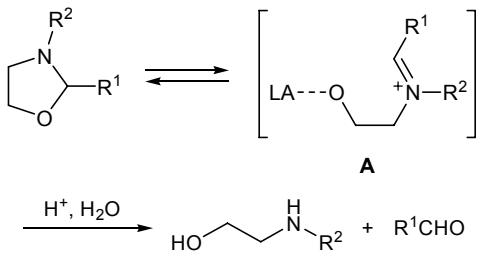
into methylglyoxal (**XII**) and alkanol (cf. [19]). Taking into account that methylglyoxal can exist as 10 different molecular structures [20], it cannot be detected at small concentrations.

We succeeded in raising the rate of hydrolysis of 2-(1-ethoxyvinyl)-3-phenyl-1,3-oxazolidine (**IXa**) and its regioselectivity along pathway *b* using microwave activation. At a power of 700 W, the conversion of oxazolidine **IXa** attained 86% in 25 min, and the yield of 2-acetyl derivative **X** was 75% (preparative yield of crude product **X** 67%). When the reaction ampule was immersed in a container charged with Al_2O_3 during microwave irradiation, the reaction time shortened to 5 min, i.e., the reaction rate increased by a factor of more than 3700 as compared to the reaction at room temperature (13 days). Analysis of purified compound **X** by GC–MS revealed two isomers with a molecular weight of 191 at a ratio of 1:3.6, which were characterized by different fragmentation patterns under electron impact. Presumably, 2-epimerization occurred during GC–MS analysis.

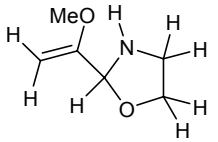
We failed to find conditions for selective hydrolysis of oxazolidines **IXc** and **IXd** at the alkoxyvinyl group (pathway *b*). The presence of an alkyl group on the nitrogen atom in **IXc** and **IXd** strongly reduces stability of the oxazolidine ring. Heating of compounds **IXc** and **IXd** in aqueous acetone, aqueous acetonitrile, or water–$CHCl_3$ at 40–60°C in the presence of TsOH or TFA (10–50 mol %) over a period of 1 h resulted in the formation of 2-ethoxyprop-2-enal (**VIIa**) (yield 10–30%). Raising the concentration of trifluoroacetic acid to 105 mol % considerably increases the efficiency of hydrolytic cleavage of oxazolidine **IXc** to 2-ethoxypropenal (yield 60%).

It is believed that regioselectivity of oxazolidine ring opening is determined by high stability of open-chain iminium intermediate **A** formed by cleavage of the C–O bond, as compared to alternative structure generated by cleavage of the C–N bond (Scheme 4). Nevertheless, opening of oxazolidine ring requires the presence of a Brønsted or Lewis acid. Activation of the C–O bond is achieved via coordination of Lewis acid at the oxygen atom. Presumably, this is the result of anomeric effect arising from stereoelectronically more favorable antiperiplanar orientation of the lone electron pair on the nitrogen atom and electron-withdrawing C–O bond [21].

Scheme 4.



LA stands for H^+ or Lewis acid.

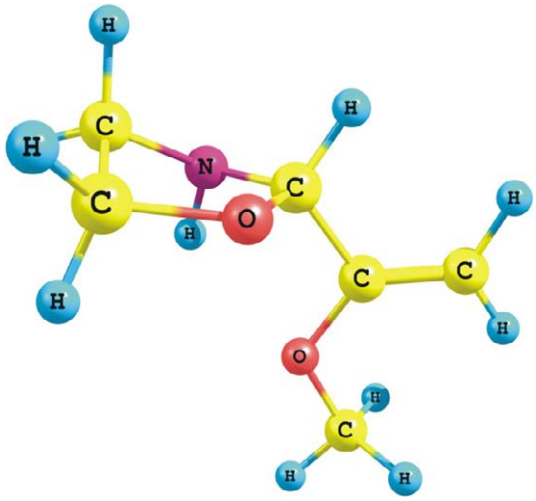


XIII

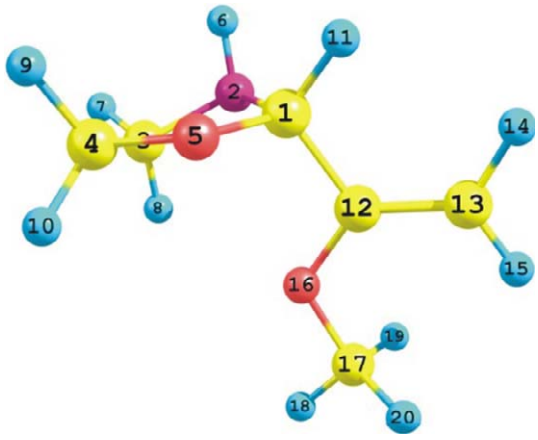
However, our quantum-chemical calculations of model oxazolidine molecule **XIII** did not confirm predominance of its structure with antiperiplanar arrangement of the nitrogen lone electron pair and polar C–O bond. The calculations were performed in terms of the density functional theory (B3PW91) with 6-311G(*d*,*p*) basis set using Gaussian 03W software package [22]. Geometric parameters were optimized. Four stable rotational isomers **XIV**–**XVII** were found for isolated molecule **XIII** (Fig. 1). The total energy of isomer **XIV** is –440.353842 a.u. The relative electronic energies of the other isomers (relative to **XIV**) are 1.79, 2.86, and 1.13 kcal/mol. Therefore, compound **XIII** may be presumed to exist mainly as conformer **XIV** despite fast transitions between rotamers (10^{-9}–10^{-10} s). The five-membered heteroring in **XIV** has no local symmetry plane, and the structure of that conformer may be regarded as intermediate between *twist* and *envelope*; the NH or CH_2 group deviates most strongly from the plane formed by the other atoms. The calculated Mulliken charges on the ether oxygen atom in the vinyloxy group and endocyclic oxygen and nitrogen atoms are given in table.

Adiabatic protonation of 2-(1-methoxyvinyl)oxazolidine was simulated. Protonation of conformer **XIV** at the ring oxygen atom was found to be considerably more favorable. The energy of protonation was calculated as the difference between the energies of the optimized cation structure and the most stable isomer. Four possible protonation centers were considered: two oxygen atoms, nitrogen atom, and β-carbon atom in the vinyl group.

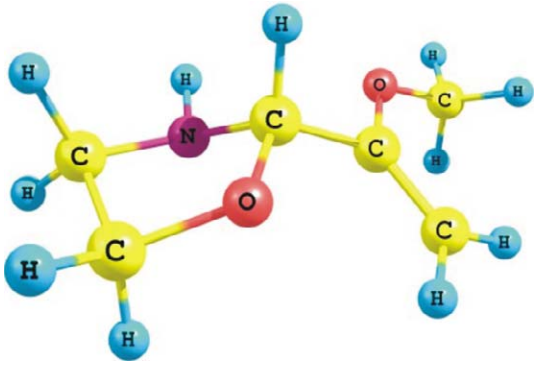
Proton interaction with the nitrogen atom is more favorable than with carbon, and the corresponding stable structures **XVIII** and **XIX** are formed without additional intramolecular rearrangements (Fig. 2). Protonation of the ether oxygen atom is followed by



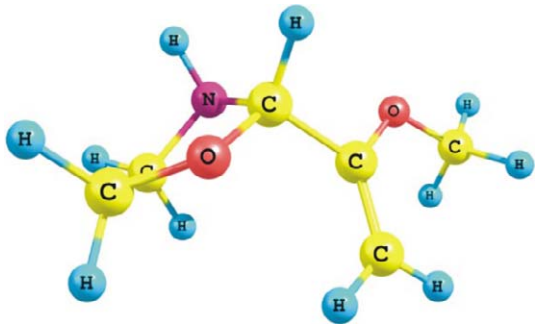
XIV, ΔE = 0 kcal/mol; μ = 1.77 D



XV, ΔE = 1.79 kcal/mol; μ = 1.1 D



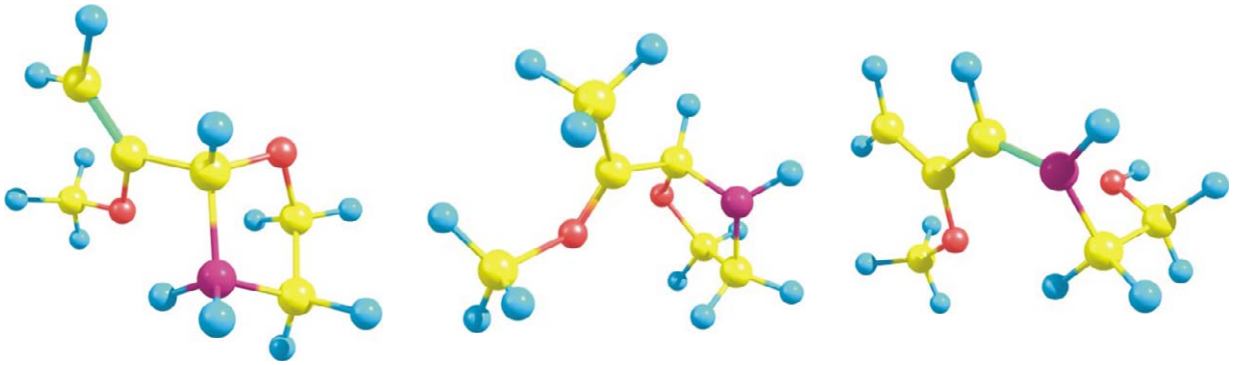
XVI, ΔE = 2.86 kcal/mol; μ = 1.6 D



XVII, ΔE = 1.13 kcal/mol; μ = 1.2 D

Fig. 1. Structures and relative energies (ΔE) of stable conformers **XIV**–**XVII** of 2-(1-methoxyvinyl)-1,3-oxazolidine (**XIII**) according to B3PW91/6-311G(*d*,*p*) calculations.

intramolecular proton transfer to the ring oxygen atom and rupture of the O–C(N) bond with formation of linear structure **XX**. In the two latter cases, the final products are similar. The methoxyvinyl group remains unchanged. Counterion was not taken into account in our calculations. The energies of protonation at the N, O_{ring}, O_{ether}, and C atoms are –234.9, –235.2, –230.0, and –226.4 kcal/mol, respectively. Presumably, the hydrolysis in acid medium begins with protonation; if protonation occurs at oxygen atoms, rearrangement products are formed with liberation of relatively large amount of energy.



XVIII **XIX** **XX**

Fig. 2. Protonated forms of compound **XIII**; energies of protonation, kcal/mol: **XVIII**, –234.9; **XIX**, –226.4; **XX**, –235.2.

Calculated Mulliken charges on the oxygen atom in the vinyloxy group and endocyclic oxygen and nitrogen atoms in the molecule of compound **XIII**

Compound no.	CH_2=CH**O**	O^1	N^3	Relative electronic energy, kcal/mol	Total energy, a.u.
XIV	–0.361	–0.379	–0.396	0	–440.353842
XV	–0.350	–0.373	–0.373	1.79	–440.350989
XVI	–0.357	–0.390	–0.421	2.86	–440.349289
XVII	–0.337	–0.383	–0.375	1.13	–440.352044

We can conclude that 2-(1-alkoxyvinyl)-substituted 1,3-oxazolidines, 1,3-thiazolidones, and imidazolidines are characterized by considerably different rates of hydrolysis and its regioselectivity. Acid hydrolysis of 2-(1-ethoxyvinyl)-1,3-thiazolidine and 2-(1-alkoxyvinyl)-3,5-diphenylimidazolidines leads to the formation of the corresponding 2-acetyl derivatives with complete regioselectivity. Hydrolysis of 2-(1-alkoxyvinyl)-1,3-oxazolidines can take alternative pathways. 2-(1-Alkoxyvinyl)-3-phenyl-1,3-oxazolidines under definite conditions (microwave irradiation) give rise to 2-acetyl derivatives (yield 86%), whereas hydrolysis of 3-methyl- and 3,5-dimethyl-2-(1-alkoxyvinyl)-1,3-oxazolidines, as well as of 3-methyl-2-(1-alkoxyvinyl)-imidazolidines, occurs mainly with opening of the heteroring.

Thus regioselective acid hydrolysis of 2-(1-alkoxyvinyl)-substituted 1,3-oxazolidines, 1,3-thiazolidines, and imidazolidines may be regarded as new methods for the preparation of cyclic methylglyoxal aminals and hemiaminals as potential source of methylglyoxal *in vivo*.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400 and 100 MHz, respectively, using hexamethyldisiloxane as internal reference. The IR spectra were measured on a Specord IR75 spectrometer. Gas chromatographic–mass spectrometric analysis was performed on a Hewlett–Packard HP 5890 gas chromatograph (Ultra-2 column, injector temperature 250°C, oven temperature programming from 70 to 280°C at a rate of 20 deg/min) coupled with an HP 5971A mass-selective detector (electron impact, 70 eV). Microwave-assisted reactions were carried out in an LG MS-1904H microwave furnace (700 W); the temperature was monitored with the aid of a TekhnoAs S-20.1 pyrometer (–18 to 500°C). The melting points were determined on a Micro-Hot-Stage Poly Term A melting point apparatus (Wagner & Munz).

Reaction of 2-(1-ethoxyvinyl)-1,3-thiazolidine (I) with *p*-toluenesulfonic acid. Compound **I**, 0.009 g (0.0566 mmol), was dissolved in 0.76 g of DMSO-d_6, 0.0097 g (0.0566 mmol) of *p*-toluenesulfonic acid was added, and the mixture was left to stand for 1 h at 20°C. ^{1}H NMR spectrum of 2-(1-ethoxyvinyl)-1,3-thiazolidinium *p*-toluenesulfonate (**II**) (DMSO-d_6), δ, ppm: 1.25 t (3H, C**H**$_3$CH$_2$, J = 7.0 Hz), 2.29 s (3H, CH_3), 3.13 m and 3.21 m (1H each, 5-H), 3.45 m and 3.55 m (1H each, 4-H), 3.80 q (2H, OCH_2, J = 7.0 Hz), 4.27 d and 4.46 d (1H each, CH_2=, J = 2.6 Hz), 5.37 s (1H, 2-H), 7.12 d (2H, *m*-H, J = 7.7 Hz), 7.50 d (2H, *o*-H, J = 7.7 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 13.94 (**C**H$_3$CH$_2$), 15.21 (CH_3), 29.85 (C^5), 48.78 (C^4), 63.40 (OCH_2), 63.88 (C^2), 87.45 (H_2C=), 125.50 and 128.20 (C^m, C^o), 138.10 (C^p), 145.00 (C^i), 154.63 (C=).

^{1}H NMR spectrum of thiazolidine **I** (DMSO-d_6), δ, ppm: 1.22 t (3H, CH_3, ^3J = 7.0 Hz), 2.76 m (2H, 5-H), 2.88 m and 3.21 m (1H each, 4-H), 3.73 q (2H, OCH_2, ^3J = 7.0 Hz), 3.94 d and 4.22 d (1H each, CH_2=, ^2J = 1.8 Hz), 4.90 s (1H, 2-H) [15].

Hydrolysis of thiazolidine I in D_2O in the presence of trifluoroacetic acid. Trifluoroacetic acid, 0.057 g (0.525 mmol), was added to a solution of 0.08 g (0.5 mmol) of 2-(1-ethoxyvinyl)-1,3-thiazolidine (**I**) in 0.5 g (0.025 mmol) of D_2O, and the mixture was heated for 1 h at 45°C. According to the ^{1}H NMR data, the product was 1-(1,3-thiazolidin-2-yl)ethanone (**III**), yield 100%. ^{1}H NMR spectrum (D_2O), δ, ppm: 2.08 s (3H, CH_3), 2.74 m (1H, CH_2N), 3.00 m (2H, CH_2S), 3.50 m (1H, CH_2N), 5.41 s (1H, NCHS). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 29.26 (CH_3), 49.62 (SCH_2), 57.23 (NCH_2), 78.21 (SCHN), 200.64 (C=O).

Hydrolysis of thiazolidine I in H_2O in the presence of *p*-toluenesulfonic acid. *p*-Toluenesulfonic acid, 0.29 g (1.69 mmol), was added to a solution of 0.267 g (1.69 mmol) of 2-(1-ethoxyvinyl)-1,3-thiazolidine (**I**) in 2.55 ml (0.14 mol) of distilled water. The mixture (pH 5) was left to stand for 2 days at 20°C and extracted with chloroform, and the extract was

neutralized with a required amount of potassium carbonate and dried over $MgSO_4$. Yield 0.16 g (72%). ^{1}H NMR spectrum of **III** ($CDCl_3$), δ, ppm: 2.26 s (3H, CH_3), 2.71 m (1H, CH_2N), 3.00 m (2H, CH_2S, CH_2N), 3.62 m (1H, CH_2S), 5.03 s (1H, NCHS).

2-Acetyl-1,3-thiazolidinium *p*-toluenesulfonate (IV). *p*-Toluenesulfonic acid, 0.207 g (1.2 mmol), was added to a solution of 0.19 g (1.2 mmol) of 2-(1-ethoxyvinyl)-1,3-thiazolidine (**I**) in 2 ml (111 mmol) of distilled water. The mixture was kept for 6 days at room temperature, dried over $MgSO_4$, and evaporated under reduced pressure. Yield 0.25 g (69%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.17 s (3H, CH_3CO), 2.26 s (3H, $CH_3C_6H_4$), 3.02 m and 3.20 m (1H each, 5-H), 3.72 m (2H, 4-H), 5.74 s (1H, 2-H), 7.13 d (2H, *m*-H, J = 7.8 Hz), 7.69 d (2H, *o*-H, J = 7.8 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.56 (**C**$H_3C_6H_4$), 25.72 (**C**H_3C=O), 49.89 (C^5), 66.53 (C^4), 77.46 (C^2), 126.25 (C^m), 129.06 (C^o), 140.03 (C^p), 142.04 (C^i), 197.93 (C=O). Found, %: C 47.64; H 5.80; N 4.4; S 20.8. $C_{12}H_{17}NO_4S_2$. Calculated, %: C 47.50; H 5.61; N 4.62; S 21.12.

Hydrolysis of 2-(1-ethoxyvinyl)-1,3-diphenylimidazolidine (Va). Compound **Va**, 0.526 g (1.8 mmol), was dissolved in 0.6 ml of chloroform, 0.065 g (20 mol %) of *p*-toluenesulfonic acid in 0.3 ml of chloroform and 0.05 g (2.7 mmol) of water were added, and the mixture was left to stand for 24 h at 22°C. According to the ^{1}H NMR data, the conversion was 100%. The mixture was extracted with diethyl ether, the extract was dried over $MgSO_4$, the solvent was distilled off under reduced pressure, and the residue was recrystallized from ethanol to isolate 0.181 g (38%) of 1-(3,5-diphenylimidazolidin-2-yl)-ethanone (**VIa**) with mp 93.1°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.87 s (3H, CH_3), 3.78 m (2H, CH_2), 3.99 m (2H, CH_2), 5.10 s (1H, CH), 6.71 d (4H, *o*-H, J = 7.8 Hz), 6.8 t (2H, *p*-H, J = 7.4 Hz), 7.24 d.d (2H, *m*-H, J = 7.4, 7.8 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 23.72 (CH_3), 46.57 (CH_2), 79.90 (CH), 113.02 (C^m), 118.98 (C^p), 129.65 (C^o), 144.94 (C^i), 156.61 (C=O). ^{15}N NMR spectrum ($CDCl_3$): δ_N –307.2 ppm. The ^{15}N–^{1}H 2D HMBC spectrum contained cross peaks due to coupling of nitrogen atoms with both CH_2 groups and 2-H proton. The NOESY spectrum of **Va** displayed cross peaks between *ortho*-protons in the benzene rings, on the one hand, and 2-H and 4(5)-H, on the other. Found, %: C 76.66; H 6.67; N 10.70. $C_{17}H_{18}N_2O$. Calculated, %: C 76.69; H 6.77; N 10.52.

Hydrolysis of 2-(1-methoxyvinyl)-1,3-diphenyl-1,3-imidazolidine (Vb). Compound **Vb**, 0.34 g (1.2 mmol), was dissolved in 2 ml of chloroform, 0.042 g (20 mol %) of *p*-toluenesulfonic acid in 1 ml of chloroform and 0.02 g (1.2 mmol) of water were added, and the mixture was kept for 24 h at 20°C. According to the ^{1}H NMR data, the conversion was 80%. The mixture was extracted with diethyl ether, the extract was dried over $MgSO_4$, the solvent was distilled off under reduced pressure, and the residue was recrystallized from ethanol to obtain 0.131 g (41%) of 1-(3,5-diphenylimidazolidin-2-yl)ethanone (**VIa**) with mp 93.1°C. The ^{1}H and ^{13}C NMR spectra of the product completely coincided with those of a sample obtained from compound **Va**.

Hydrolysis of 2-(1-methoxyvinyl)-3-methylimidazolidine (Vd). *a*. Compound **Vd**, 0.62 g (4.4 mmol), was dissolved in 1 ml of chloroform, 0.53 g (70 mol %) of *p*-toluenesulfonic acid in 0.08 g (4.4 mmol) of water was added, and the mixture was kept for 6 days at 20°C. According to the ^{1}H NMR data, the mixture contained mainly initial compound **Vd** and a small amount of 2-methoxyprop-2-enal.

b. Compound **Vd**, 0.72 g (5 mmol), was added to a solution of 0.17 g (20 mol %) of *p*-toluenesulfonic acid in 0.45 g (2.25 mmol) of water, and the mixture was subjected to microwave irradiation over a period of 2 min at a power of 700 W. According to the ^{1}H NMR data, initial compound **Vd** remained unchanged.

2-(1-Methoxyvinyl)-3-methylimidazolidine (Vd) was synthesized according to the procedure described in [16] from 1.64 g (19 mmol) of 2-methoxyprop-2-enal and 1.4 g (19 mmol) of *N*-methylethane-1,2-diamine. Yield 1.64 g (61%), bp 40–42°C (1 mm). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.28 m (1H, CH_2), 2.31 s (3H, NMe), 2.99 m (1H, CH_2), 3.21 m (2H, CH_2), 3.36 s (1H, CH), 3.60 s (3H, OMe), 4.14 d and 4.23 d (1H each, =CH_2, J = 2.0 Hz), 4.81 s (1H, =CH_2, J = 2.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 38.53 (CH_3), 44.3 (CH_2), 55.04 (CH_2), 55.26 (CH_3), 83.81 (NCHN), 85.43 (CH_2=), 159.21 (C). Found, %: C 59.15; H 9.86; N 19.72. $C_7H_{14}N_2O$. Calculated, %: C 59.12; H 9.42; N 19.79.

Hydrolysis of 2-(1-ethoxyvinyl)-1-methylimidazolidine (Vc) in the presence of 20 mol % of *p*-toluenesulfonic acid. Compound **Vc**, 0.28 g (1.8 mmol), was dissolved in 1 ml of chloroform, 0.04 g (2.2 mmol) of water and 0.06 g (20 mol %) of *p*-toluenesulfonic acid in 0.5 ml of chloroform were added, and the mixture was left to stand at 20°C. After 6 days,

the mixture contained only the initial compound (^{1}H NMR data).

Hydrolysis of imidazolidine (Vc) in the presence of excess acid. *a*. Compound **Vc**, 0.142 g (0.91 mmol), was dissolved in 1 ml (0.056 mmol) of water, 0.109 g (105 mol %) of trifluoroacetic acid in 0.6 ml of acetonitrile was added, and the solution was left to stand for 18 h at 20°C. After neutralization with potassium carbonate, drying over $MgSO_4$, and evaporation, the conversion of **Vc** was 45% (^{1}H NMR). The mixture also contained 2-ethoxyprop-2-enal (yield 35%).

b. Analogous results were obtained when the hydrolysis of **Vc** was carried out in the presence of 105 mol % of *p*-toluenesulfonic acid at 45°C (reaction time 3 h).

Hydrolysis of 2-(1-ethoxyvinyl)-3-phenyl-1,3-oxazolidine (IXa). *a*. Compound **IXa**, 0.474 g (2.2 mmol), was dissolved in 0.5 ml of chloroform, 0.075 g (20 mol %) of *p*-toluenesulfonic acid in 0.5 ml of chloroform and 0.042 g (2.2 mmol) of water were added, and the mixture was subjected to microwave irradiation (25×1 min, 700 W; ^{1}H NMR monitoring). After 25 min, the conversion of **IXa** was 86%, and the yield of 1-(3-phenyl-1,3-oxazolidin-2-yl)ethanone (**X**) was 75%. The mixture was extracted with diethyl ether, and the extract was dried over $MgSO_4$ and evaporated under reduced pressure. Yield of crude product **X** 0.28 g (67%). It contained initial oxazolidine **IXa** and 2-ethoxyprop-2-enal (~10%) as impurities. Pure oxazolidine **X** was isolated by column chromatography on silica gel 60 (70–200 mesh, Merck) using hexane–diethyl ether (1 : 5) as eluent. The presence of a large amount of 2-phenylaminoethanol in fractions eluted after oxazolidine **X** indicated that hydrolysis of the heteroring occurred during chromatographic isolation on silica gel. IR spectrum, ν, cm^{-1} (first isomer): 2870 br, 1705 (C=O), 1580, 1480, 1340, 1300, 1210, 1160, 890. ^{1}H NMR spectrum of **Xa** ($CDCl_3$), δ, ppm: 2.13 s (3H, CH_3), 3.51 m and 3.71 m (1H each, CH_2N), 4.21 m and 4.30 m (1H each, CH_2O), 4.97 s (1H, NCHO), 6.60 d (2H, *o*-H, *J* = 7.9 Hz), 6.80 t (1H, *p*-H, *J* = 7.2 Hz), 7.21 d.d (2H, *m*-H, *J* = 7.9, 7.2 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 23.89 (CH_3), 47.44 (NCH_2), 67.16 (OCH_2), 91.94 (CH), 113.26 (C^m), 118.94 (C^p), 129.46 (C^o), 144.95 (C^i), 206.15 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): first isomer: 191 (2) $[M]^{+\cdot}$, 176 (1), 160 (2), 148 (100) [*M* – CH_3CO], 120 (32) [*M* – CH_3CO – CH_2=CH_2], 103 (7) [PhNC], 91 (8) [PhN], 77 (20) [Ph], 65 (8), 43 (4) [MeC=O], 28 (1) [C=O], 15 (1); second isomer: 191 (35) $[M]^{+\cdot}$, 176 (8) [*M* – CH_3], 162 (2), 147 (9) [*M* – CH_3CO – H], 132 (20), 119 (100) [*M* – CH_3CO – CH_2=CH_2 – H], 104 (58) [PhNCH], 91 (47) [PhN], 77 (50) [Ph], 65 (5), 51 (18), 42 (6). Found, %: C 69.50; H 6.96; N 6.95. $C_{11}H_{13}N_1O_2$. Calculated, %: C 69.11; H 6.80; N 7.33.

b. Analogous experiment with the same amounts of the reactants was carried out under microwave irradiation (700 W), but the reaction ampule was sealed and immersed in a Teflon container charged with Al_2O_3. After irradiation (5×1 min; temperature in the reaction zone 59–73°C), the yield of oxazolidine **X** was 75% (^{1}H NMR). The product also contained unreacted initial compound **IXa** and 2-ethoxyprop-2-enal in equal amounts as impurities.

Hydrolysis of 2-(1-methoxyvinyl)-3-phenyl-1,3-oxazolidine (IXb). A solution of 0.15 g (20 mol %) of *p*-toluenesulfonic acid in 1 ml of chloroform and 0.09 g (4.6 mmol) of water were added to 0.95 g (4.6 mmol) of compound **IXb** in 1 ml of chloroform, and the mixture was subjected to microwave irradiation (25×1 min, 700 W). According to the ^{1}H NMR data, the yield of **X** was 40%. The solvent was distilled off under reduced pressure. The ^{1}H NMR spectrum of the product coincided with the spectrum of **X** given above.

Hydrolysis of 2-(1-ethoxyvinyl)-3-methyl-1,3-oxazolidine (IXc). Compound **IXc**, 0.291 g (1.85 mmol), was dissolved in 0.951 g of acetonitrile, a solution of 0.22 g (105 mol %) of trifluoroacetic acid in 0.255 g (0.03 mol) of water was added, the mixture was heated for 1 h at 40°C and extracted with chloroform, and the extract was dried by passing it through a layer of K_2CO_3 and evaporated. According to the ^{1}H NMR data, the yield of 2-ethoxyprop-2-enal was 60%.

Hydrolysis of 2-(1-ethoxyvinyl)-3,5-dimethyl-1,3-oxazolidine (IXd). *a*. Compound **IXd**, 0.200 g (1.17 mmol) was dissolved in 1 ml of chloroform, 0.060 g (30 mol %) of *p*-toluenesulfonic acid and 0.02 g (1.7 mmol) of water were added, and the mixture was kept for 13 days at 20°C. The mixture contained 2-ethoxyprop-2-enal (yield 17%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.40 t (3H, CH_3), 3.90 q (2H, OCH_2), 5.05 d and 5.18 d (1H each, CH_2=), 9.26 s (1H, CHO).

b. Oxazolidine **IXd**, 0.138 g (0.81 mmol), was dissolved in 1 ml of acetone, a solution of 0.095 g (105 mol %) of trifluoroacetic acid in 0.47 ml (26 mmol) of water was added, and the mixture was heated for 1 h at 45°C. After appropriate treatment (extraction, neutralization, and drying), the mixture

contained initial oxazolidine **IXd** and 2-ethoxyprop-2-enal (yield 33%; ^{1}H NMR data).

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 08-03-00396).

REFERENCES

1. Wagner, B., Gonzalez, G.I., Tran Hun Dau, M.E., and Zhu, J., *Bioorg. Med. Chem*., 1999, vol. 7, p. 737.
2. Agami, C., Couty, F., Lam, H., and Mathieu, H., *Tetrahedron*, 1998, vol. 54, p. 8783; O'Brien, P. and Warren, S., *Tetrahedron Lett*., 1996, vol. 37, p. 3051.
3. Gros, C., Boulègue, C., Galéotti, N., Niel, G., and Jouin, P., *Tetrahedron*, 2002, vol. 58, p. 2673; Willmore, B.H., Cassidy, P.B., Walters, R.L., and Roberts, J.C., *J. Med. Chem*., 2001, vol. 44, p. 2661.
4. Fernandez, X., Fellous, R., and Duňach, E., *Tetrahedron Lett*., 2000, vol. 41, p. 3381.
5. Fife, T.H., Hutchins, J.E.C., and Pellino, A.M., *J. Am. Chem. Soc*., 1978, vol. 100, p. 6455.
6. O'Brien, P. and Warren, S., *Tetrahedron Lett*., 1995, vol. 36, p. 2681.
7. Agami, C., Couty, F., and Mathieu, H., *Tetrahedron Lett*., 1998, vol. 39, p. 3505.
8. Zimenkovskii, B.S., Kutsyk, R.V., Lesyk, R.B., Matiichuk, V.S., Obushak, N.D., and Klyufinskaya, T.I., *Khim.-Farm. Zh*., 2006, vol. 40, no. 6, p. 13.
9. Ino, A. and Murabayashi, A., *Tetrahedron*, 1999, vol. 55, p. 10271; Ino, A., Hasegawa, Y., and Murabayashi, A., *Tetrahedron*, 1999, vol. 55, p. 10283; Ino, A. and Murabayashi, A., *Tetrahedron*, 2001, vol. 57, p. 1897; Zamri, A. and Abdallah, M.A., *Tetrahedron*, 2000, vol. 56, p. 249.
10. Roberts, J.C., Nagasawa, H.T., Zera, R.T., Fricke, R.F., and Goon, D.J.W., *J. Med. Chem*., 1987, vol. 30, p. 1891; Nagasawa, H.T., Goon, D.J.W., Zera, R.T., and Yuzon, D.L., *J. Med. Chem*., 1982, vol. 25, p. 489; Nagasawa, H.T., Goon, D.J.W., Muldon, W.P., and Zera, R.T., *J. Med. Chem*., 1984, vol. 27, p. 591.
11. Chiarino, D., Ferrario, F., Pellacini, F., and Sala, A., *J. Heterocycl. Chem*., 1989, vol. 26, p. 589.
12. Fife, T.H., Nagarajan, R., Shen, C.C., and Bembi, R., *J. Am. Chem. Soc*., 1991, vol. 113, p. 3071.
13. Walker, R.B., Huang, M.-J., and Leszczynski, J., *J. Mol. Struct. (Theochem)*, 2001, vol. 549, p. 137; Fife, T.H. and Hutchins, J.E.C., *J. Org. Chem*., 1980, vol. 45, p. 2099; McClelland, R.A. and Somani, R., *J. Org. Chem*., 1981, vol. 46, p. 4346.
14. Keiko, N.A., Funtikova, E.A., Stepanova, L.G., Chuvashev, Yu.A., and Larina, L.I., *Russ. J. Org. Chem*., 2003, vol. 39, p. 1477.
15. Keiko, N.A., Funtikova, E.A., Stepanova, L.G., and Larina, L.I., *Russ. J. Org. Chem*., 2005, vol. 41, p. 517; Keiko, N.A., Funtikova, E.A., Stepanova, L.G., Chuvashev, Yu.A., Larina, L.I., and Voronkov, M.G., *J. Sulfur Chem*., 2004, vol. 25, p. 351.
16. Keiko, N.A., Vchislo, N.V., Stepanova, L.G., Larina, L.I., Chuvashev, Yu.A., and Funtikova, E.A., *Khim. Geterotsikl. Soedin*., 2008, vol. 12, p. 1809.
17. Kalapos, M.P., *Toxicol. Lett*., 1999, vol. 110, p. 145.
18. Hayashi, T. and Shibamoto, T., *J. Agric. Food Chem*., 1985, vol. 33, p. 1090; Hofmann, T. and Schieberle, P., *J. Agric. Food Chem*., 1995, vol. 43, p. 2946.
19. Mamashvili, T.N., Keiko, N.A., Sarapulova, G.I., and Voronkov, M.G., *Izv. Ross. Akad. Nauk, Ser. Khim*., 1998, p. 2547.
20. Nemet, I., Vikić-Topić, D., and Varga-Defterdarović, L., *Bioorg. Chem*., 2004, vol. 32, p. 560.
21. Sélambarom, J., Mouge, S., Carré, F., Roque, J.P., and Pavia, A.A., *Tetrahedron*, 2002, vol. 58, p. 9559.
22. Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Montgomery, Jr., J.A., Vreven, T., Kudin, K.N., Burant, J.C., Millam, J.M., Iyengar, S.S., Tomasi, J., Barone, V., Mennucci, B., Cossi, M., Scalmani, G., Rega, N., Petersson, G.A., Nakatsuji, H., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Klene, M., Li, X., Knox, J.E., Hratchian, H.P., Cross, J.B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R.E., Yazyev, O., Austin, A.J., Cammi, R., Pomelli, C., Ochterski, J.W., Ayala, P.Y., Morokuma, K., Voth, G.A., Salvador, P., Dannenberg, J.J., Zakrzewski, V.G., Dapprich, S., Daniels, A.D., Strain, M.C., Farkas, O., Malick, D.K., Rabuck, A.D., Raghavachari, K., Foresman, J.B., Ortiz, J.V., Cui, Q., Baboul, A.G., Clifford, S., Cioslowski, J., Stefanov, B.B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Martin, R.L., Fox, D.J., Keith, T., Al-Laham, M.A., Peng, C.Y., Nanayakkara, A., Challacombe, M., Gill, P.M.W., Johnson, B., Chen, W., Wong, M.W., Gonzalez, C., and Pople, J.A., *Gaussian 03, Revision B.03*, Wallingford CT: Gaussian, 2004.