Reactions of vicinal aliphatic bis(hydroxylamines) with trifunctionalized methane derivatives

Evgeny A. Mostovich,[a,b]* Dmitrii G. Mazhukin,[a,b] and Tatyana V. Rybalova[a]

[a]N.N. Vorozhtsov Novosibirsk Institute of Organic Chemistry SB RAS, ave. Acad. Lavrent'eva 9, Novosibirsk 630 090, Russia
[b]Novosibirsk State University, Pyrogova, 2, Novosibirsk, 630 090, Russia
E-mail: chemmea@gmail.com

DOI: http://dx.doi.org/10.3998/ark.5550190.0012.b03

Abstract
The reactions of *cis*-1,2-bis(hydroxylamino)cyclohexane and 2,3-bis(hydroxylamino)-2,3-dimethylbutane with polyelectrophilic carbonyl compounds in ethanol were studied. It has been shown that such reactions result in the formation of predominantly five-membered heterocyclic rings with one or two nitrogen atoms. A nitronylnitroxide radical of 2-imidazoline type bearing a 1,3-dicarbonyl function was synthesized.

Keywords: 1,2-Bis(hydroxylamines), carbonyl compounds, nitrogen heterocycles, nitronylnitroxides

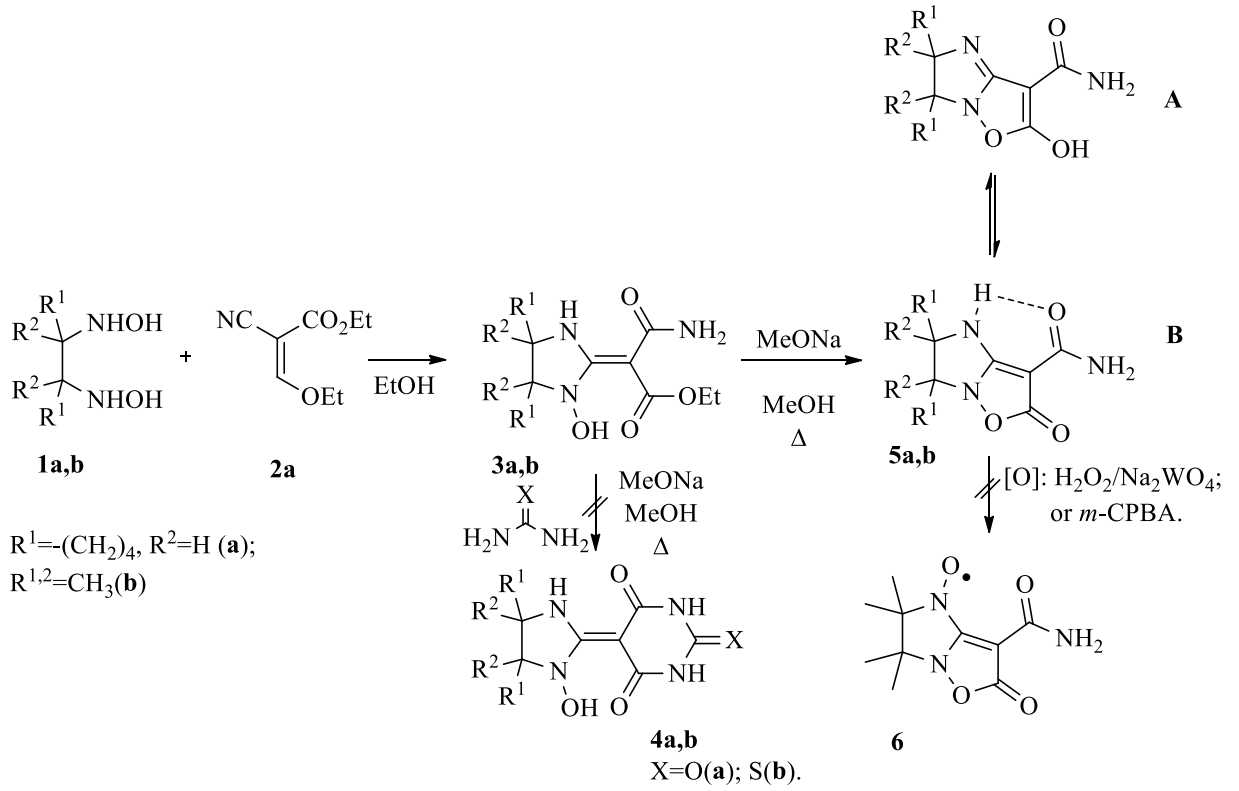
Introduction

Aliphatic 1,2-bis(hydroxylamines) (BHAs) were regarded as a suitable precursors in the synthesis of heterocyclic compounds such as 1,2-diazetes[1], imidazoles[2], pyrazines[3], 1,4-diazepines[4] bearing *N*-oxide-, *N*-hydroxy-, hydroxamic, *N*-alkoxy- moieties. Many of such compounds possess wide diversity of biological activity. 1,2-Diazete derivatives has been shown as effective NO-donors[5], 2-imidazolidine carboxylic acids and 2,3-piperazinedione derivatives revealed potent antiaggregatory properties[6]. Furthermore, 1,3-dihydroxyimidazolidines are key intermediates for the synthesis of stable nitronyl- and iminonitroxide radicals which are widely used to design organic and hybrid magnetic materials[7]. On the other hand, the recent observations that C_2-symmetric bishydroxamic acids and dinitrones serve as effective ligands and catalysts for enantioselective epoxidation of allylic and homoallylic alcohols[8], oxidation of sulfides and disulfides[9] and asymmetric allylation of aldehydes[10], correspondingly, have drawn special attention to new chiral BHAs[11]. Therefore, systematic study of chemical behavior of these BHAs is of particular interest due to their both theoretical and practical application. This

paper is aimed at studying the reactions of BHAs **1a,b** with polyelectrophilic carbonyl compounds **2a-e**, derivatives of trifunctionalized methane. The latter compounds containing aldehyde, ketone, alkoxycarbonyl, nitrile groups, etc. as it was shown by Nishiwaki, Ariga *et al.* are effective synthetic blocks for the construction of heterocycles with desired functional group(s).[12]

Results and Discussion

We have found that the reactions of carbonyl containing compounds with symmetric BHAs **1a,b** lead predominantly to the formation of 5-membered rings. Thus the reaction of *cis*-1,2-bis(hydroxylamino)cyclohexane **1a** with ethyl ester of ethoxymethylenecyanoacetic acid **2a** in ethanol at room temperature give 1-hydroxyimidazol-2-ylidene **3a** (Scheme 1). NMR ^{13}C Spectrum of **3a** contains characteristic signals of carbon atoms from exocyclic C=C bond at 171.2 and 76.6 ppm, whereas the singlets of ester and amide carbon atoms appeared at 168.0 and 167.1 ppm respectively. Spectral characteristics of compound **3a** are similar to those for the earlier prepared derivative **3b**[13].



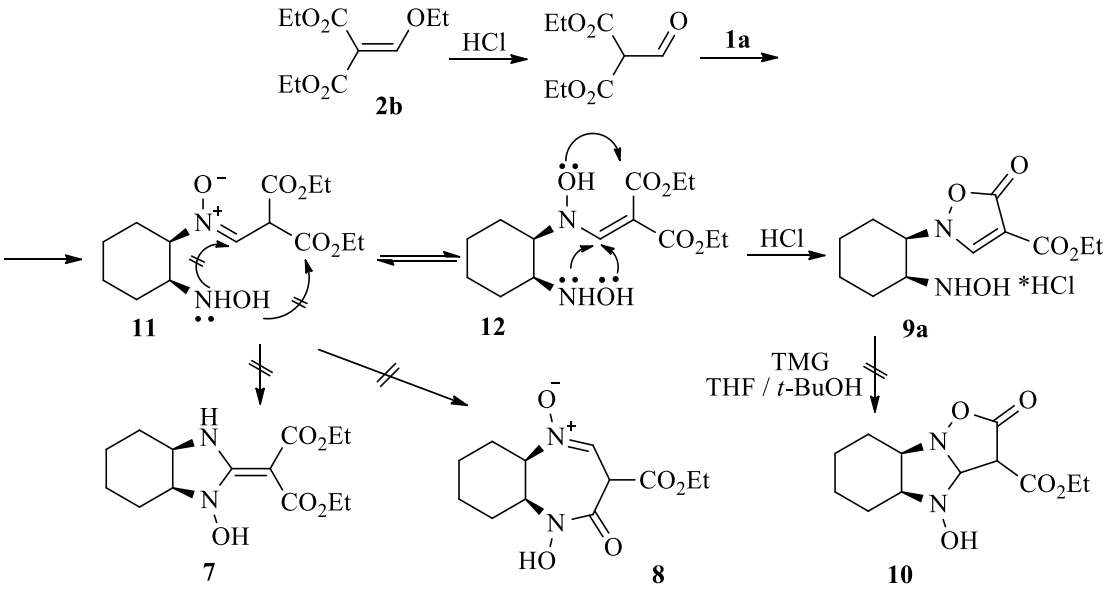
Scheme 1. Reaction of BHA **1a,b** with ether **2a** and **3a,b** cyclization.

It seems relevant to note that in the course of reaction nitrile function in **2a** undergoes hydrolysis both in case of **1a** with secondary hydroxylamino groups and **1b** with sterically hindered tertiary hydroxylamino groups.[13]

Taking into consideration the synthesis of physiologically active barbituric acid derivatives, compounds **3a,b** were treated with carbamide and thiocarbamide. However, the desired pyrimidine derivatives **4a,b** were not observed in this reaction. It was shown that independent refluxing of **3a,b** in methanol with MeONa led to imidazo[1,2-*b*]isoxazoles **5a,b**. High downfield shift of NH proton of enamine group in NMR ^{1}H spectrum at 9.43÷9.50 ppm can be explained either by the existence of strong intramolecular hydrogen bonding between NH proton and oxygen atom of amide group or fast equilibrium between tautomeric forms **A** and **B.**

An attempt of oxidation of bicycle **5b** in H_2O_2/Na_2WO_4 medium has led to 100% conversion of initial compound, but none of the paramagnetic species such as **6** were observed in the reaction mixture.

Reaction of BHA **1a** with a masked form of diethyl 2-formylmalonate, compound **2b** in the presence of ~10 eq HCl gave a fine crystalline precipitate of product with elemental formula $C_{12}H_{21}ClN_2O_6$ in 47% yield. Spectral data of the compound does not correspond to either neither imidazolidine **7** or diazepine **8** structures. In fact, according to NMR ^{1}H spectrum only one set of protons with relative intensity 5 was observed for the ethyl group, whereas the IR spectrum of this product contains a strong band at 1776 cm^{-1} which is not typical for carbonyl group in cyclic hydroxamic acids.



Scheme 2. Reaction of BHA **1a,b** with ether **2b** and **9a** synthesis.

The crystals of isolated compound suitable for X-ray analysis were grown by slow vaporization of its ethanol solution and the structure was determined as isoxazolin-5-one

hydrochloride hydrate **9a**. Figure 1 depicts the solid-state molecular structure. Isoxazol cycle is plane within ±0.013(1) Å, with bond lengths being close to the corresponding ones in 4-(2-methoxybenzyl)-3-phenyl-2H-isoxazol-5-one[14]. The O2, O4 and C10 atom deviations from isoxazol ring plane equal to 0.065(4), 0.012(4) and 0.012(4) Å respectively. Cyclohexyl ring adopts chair conformation. The torsional angle C2C1N1O1 characterizing orientation of izoxazol ring to cyclohexyl one is 63.6(3)°. The shortened intramolecular contact O2…O4 equal to 3.021(2) Å and weak intramolecular hydrogen bond C3-H3A…O1 with parameters: C-H 0.96(2), H…O 2.55(2), C…O 3.144(3) Å, C-H…O 120(2) were observed. The crystal structure of compound under investigation is characterized by a big number of hydrogen bonds due to water molecules and chlorine anion (Table 1).

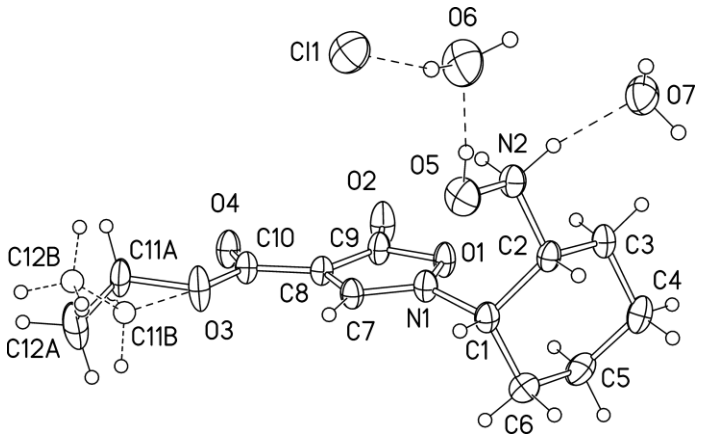


Figure 1. The structure of 2-(2-(Hydroxyamino)cyclohexyl)-5-oxo-2,5-dihydroisoxazole-4-carboxylic acid ethyl ester hydrochloride hydrate **9a**.

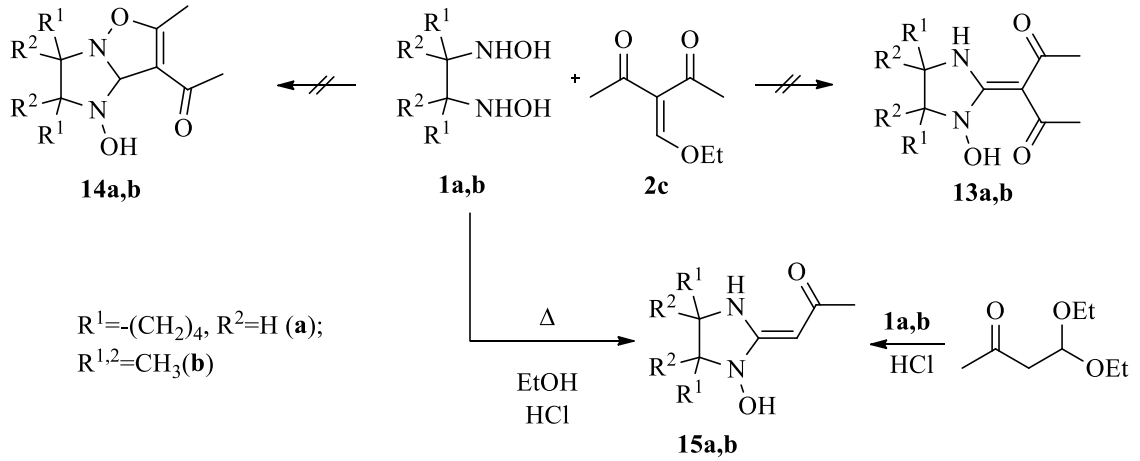
Table 1. Intermolecular hydrogen bonds in crystal of 2-(2-(Hydroxyamino)cyclohexyl)-5-oxo-2,5-dihydroisoxazole-4-carboxylic acid ethyl ester hydrocloride **9a**

Bond	Parameters of hydrogen bonds			
	D – H (Å)	H...A (Å)	D...A (Å)	D - H...A (°)
N2-H2…O7	0.94(2)	1.78(2)	2.693(3)	167(2)
N2-H1…O2	0.92(2)	2.40(2)	2.925(3)	116(2)
N2-H1…O4	0.92(2)	2.02(2)	2.877(2)	153(2)
O5-H1…O6	0.87(2)	1.74(2)	2.598(3)	174(2)
O6-H2…Cl1	0.85(3)	2.33(3)	3.164(3)	167(3)
O6-H1…Cl1	0.87(3)	2.39(3)	3.259(3)	176(3)
O7-H2…Cl1	0.85(3)	2.27(3)	3.122(2)	178(4)
O7-H1…Cl1	0.86(3)	2.31(3)	3.162(2)	177(3)

Plausible explanation of such unexpected result of this reaction is the initial formation of acylic nitrone **11** followed by tautomeric shift to hydroxylamine **12** and final intramolecular ring

closure (Scheme 2). The formation of hydrochloride salt has obviously stopped any further transformations. We did not succeed in performing intramolecular cyclization of **9a** into tricycle **10** at the presence of tetramethylguanidine (TMG).

Again, the increase of electronegative character of polycarbonyl compound has led to the unusual result in the reaction with BHAs. When 3-ethoxymethylene-2,4-pentanedione **2c** was involved in condensations with BHAs **1a,b** neither the expected cyclic ketenaminals **13a,b** nor isoxazoline derivatives **14a,b** were obtained. The synthesized substances proved to be identical with the products prepared earlier in the reaction of acetoacetaldehyde diethylacetal with BHA **1a,b** in acidic medium[13], i.e. acetylimidazolidine-2-ylidenes **15a,b** (Scheme 3). When optimizing this reaction, we found that heating of the components in the mixture of HCl and EtOH affords **15a** quantitatively. Thus, ketenaminal **15a** was isolated with 95% yield applying the above mentioned conditions, while running this reaction in neutral medium led to a dramatic drop in yield of **15a** down to 41%, which is supposed to make **2c** a useful alternative of 4,4-diethoxybutan-2-one for efficient preparation of acetylated imidazolidin-2-ylidenes.

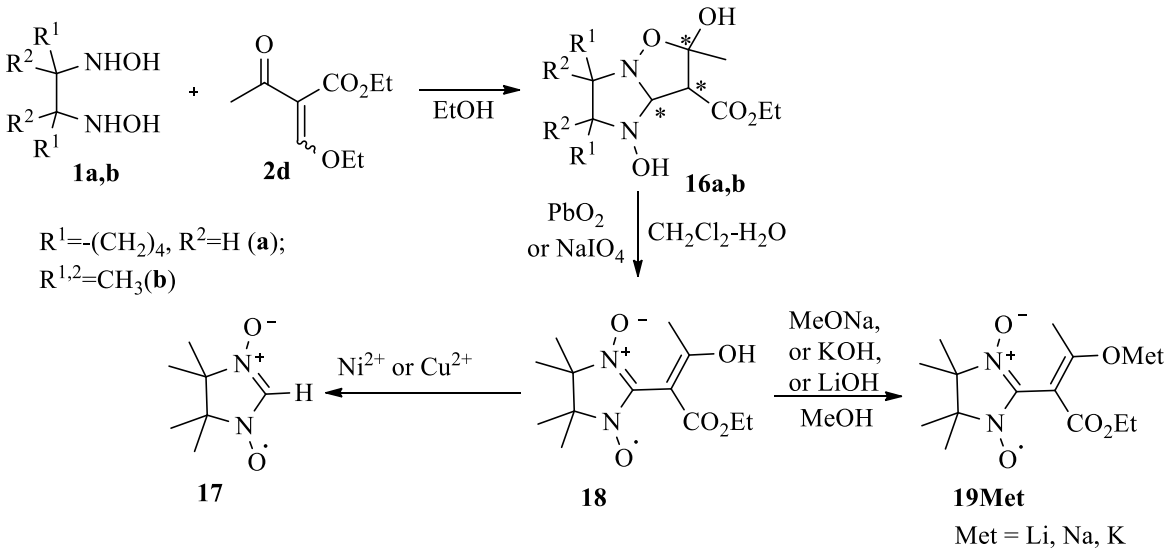


Scheme 3. Reaction of BHA **1a,b** with ether **2c**.

The similar deacylation reactions with ketene aminals were described earlier in literature. Thus, Huang *et al.* has observed monodeacetylation process for diacetylmethylene derivatives of imidazolidine, oxazolidine, hexahydropyrimidine by treatment of the listed heterocycles with alkali[15]. At the same time, the related process was registered when dibenzoylmethyleneimidazolidine was subject to hydrolysis furnished to monobenzoylated product[16].

Reaction of BHA **1a** with 2-ethoxymethylene derivative of ethyl acetoacetate **2d** in ethanol at room temperature led to the precipitation of white solid. IR-spectrum of a product reveals an intensive absorption at 1716 cm^{-1} that is specific for ester's group valent vibrations. The analysis of NMR spectra of an isolated compound reveals that this product consists of the mixture of

diastereomers of imidazo[1,2-*b*]isoxazole **16a**. Likewise, BHA **1b** reacted with **2d**, giving isoxazole **16b** (Scheme 4)**.**



Scheme 4. Synthesis of imidazo[1,2-*b*]isoxazoles **16a,**b and nitronyl nitroxides **18-19Met**.

Besides, the synthesis of nitronyl nitroxides (NNR) possessing 1,3-dicarbonyl functionality oxidation of **16b** was studied. When treating the solution of imidazo[1,2-*b*]isoxazole **16b** with an excess of PbO_2 (or aqueous $NaIO_4$) in a few minutes, there is a deep coloration of organic phase in the red-purple color due to the formation of radical **18**. Despite the fact that only a single product was formed in this reaction (as monitored by TLC), obtaining NNR **18** in its pure form seems to be quite problematic since it is a strong CH-acid which is very labile. In particular, the color of the mixture changed from dark purple to a dirty-yellow upon standing of NNR solution at room temperature for 12 h. To obtain nitronyl nitroxide in a persistent form of freshly prepared solution of **18** was treated with alkali solutions (MeONa, LiOH and KOH were used) in MeOH. As a result, a deep violet sodium salt **19Na** as well as other salts were isolated and characterized by IR, UV and ESR-spectroscopy. To illustrate, UV-spectrum of **19Na** is represented by two absorption maxima at 314 and 573 nm (characteristic for $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions). In ESR spectrum there is a characteristic quintet with relative intensities as 1:4:6:4:1 and with hyperfine coupling constant for two equivalent imidazoline nitrogen nuclei $a_{N1}=a_{N2}=0.750$ mT, $g_{iso}=2.0065$, which is typical of nitronylnitroxides (Figure 2).

Crystallization of NNR **18** with the salt of nickel has led to an unexpected formation of red paramagnetic crystals, which, as it turned out, are known as NNR **17**[17], unsubstituted at the 2-position of the heterocycle. The same results were obtained when $Cu(OAc)_2$ was used. Complexation of radical salt **19Na** with $Mn(hfac)_2$ or $Cu(hfac)_2$ has led to noncrystalline material with nonconstant chemical composition.

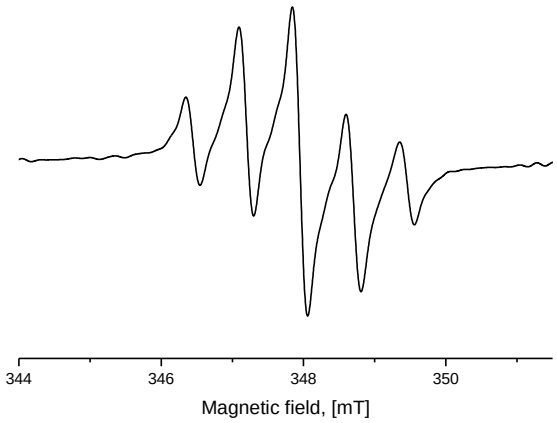
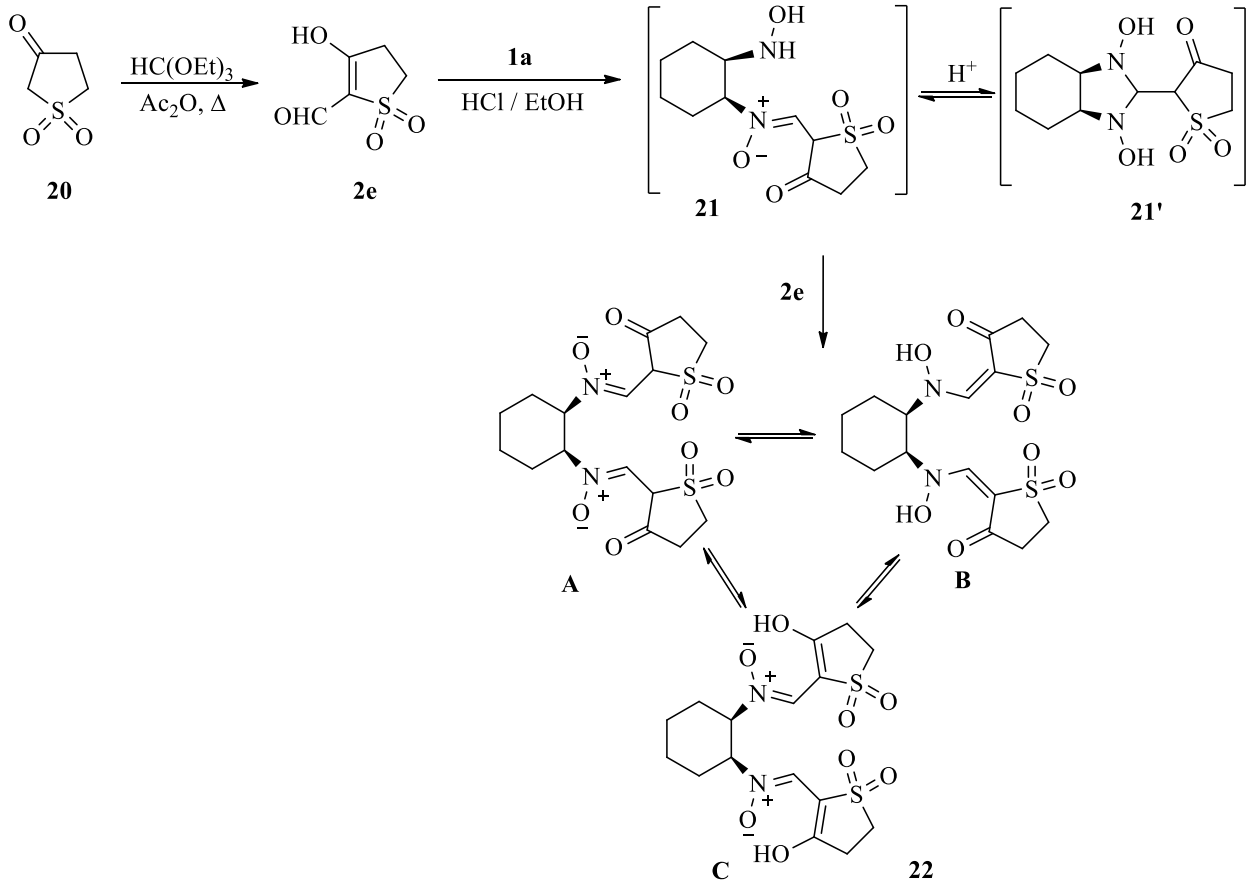


Figure 2. ESR spectra of **19Na** ($c=10^{-6}$M, $CHCl_3$).

In order to study the elimination of acyl fragment in the reaction of BHAs with polycarbonyl compounds we synthesized cyclic 1,3-ketoaldehyde – 2-formyl-3-ketosulpholane **2e** by acylation of useful synthetic block, 3-sulpholanone **20**[19] according to Claisen procedure[18]. We assumed that the structural rigidity of molecule **2e** will prevent the rupture of the C-C bond in the reagent, so that the reaction product will be imidazolidinylidene with two electron-withdrawing substituents at the terminal atom of enamine fragment.

However, the reaction of 1,3-ketoaldehyde **2e** with BHA **1a** in acid containing media has led to the compound with molecular formula $C_{16}H_{22}N_2O_8S_2$, which corresponds to the adduct of one molecule of 1,2-bishydroxylamine with two molecules of ketosulpholane. Indeed, the set of spectral data allowed us to assign the structure of a symmetric dinitrone **22** for separated compound.

According to NMR spectra, dinitrone **22** exists in DMSO solution in a conjugated tautomeric form **22C** rather than in the enamine form **22B** or alternative form of ketonitrone **22A**. In NMR ^{1}H spectrum of **22,** the singlet signal from aldonitrone proton appears at 7.79 ppm while the corresponding signal from carbon atom in NMR ^{13}C spectra has a chemical shift of 138.2 ppm that agrees with the spectra of conjugated nitrones. Also, the signals from carbon atoms of cyclohexane CH-groups appear at 66.3 ppm which points at their coupling to sp^2-nitrogen atom. The formation of dinitrone in this reaction is likely to occur due to the preferential attack of the second molecule of carbonyl compound by hydroxylamino group in acyclic tautomeric form **21**.



Scheme 5

Conclusions

Thus, we have investigated the reactivity of two different aliphatic symmetric BHAs with respect to various acyclic polycarbonyls containing electrophilic moieties, with5-membered heterocyclic rings being the dominant products in these reactions. For the first time, we have synthesized nitronyl nitroxide radical bearing 1,3-dicarbonyl function and studied some of its complexationabilities. The reaction of BHA with cyclic 2-formyl-3-ketosulpholane leads to the formation of open-chain dinitrone.

Experimental Section

General. BHAs - *cis*-1,2-bis(hydroxylamino)cyclohexane[20] **1a** and 2,3-bis(hydroxyamino)-2,3-dimethylbutane[21] **1b** were synthesized as described in literature. Polycarbonyl compounds **2c** and **2d** were prepared by formylation of acetylacetone[22a] and ethyl acetoacetate[22b]. Other reagents

and solvents from commercial sources were of the highest purity available and were used as received. Silufol UV 254 and Merck Kieselgel 60 F_{254} plates were used for TLC monitoring. Chromatography was carried out with the use of "Merck" silica gel (0.063–0.100 mm) for column chromatography. C, H, N, Cl and S elemental analyses were carried out by the Chemical Service Center of the Novosibirsk Institute of Organic Chemistry. The melting points were determined on a Boethius type apparatus and not corrected.

IR spectra were recorded on Bruker IFS-66 in KBr pellets (conc. 0.25%, d=1 mm). UV spectra were registered on Specord M-40. NMR ^{1}H and ^{13}C spectra were obtained on Bruker AC-200, AV-300 and AM-400. X-Band CW ESR spectra were recorded in dilute degassed $CHCl_3$ solutions at room temperature on a Bruker EMX spectrometer.

(*E*)-3-Amino-2-(1-hydroxy-1*H*-benzo[*d*]imidazol-2(3*H*,3a*H*,4*H*,5*H*,6*H*,7*H*,7a*H*)-ylidene)-3-oxopropanoic acid ethyl ester (3a). To a stirred suspension of **1a** (0.50 g, 3.4 mmol) in ethanol (5 ml) a 2-ethoxymethylenecyanoacetic acid ethyl ester **2a** (0.57 g, 3.4 mmol) was added. Light yellow solution was kept 24 h at room temperature and concentrated *in vacuo*. Oily residue was chromatographed on a short column with SiO_2 using a $CHCl_3$ as eluent. The fractions containing **3a** were concentrated under reduced pressure. Viscous oil, yield 92%, 0.87 g, R_f 0.50 ($CHCl_3$ – methanol 40:1); IR (ν_{max}, cm^{-1}): 3327 (NH/OH), 1607 and 1550-1420 (N-C=C-C=O). ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 1.29 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.38 - 2.18 (3m, 8H, $(CH_2)_4$), 3.78 (m, 2H, $(CH)_2$), 4.22 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 5.40 (br s, 1H, NH), 7.87 (br s, 1H, NH_2), 8.12 (br s, 1H, NH_2), 11.6 (br s, 1H, NOH). ^{13}C NMR (60.13 MHz, $CDCl_3$): δ 14.3 (OCH_2CH_3), 19.9, 21.6, 23.6, 31.3 (CH_2 cyclohexane), 52.0, 61.4 (CH cyclohexane), 59.8 (OCH_2CH_3), 76.6 (=*C*-$CONH_2(CO_2Et)$), 167.1 (C=O), 168.0 (C=O), 171.2 ((NOH)NH-*C*=). Anal. Calcd for $C_{12}H_{19}N_3O_4$ (269.30): C, 53.52; H, 7.11; N, 15.60%. Found: C, 53.57; H, 7.05; N, 15.56 %.

(*E*)-3-Amino-2-(1-hydroxy-4,4,5,5-tetramethylimidazol-2-ylidene)-3-oxopropanoic acid ethyl ester (3b)[13] was obtained by the procedure described for **3a** from **1b** (1.50 g, 10 mmol) and 2-ethoxymethylenecyanoacetic acid ethyl ester (1.70 g, 10 mmol). Light yellow crystals, yield 73%, 1.97 g, R_f 0.30 ($CHCl_3$); mp 118–120 °C; IR(ν_{max}, cm^{-1}): 3378-3300 (NH/OH), 1618 and 1528 (N-C=C-C=O). ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 1.22 (s, 12H, CH_3), 1.27 (t, J = 6.97 Hz, 3H, OCH_2CH_3), 4.17 (q, J = 6.97 Hz, 2H, OCH_2CH_3), 5.27 (br s, 1H, NH), 7.09 (br s, 1H, NH_2), 8.21 (br s, 1H, NH_2), 12.5 (br s, 1H, N-OH).

2-Oxo-2,4,4a,5,6,7,8,8a-octahydrobenzo[*d*]isoxazolo[2,3-*a*]imidazole-3-carboxamide (5a). Compound **3a** (1.11 g, 3.9 mmol) was refluxed in MeOH (20 ml) and MeONa (2 ml, 4.95 M MeOH solution) mixture for 3 h. Solvent was removed under reduced pressure, H_2O (20 ml) and AcOH were added till pH = 7 and extracted by $CHCl_3$ (3×20 ml). Combined organic phases dried under $MgSO_4$, filtered off and solvent was removed under reduced pressure. The so obtained residue was recrystallized from *i*-PrOH. Pale crystals, yield 88%, 0.82 g, R_f 0.20 ($CHCl_3$ – methanol 40:1); mp 199-201 °C; IR (ν_{max}, cm^{-1}): 3190 (NH), 2940 (CH_3), 1735, 1657 and 1582 (N-C=C-C=O). ^{1}H NMR (300.13 MHz, $(CD_3)_2SO$): δ 1.10-1.90 (m, 8H, $(CH_2)_4$), 3.90-4.10 (m, 2H, $(CH)_2$), 6.68 (br s, 1H, NH_2), 7.07 (br s, 1H, NH_2), 9.43 (br s, 1H, NH or OH). ^{13}C

NMR (75.47 MHz, $(CD_3)_2SO$): δ 20.9, 21.4, 23.0 (4C, CH_2 cyclohexane), 57.0, 64.3 (2C, CH cyclohexane), 78.3 (=*C*-$CONH_2$), 164.0 (C=O), 172.1 ((N)NH-*C*=), 172.3 (C=O). Anal. Calcd for $C_{10}H_{13}N_3O_3$ (223.23): C, 53.80; H, 5.87; N, 18.82. Found: C, 53.96; H, 5.82; N, 18.63;

2,2,3,3-Tetramethyl-6-oxo-1,2,3,6-tetrahydroimidazo[1,2-*b*]isoxazole-7-carboxamide (5b) was obtained by the procedure described for **5a** from **3b** (0.27 g, 1 mmol). Pale crystals, yield 70%, 0.18 g, R_f 0.15 ($CHCl_3$ – methanol 40:1); dec .>180 °C; IR(ν_{max}, cm^{-1}): 3417 (NH), 2972 (CH_3), 1724, 1667, 1600 and 1542 (N-C=C-C=O). ^{1}H NMR (300.13 MHz, $(CD_3)_2SO$): δ 1.13-1.20 (s, 6H, CH_3), 1.29-1.34 (s, 6H, CH_3), 6.82 (br s, 1H, NH_2), 7.47 (br s, 1H, NH_2), 9.50 (br s, 1H, NH or OH). ^{13}C NMR (75.47 MHz, $(CD_3)_2SO$): δ 17.6, 22.7 (4C, CH_3), 59.0, 67.3 (2C, $C(CH_3)_2$), 77.7 (=*C*-$CONH_2$), 163.5 (C=O), 171.6 ((N)NH-*C*=), 171.8 (C=O). Anal. Calcd for $C_{10}H_{15}N_3O_3$ (225.24): C, 53.32; H, 6.71; N, 18.66%. Found: C, 52.66; H, 6.57; N, 18.30%.

2-(2-(Hydroxyamino)cyclohexyl)-5-oxo-2,5-dihydroisoxazole-4-carboxylic acid ethyl ester hydrocloride (9a). To solution of **1a** (1.46 g, 10 mmol) in EtOH (8 ml) $HCl_{(conc.)}$ (1.3 ml) was added till pH=3-4, then solution of 2-methylendioxydiethylmalonate **2b** (2.59 g; 12 mmol) in EtOH (2 ml) was added and obtained mixture was left for 72 h at room temperature. The so obtained residue was filtered off, washed with EtOH (5 ml) and dried on air. Colorless crystals, yield 39%, 1.26 g, R_f 0.20 ($CHCl_3$ – methanol 40:1); mp 135-137 °C; IR(ν_{max}, cm^{-1}): 3470 (OH), 1776, 1695 and 1566 (C=C-C=O). ^{1}H NMR (200.13 MHz, $(CD_3)_2SO$): δ 1.18 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.40-2.83 (m, 8H, $(CH_2)_4$), 3.33 and 4.41 (m, 2H, $(CH)_2$), 4.19 (q, J = 7.2 Hz, 2H, OCH_2CH_3); 4.70-6.70 (br s, 2H, NHOH), 8.97(s, 1H, NCH=C). ^{13}C NMR (200.13 MHz $(CD_3)_2SO$): δ 13.3(OCH_2CH_3), 20.9, 25.1(4C, CH_2, cyclohexane), 47.7, (C, CH, cyclohexane), 58.4(OCH_2CH_3), 60.1(C, CH, cyclohexane), 87.4 (=C), 150.3 (NCH=), 160.1, 163.9 (C=O). Anal. Calcd for $C_{12}H_{18}N_2O_5 \cdot HCl \cdot H_2O$ (324.76): C 44.38, H 6.52, Cl 10.92, N 8.63%. Found: C 44.62, H 6.35, Cl 10.82, N 8.64%.

1-(1-Hydroxy-1*H*-benzo[*d*]imidazole-2(3*H*,3a*H*,4*H*,5*H*,6*H*,7*H*,7a*H*)-ylidene)propane-2-one (15a).[13] Solution of **1a** (146 mg, 1 mmol), 3-ethoxymethylene-2,4-pentanedione **2c** (156 mg, 1 mmol) and $HCl_{(conc.)}$(0.3 ml) in EtOH (5 ml) was refluxed for 12 h. Solvent was removed under reduced pressure, the so obtained residue was diluted with Et_2O (10 ml) and kept at -12ºC for 24 h. Pale crystals were filtered off, dissolved in minimum $CHCl_3$ and chromatographed by TLC on SiO_2 using mixture of $CHCl_3$-MeOH (20:1) as eluent. Pale crystals, yield 91%, 180 mg, R_f 0.30 ($CHCl_3$-MeOH, 20:1), mp 182-185 °C (lit.[13] 185 °C). IR(ν_{max}, cm^{-1}): 3327 (NH/OH), 1607, 1550-1420 (N-C=C-C=O). ^{1}H NMR (400.13 MHz, $(CD_3)_2SO$): δ 1.12-1.83 (m, 8H, $(CH_2)_4$), 1.85 (s, 3H, $COCH_3$), 3.37 and 3.59 (m, 2H, $(CH)_2$), 4.85 (s, 1H, C=*C*H), 8.73 and 9.30 (br s, 1H, NH/OH). ^{13}C NMR (100.13 MHz $(CD_3)_2SO$): δ 20.2, 21.4, 23.5, 28.8 (4C, CH_2 cyclohexane), 28.9 ($COCH_3$), 51.3, 61.5 (2C, CH cyclohexane), 78.6 (=CH), 165.3 (C=O), 190.6 (C=).

1-(1-Hydroxy-4,4,5,5-tetramethylimidazolidine-2-ylidene)propan-2-one (15b)[13] was obtained by the procedure described for **15a** from **1b** (146 mg, 1 mmol) and **2c** (150 mg, 1 mmol). Pale crystals, yield 25 %, 50 mg, R_f 0.40 ($CHCl_3$ – methanol 20:1); mp 143-146 °C (lit.[13] 142 °C). IR(ν_{max}, cm^{-1}): 3324 (NH/OH), 1608, 1540-1420 (N-C=C-C=O).

2,4-Dihydroxy-2-methyldecahydrobenzo[*d*]isoxazolo[2,3-*a*]imidazol-3-carboxylic acid ethyl ester (16a). Mixture of **1a** (0.3 g, 2 mmol) and ethyl-2-methyleneethoxyacetoacetate **2d** (0.38 g, 2 mmol) in EtOH (2 ml) was kept 12 h at room temperature. White solid was filtered off, washed with EtOH (3×1 ml) and recrystallized from EtOH. White solid, yield 63 %, 0.36 g, mp 121-123 °C; IR (ν_{max}, cm^{-1}): 3405 (OH), 2980 (CH_3), 1716 (C=O), 1207 (C-OEt). ^{1}H NMR (400.13 MHz, $CDCl_3$+$(CD_3)_2SO$): δ 0.82-1.72 (m, 8H, $(CH_2)_4$), 0.91 (t, J = 7.08 Hz 3H, OCH_2CH_3), 1.23(1.06) (s, 3H, CH_3), 2.92 (m, 2H, $(CH)_2$), 3.12 (2.83) (d, J = 5.61(6.13) Hz, 1H, $CHCO_2Et$), 3.82 (m, 2H, OCH_2CH_3), 4.98 (4.71) (d, J = 5.61(6.13) Hz, 1H, NCHN), 5.26 (br s, 1H, OH), 7.43 (br s, 1H, OH). ^{13}C NMR (100.63 MHz, $CDCl_3$+$(CD_3)_2SO$): δ 13.8, 23.3 (4C, CH_2 cyclohexane), 23.0 (22.3) (OCH_2CH_3), 26.3 (24.1) (CH_3), 60.3 (OCH_2CH_3), 60.7 (2C, CH cyclohexane), 63.1 (65.5) ($CHCO_2Et$), 102.6(105.8) (NCHN), 118.4(118.5) (OCOH), 168.2 (C=O) (minor component in parenthesis). Anal. Calcd for $C_{13}H_{22}N_2O_5$ (286.32): C, 54.53; H, 7.74; N, 9.78; Found: C, 54.33; H, 7.79; N, 9.85.

1,6-Dihydroxy-2,2,3,3,6-pentamethylhexahydroimidazo[1,2-*b*]isoxazole-7-carboxylic acid ethyl ester (16b) was obtained by the procedure described for **16a** from **1b** (150 mg, 1 mmol) and **2d** (190 mg, 1 mmol). White solid, yield 86 %, 250 mg, dec. > 90 °C; IR (ν_{max}, cm^{-1}): 3143 (OH), 2986 (CH_3), 1746 (C=O), 1131 (COEt). ^{1}H NMR (400.13 MHz, ($CDCl_3$): δ 0.93, 0.98, 0.99 and 1.00 (s, 12H, CH_3), 1.13 (t, J = 7.3 Hz, 3H, OCH_2CH_3), 1.45 (1.29) (s, 3H, CH_3), 3.05 (3.04) (d, J = 6.76 Hz (J = 6.8 Hz) 1H, $CHCO_2Et$), 4.89 (4.88) (J = 6.76 Hz (J = 6.78 Hz) 1H, NCHN), 4.05 (m, 2H, OCH_2CH_3), 4.71 (4.23) (br s, 1H, OH); 6.64 (7.58) (br s, 1H, OH) (minor component in parenthesis). Anal. Calcd for $C_{13}H_{24}N_2O_5$ (288.34): C, 54.15; H, 8.39; N, 9.72; Found: C, 53.85; H, 8.19; N, 9.90.

Oxidation of (16b) into NNR (18b) and (19Na) isolation. To solution of **16b** (0.57 g, 2 mmol) in MeOH (10 ml) PbO_2 (40 mmol) was added and mixture was vigorously stirred at r.t. for 30 min. Red-violet solution was filtered off from oxidant and treated with equivalent amount of MeONa (0.4 ml; 4.95 M in MeOH). Deep violet solution was formed immediately and solvent was removed under reduced pressure. Dark violet residue was dissolved in minimum of acetone and filtered off. Acetone was removed under reduced pressure and residue was treated with hexane and filtered off. Dark violet powder, yield 32%, 202 mg, dec .> 100 °C; UV (MeOH, λ_{max}, nm (lg ε)): 262 (4.17), 314 (4.12), 573 (3.10). Anal. Calcd for $C_{13}H_{20}N_2NaO_5 \cdot 2H_2O$ (343.33): C, 45.48; H, 7.05; N, 8.16. Found: C, 45.47; H, 6.71; N, 7.79. The same protocol was used to obtain **19Li** and **19K**.

3-Oxotetrahydrothiophene-2-carbaldehyde-1,1-dioxide (2e). Mixture of 3-oxotetrahydrothiophene-1,1-dioxide **20** (4.15 g, 31.0 mmol), triethyl orthoformate (11.7 g, 80.0 mmol) and Ac_2O (16.6 g, 163.0 mmol) was refluxed for 1 h. After cooling to 20 °C needle precipitate was immediately formed. Residue was filtered off, washed carefully with Et_2O (3×20 ml) and recrystallized from AcOH. Pale pink crystals, yield 83%, 4.14 g, mp 175-179 °C; IR (ν_{max}, cm^{-1}): 2700-2300 (–OH), 1573 (C=C−C=O). ^{1}H NMR (200.13 MHz, $(CD_3)_2SO$): δ 2.87 (t, J = 7.5 Hz, 2H, CH_2COH), 3.41 (t, J = 7.5 Hz, 2H, CH_2SO_2), 6.18 (br s, 1H, OH), 9.18 (s, 1H,

CHO). Anal. Calcd for $C_5H_6O_4S$ (162.16): C, 37.03%; H, 3.73%; S, 19.77% $C_5H_6O_4S$; Found: C, 36.37%; H, 3.71%; S, 19.55%.

***cis*-1,2-Bis(hydroxy-(2-methylene-1,1-dioxotetrahydrothiophene-3-on)amino)cyclohexane (22).** To suspension of **1a** (0.146 g, 1 mmol) in EtOH (1 ml) $HCl_{(conc.)}$was added till pH=2-3. Then aldehyde **2e** (0.170 g, 1 mmol) was added by small portions and obtained solution was kept for 24 h at room temperature. Deposited crystals were separated, washed with EtOH (2×1 ml) and dried. Dark brown crystals, yield 50%, 0.110 g, mp 253-257 °C; IR (ν_{max}, cm^{-1}): 1606 (C=C-C=O(N)), 1286, 1104 (SO_2). ^{1}H NMR (400.14 MHz, $(CD_3)_2SO$): δ 1.46-2.26 (3m, 8H, $(CH_2)_4$), 2.82 (s, 4H, CH_2COH), 3.41 (s, 4H, CH_2SO_2), 4.07 (s, 2H, $(CH)_2$), 7.79 (s, 1H, N=*C*H), 15.7 (br s, 2H, OH). ^{13}C NMR (400.13 MHz $(CD_3)_2SO$): δ 21.8, 26.9 (8C, CH_2 cyclohexane), 30.6 (2C, CH_2COH), 50.5 (2C, CH_2SO_2), 66.3 (4C, CH cyclohexane), 104.3 (CSO_2), 138.2 (CHNO), 186.6 (=COH). Anal. Calcd for $C_{16}H_{22}N_2O_8S_2$ (433.48): C, 44.33; H, 4.88; N, 6.46; S, 14.79 Found: C, 43.68; H, 5.09; N, 6.46; S, 14.62.

X-Ray structure determinations

XRD data (Table 1) for compound **9a** were obtained on a Bruker P4 diffractometer with graphite-monochromated Mo-*K*α radiation. The structure was solved by direct methods using the SHELXS-97 program[23] and refined by the least-squares method in the full-matrix anisotropic (isotropic for all H atoms) approximation using the SHELXL-97 program.[23] Absorption correction was applied by integration method (transmission 0.9691-0.9005).The hydrogen positions were taken from difference Fourier map and those which bonded to oxygens and nitrogens were refined with the distance restraints O-H 0.85 N-H 0.92 Å. The asymmetric part of the unit cell includes two molecules of water. The obtained crystal structure was analyzed for short contacts between non-bonded atoms and hydrogen bonding (Table 1) using the PLATON program.[24] CCDC-734585 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

Crystallographic data for comp **9a**: $C_{12}H_{23}N_2O_7Cl$, M = 342.76 g/mol, monoclinic, $P2_1/c$, a = 8.1462(12), b = 23.630(3), c = 8.7648(10) Å, β = 95.272(9)°, V = 1680.1(4) Å3, Z = 4, D_{calcd} = 1.355 g•cm^{-3}, μ(Mo-Kα) = 0.261 mm^{-1}, F(000) = 728, (θ 2.49 - 26.00°, completeness 100%), T 296(2) K, colorless alongated plate, (0.96 × 0.40 × 0.12) mm^3, 3526 measured reflections in index range 0<=h<=10, -29<=k<=0, -10<=l<=11, 3290 independent (R_{int} = 0.0309), 13 restraints, 290 parameters, 2558 observed [I> 2σ(I)], R_1 = 0.0438, wR^2 = 0.1192 (all data), GOOF 1.012, largest diff. peak and hole 0.241 and -0.212 e.A^{-3}.

References

1. (a) Mazhukin, D. G.; Volodarskii, L. B.; Tikhonova, L. A.; Tikhonov, A. Y. *Mendeleev Commun.* **1992**, *2*, 29. (b) Utepbergenov, D. I.; Khramtsov, V. V.; Vlassenko, L. P.; Markel, A. L.; Mazhukin, D. G.; Tikhonov, A. Y.; Volodarsky, L. B. *Biochem. Biophys. Res. Commun.* **1995,** *214*, 1023.
2. Mazhukin, D. G.; Tikhonov, A. Y.; Reznikov, V. A.; Volodarsky, L. B. *Mendeleev Commun.* **2000,** *10*, 69.
3. (a) Mazhukin, D. G.; Tikhonov, A. Y.; Volodarskii, L. B.; Konovalova, E. P. *Chem. Heterocycl. Compd.* **1993**, *29*, 437; *Chem. Abstr.* **1994**, *120*, 134422. (b) Mazhukin, D. G.; Tikhonov, A. Y.; Volodarsky, L. B., Evlampieva, N. P.; Vetchinov, V. P.; Mamatyuk, V. I. *Liebigs Ann. Chem.* **1994**, 983.
4. Butakov, V. V.; Khlestkin, V. K.; Mazhukin, D. G. *Mendeleev Commun.* **2005**, *15*, 162.
5. (a) Severina, I. A.; Ryaposova, I. K.; Volodarsky, L. B.; Mazhukin, D. G.; Tikhonov, A. Y.; Schwartz, G. Y.; Granik, V. G.; Grigor'ev, D. A.; Grigor'ev, N. B. *Biochem. Mol. Biol. Int.* **1993**, *30*, 357. (b) Schwartz, G. Y.; Grigor'ev, I. B.; Severina, I. A.; Ryaposova, I. K.; Lapitskaya, A. S.; Volodarsky, L. B.; Tikhonov, A. Y.; Kurbnikova, I. F.; Mazhukin, D. G.; Granik, V. G. *Khim. Pharm. Zh. (Russ.)* **1994**, *28*, 4, 38; *Chem. Abstr.* **1994,** *121*, 170187.
6. Tikhonov, A. Y.; Mazhukin, D. G.; Grigor'eva, L. N.; Khlestkin, V. K.; Voinova, N. N.; Syropyatov, B. Y.; Shirinkina, S. S.; Volodarsky, L. B. *Arch. Pharm. – Pharm Med. Chem.* **1999**, *332*, 305.
7. (a) Volodarsky, L. B.; Reznikov, V. A.; Ovcharenko, V. I. *Synthetic chemistry of stable nitroxides*; CRC Press Inc: Boca Raton, Florida, 1994, p 221. (b) Tretyakov, E. V.; Ovcharenko V. I. *Russ. Chem. Rev.* **2009**, *78*, 971.
8. (a) Zhang, W.; Basak, A.; Kosugi, Y.; Hoshino, Y.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 4389. (b) Zhang, W.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 286.
9. Basak, A.; Barlan, A. U.; Yamamoto, H. *Tetrahedron: Asymmetry* **2006**, *17*, 508.
10. Oh, Y. S.; Kotani, S.; Sugiura, M.; Nakajima, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1833.
11. Barlan, A. U.; Zhang, W.; Yamamoto, H. *Tetrahedron* **2007**, *63*, 6075.
12. (a) Nishiwaki, N.; Takada, Y.; Inoue, Y.; Tohda, Y.; Ariga, M. *J. Heterocyclic Chem.* **1995**, *32*, 473. (b) Nishiwaki, N.; Nogami, T.; Kawamura, T.; Asaka, N.; Tohda, Y.; Ariga, M. *J. Org. Chem.* **1999**, *64*, 6476. (c) Matsushima, K.; Tamura, M.; Hori, K.; Tohda, Y.; Nishiwaki, N.; Ariga, M. *Nippon Kagakkai Koen Yokoshu* **2002**, *81*, 1022. (d) Nishiwaki, N.; Ogihara, T.; Takami, T.; Tamura, M.; Ariga, M. *J. Org. Chem.* **2004**, *69*, 8382. (e) Nishiwaki, N.; Ariga, M. In *Bioactive Heterocycles*; Eguchi, S.; Gupta, R. R. Eds.; Springer: Berlin, Heidelberg, 2007; Vol. 2, pp. 43-72. (f) Nakaike, Y.; Hayashi, D.; Nishiwaki, N.; Tobe, Y.; Ariga, M. *Org. Biomol. Chem.* **2009**, *7*, 325.
13. Reznikov, V. A.; Roshchupkina, G. I.; Mazhukin, D. G.; Petrov, P. A.; Popov, S. A.; Fokin, S. V.; Romanenko, G. V.; Rybalova, T. V.; Gatilov, Y. V.; Shvedenkov, Y. G.; Irtegova, I. G.; Shundrin, L. A.; Ovcharenko, V. I. *Eur. J. Org. Chem.* **2004**, 749.

14. Grassi, G.; Bruno, G.; Risitano, F.; Foti, F.; Caruso, F.; Nicolo, F. *Eur. J. Org. Chem.* **2001**, 4671.
15. Wang, H.-T.; Wang, X.-J.; Huang, Z.-T. *Chem. Ber.* **1990**, *123*, 2141.
16. Nair, M. D.; Rajappa, S.; Desai, J. A. *Indian J. Chem., Sect. B* **1982**, *21*, 1; *Chem. Abstr.* **1982**, *96*, 217794.
17. Boocock, D. G. B.; Darcy, R.; Ullman E. F. *J. Am. Chem. Soc*. **1968**, *21*, 5945.
18. (a) Claisen, L. *Ber. Deutsch. Chem. Gesell.* **1893**, *26*, 2729. (b) Jones, R. G. *J. Am. Chem. Soc*. **1952**, *74*, 4889.
19. Belletire, J. L.; Spletzer, E. G. *Synthetic Commun.* **1983**, *13*, 269.
20. Mazhukin, D. G.; Tikhonov, A .Y.; Volodarskii, L. B.; Konovalova, E. P.; Tikhonova, L. A.; Bagryanskaya, I. Y.; Gatilov, Y. V. *Russ. Chem. Bull*. **1993**, *42*, 851 (Engl. Transl.).
21. (a) Ovcharenko, V. I.; Fokin, S. V.; Korobkov, I. V.; Rey P. *Russ. Chem. Bull*. **1999**, *48*, 1519 (Engl. Transl.). (b) Hirel, C.; Vostrikova, K. E.; Pecaut, J.; Ovcharenko, V. I.; Rey. P. *Chem. Eur. J*. **2001**, *7*, 2007.
22. (a) Wang, J.-H.; Shen, Y.-Q.; Yu, C.-X.; Si, J.-H. *J. Chem. Soc., Perkin Trans. 1*. **2000**, 1455. (b) Jones, R. G. *J. Am. Chem. Soc*. **1951**, *73*, 3684.
23. Sheldrick, G. M. *SHELX-97 – Programs for Crystal Structure Analysis*, Release 97-2, University of Goettingen, Goettingen, Germany.
24. (a) Spek, A. L. *PLATON, A Multipurpose Crystallographic Tool*, Version 10M, Utrecht University, Utrecht, The Netherlands, 2003. (b) Spek, A. L. *J. Appl. Crystallogr*. **2003**, *36*, 7.

