Synthesis and structure of 5-acylhydrazine-3,3,5-trimethylisoxazolidines

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Dedicated to Academician Oleg Nikolaevich Chupakhin on the occasion of his 70th birthday
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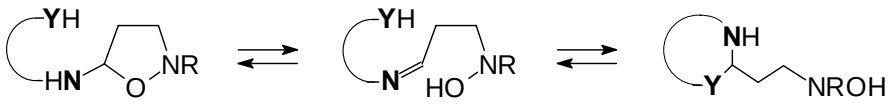
Abstract
The interaction between 5-hydroxy-3,3,5-trimethylisoxazolidine and hydrazides of acetic, isobutyric, thiobenzoic, and thioglycolic acids was investigated. The structures of the final products and their tendency to tautomeric transformations in solution were studied by ^{1}H- and ^{13}C- NMR spectroscopy.

Keywords: Isoxazolidines, 1,3,4-thiadiazin-5(4H)-ones, ring–chain–ring tautomerism

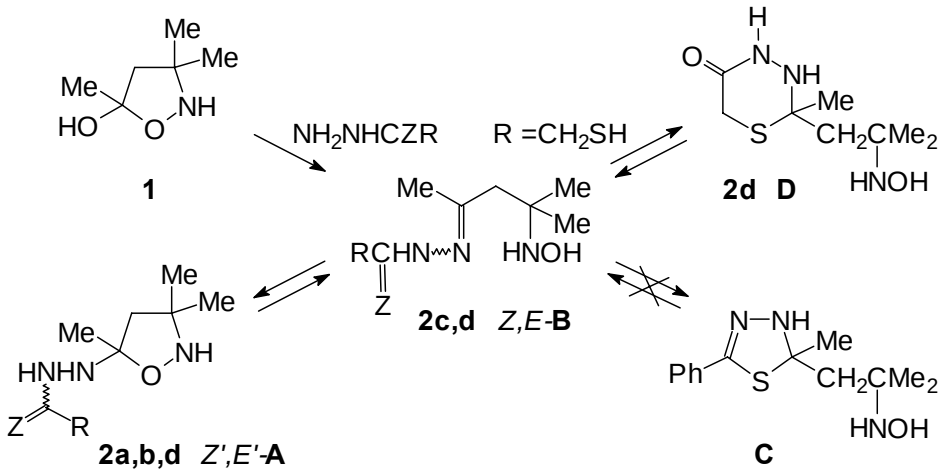
Introduction

The presence of a cyclic hemiacetal (or hemi-aminal) fragment in the isoxazolidine molecule confers a high tendency to cleavage of the C(5)–O bond with the formation of a linear structure, *i.e.*, ring–chain isomerism or tautomerism take place.[1–3] If the isoxazolidine molecule contains complex functional nucleophilic substituents, qualitatively new structural possibilities appear because these functions participate in further transformations (Scheme 1). Intermolecular nucleophilic attacks of these fragments at the C=N polar bond contained in the linear structure can lead to repeated cyclization with the formation of new cyclic forms.[4]



A **B** **C**

Scheme 1



2a R=Me, Z=O; **2b** R=*i*-Pr, Z=O; **2c** R=Ph, Z=S; **2d** R=CH_2SH, Z=O

Scheme 2

Results and Discussion

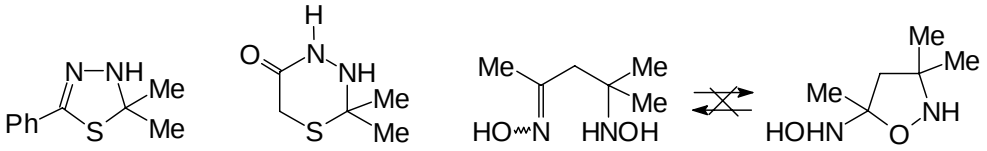
In this paper we continue our previous investigations in the series of 5-functionally-substituted isoxazole derivatives[5–8] and investigated the interaction between 5-hydroxy-3,3,5-trimethylisoxazolidine 1 and hydrazides of acetic, isobutyric, thiobenzoic, and thioglycolic acids (Scheme 2).

The corresponding compounds **2a–d** are formed in high yields after the storage of equimolar amounts of the initial reagents in methanol at room temperature for several days in the presence of catalytic amounts of acetic acid (see Experimental Section).

The products of condensation of 5-hydroxy-3,3,5-trimethylisoxazolidine **1** with thiobenzoyl-hydrazine and mercaptoacetylhydrazine (compounds **2c,d**) were chosen for investigation because of possible variants of tautomeric (isomeric) transformations. Apart from the isoxazolidine **A** and linear **B** forms, additional cyclic forms also participate in these transformations. The tendency to cyclization of thiobenzoylhydrazones and mercaptoacetylhydrazones into derivatives of 1,3,4-thiadiazoline and 1,3,4-thiadiazin-5-one, respectively, is a general property of these classes of compounds.[8,9]

To confirm the presence of cyclic forms, in addition to the isoxazolidine ring, the spectroscopic characteristics of compounds **3–5** known in the literature[8–10] were studied. These compounds are models for the corresponding forms **B**, **C**, and **D** of the studied compounds (Scheme 3). The ^{13}C NMR spectroscopic data provide the main criterion for choosing some cyclic structures of compounds **2a–d**. Thus, the signal of the sp^3- C-5 atom at 80 ppm has been observed in the carbon spectrum of 2-phenyl-5,5-dimethyl-1,3,4-Δ2-thiadiazoline **3**.[9] Six-membered rings, unlike five-membered rings, are characterized by an upfield shift of signals of the hemiacetal carbon atoms by 10–15 ppm. Therefore, for the signals of the C-2 atom in the

1,3,4-thiadiazine ring of compound **4** a chemical shift will be observed at 70 ppm.[8,10] The transition from cyclic to linear structures should cause the disappearance of hemiacetal signals in the range of 70–100 ppm and to the appearance in the ^{13}C-NMR spectrum of a downfield signal at 150–160 ppm. This signal is characteristic of carbon atom in the C=N bond. This is easily simulated by the spectral characteristics of compound **5** which has a linear 1,3-hydroxyamine oxime, **5A**, and not a cyclic 5-(hydroxyamine)isoxazolidine, **5B**, structure.[11]



3 **4** **5 A** **5 B**

Scheme 3

We will consider the products of interaction between 5-hydroxy-3,3,5-trimethylisoxazolidine **1** and the hydrazides of acetic and isobutyric acids (compounds **2a,b**). Both compounds in the crystalline state have a cyclic isoxazolidine structure **A**. This can be confirmed by the appearance of a signal of the C-5 atom at 100 ppm in their ^{13}C NMR solid-state spectra. The doubling of individual signals in the ^{1}H NMR spectrum of compound **2a** in DMF-d_7 solution is observed due to hindered amide rotation of the acetyl group relative to the C–N bond (*Z*',*E*'-isomerism). This is easily confirmed by the coalescence of doubled signals when the spectrum is taken at 80 ^{o}C in DMF-d_7. Compound **2b** is conformationally homogeneous. In both cases the formation in solution of an alternative linear form **B**, due to the opening of the isoxazolidine ring was not observed.

Compound **2c**, a product of interaction between 5-hydroxy-3,3,5-trimethylisoxazolidine **1** and thiobenzoic acid hydrazide in the crystalline state has the hydrazone structure **B**. This is confirmed by the appearance of a downfield signal at 157 ppm characteristic of the sp^2-hybrid carbon atom of the C=N bond in its ^{13}C NMR solid-phase spectrum. In solutions of polar basic solvents (DMSO-d_6, DMF-d_7, and pyridine-d_5), compound **2c** also exists in the linear form **B**, although in all cases the doubling of hydrazone form signals is observed. This is due to steric *Z*,*E*-isomerism with respect to the C=N bond.

Signals were assigned to geometric isomers on the basis of the deshielding effect of the hydrazone fragment on *cis*- arranged methylene protons in the ^{1}H NMR spectrum. This effect was detected for hydrazones and is well known in the literature.[12] Therefore, the less intense downfield signal at 2.58 ppm in the spectrum of compound **2c** in $CDCl_3$ should be assigned to the *Z*-isomer and the upfield signal at 2.45 ppm to the *E*-isomer. The content of *E*-isomer of linear form **B** exceeds twice the analogous content of the *Z*-isomer. In weakly polar solvents, for example $CDCl_3$, compound **2c** exists as a three-component ring–chain tautomeric mixture of two *Z*,*E*-isomers of linear form **B** and cyclic isoxazolidine form **A** in an approximate ratio: *E*-**B** ⇄ *Z*-

B ⇄ **A**, 60:30:10. It should be mentioned that the formation in solution of the second cyclic form, the thiadiazoline form **C** — and thus the implementation of a more complex equilibrium with the participation of two cyclic forms — was not observed. This was shown by taking spectra in a large set of solvents with variation of temperature and time parameters over a wide range. Thus, even in trifluoroacetic acid solution which is known[9] to favor cyclization into a 1,3,4-thiadiazoline ring, compound **2c** also has a linear hydrazone structure **B**.

A more complex variant of a three-component tautomeric equilibrium with the participation of two cyclic and one linear form was observed for the product of a reaction of 5-hydroxy-3,3,5-trimethylisoxazolidine **1** with thioglycolic acid hydrazide. Immediately after the dissolution of 5-(2-mercaptoacetylhydrazine)-3,3,5-trimethylisoxazolidine **2d** in DMSO-d_6 the tautomeric equilibrium between the cyclic **A** and linear **B** forms is fixed spectrally. The linear **B** form exists here as one steric *E*-isomer. In three days additional singlet signals of methyl protons at 1.01 and 1.48 ppm appear in the ^{1}H NMR spectrum of compound **2d**. They correspond to one more cyclic form to which the 1,3,4-thiadiazine structure **D** should be assigned on the basis of comparison of its spectral characteristics with those for model compound **4**. The ^{13}C NMR chemical shifts: 31.6 (C(6)), 69.7 (C(2)), and 173.6 ppm (C(5)), are in complete agreement with the assumed cyclic structure of form **D** of compound **2d**.

We compare 1,3-hydroxyamine acylhydrazones **2a**–**d** with *bis*-functional derivatives of β-dicarbonyl compounds, 1,3-acylhydrazone oximes, exhibiting similar structures. The latter are also characterized by a tendency to reversible recyclizations in solutions[13,14] and to the implementation of complex variants of isomeric or tautomeric transformations. It is noteworthy that for acetylacetone 1,3-mercaptoacetylhydrazone oxime we have observed a rare case of the simultaneous presence in solution of three different cyclic forms: three-ring tautomerism of the Δ^2-isoxazoline–Δ^2-pyrazoline–1,3,4-thiadiazine system.[14]

Hence, these data, on one hand, indicate very high mobility of isoxazole derivatives in molecular recyclizations and possibility of their use as synthons in organic synthesis. On the other hand, these transformations widen the concept of recyclization mechanism in the heterocyclic series by the SN(ANRORC) (Addition–Nucleophile–Ring Opening–Ring Closure) type. Numerous examples of these recyclizations have been investigated and generalized in recent reviews[15,16] by academician Chupakhin for the series of 1,2,4-triazine ring.

Experimental Section

General Procedures. The ^{1}H- and ^{13}C- NMR spectra in solutions were recorded on Bruker AC 200 and AM 500 spectrometers, and in the solid phase on a Bruker CXP 100 spectrometer (25 MHz) by a standard procedure using polarization transfer and, “magic angle” spinning at a frequency of 3 kHz. The quantitative composition of the tautomeric forms was determined by integration of the appropriate signals in the ^{1}H NMR spectra. Chromatographic separation was carried out on a glass column packed with Chemapol L 100/160 silica gel. The eluent was

benzene–ethyl acetate, 2:1. Compound **1** was obtained by a known method.[3] "Ether" refers to diethyl ether.

General procedures for compounds 2a–d

A mixture of compound **1** (3.91 g, 0.03 mole), acyl hydrazine (0.025 mole), and several drops of acetic acid in methanol (25 ml) was maintained at 25 °C for three days. After removal of the solvent under reduced pressure the residue was washed with ether, and recrystallized from a 2:1 hexane–ethyl acetate mixture, or purified on the column.

5-(2-Acetylhydrazine)-3,3,5-trimethylisoxazolidine (2a). (51%), m.p. 137–140 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: *Z*'-*A* form, (90%): 1.20, 1.22 (2s, 6H, $2CH_3C_{(3)}$), 1.39 (s, 3H, $CH_3C_{(5)}$), 1.74, 1.96 (AB-system, J_{AB} = 13 Hz, 2H, H-4), 1.95 (s, 3H, CH_3CO), 4.82 (br. s, 1H, NH), 6.21 (br. s, 1H, NH), 8.37 (br. s, 1H, NHCO), *E'*-**A** form, (10%): 1.17 (s, 3H, $CH_3C_{(3)}$), 1.36 (s, 3H, $CH_3C_{(5)}$), 1.92 (s, 3H, CH_3CO), 2.05 (s, 2H, H-4), 7.41 (br. s, 1H, NH). ^{13}C NMR ($CDCl_3$) δC/ppm: *Z*'-**A** form: 21.8 (CH_3C=O), 22.8, 25.1 ($2CH_3C_{(3)}$), 28.6 ($CH_3C_{(5)}$), 52.8 ($C_{(4)}$), 62.5 ($C_{(3)}$), 100.1 ($C_{(5)}$), 168.5 (C=O), *E*'-**A** form: 28.2 ($CH_3C_{(5)}$), 52.2 ($C_{(4)}$), 60.7 ($C_{(3)}$), 99.7 ($C_{(5)}$), 175.8 (C=O). ^{13}C NMR (solid phase) δC/ppm: *Z*'-**A** form, (100%): 22.3 (CH_3C=O), 23.5 ($2CH_3$C(3)), 29.1 ($CH_3C_{(5)}$), 53.1 ($C_{(4)}$), 61.8 ($C_{(3)}$), 99.8 ($C_{(5)}$), 170.3 (C=O). Anal.: Calcd for $C_8H_{17}N_3O_2$ (187.24): C, 51.32; H, 9.15; N, 22.44. Found: C, 51.27; H, 9.20; N, 22.49%.

5-(2-Isopropanoylhydrazine)-3,3,5-trimethylisoxazolidine (2b). (55%), m.p. 123–125 °C. ^{1}H NMR (DMSO-d_6) δ/ppm: *Z*'-**A** form, (100%): 1.01 (s, 6H, $2CH_3C_{(3)}$); 1.14 (d, 6H, $2CH_3$CH); 1.79 (s, 3H, $CH_3C_{(5)}$); 2.16 (s, 2H, H-4); 2.37 (m, 1H, CH); 3.38 (br. s, 1H, NH); 8.03 (br. s, 1H, NH); 10.41 (br. s, 1H, NHCO). ^{13}C NMR (DMSO-d_6) δC/ppm: 20.5 ($2CH_3$CH); 23.1; 24.6 ($2CH_3C_{(3)}$); 28.7 ($CH_3C_{(5)}$); 33.1 (CH); 53.0 ($C_{(4)}$); 62.6 ($C_{(3)}$); 100.4 ($C_{(5)}$); 170.3 (C=O). ^{13}C NMR (solid phase) δC/ppm: 21.2 ($2CH_3$CH); 22.8 ($2CH_3C_{(3)}$); 28.3 ($CH_3C_{(5)}$); 33.5 (CH); 52.9 ($C_{(4)}$); 62.0 ($C_{(3)}$); 100.2 ($C_{(5)}$); 172.6 (C=O). Anal. Calcd for $C_{10}H_{21}N_3O_2$ (215.29): C, 55.79; H, 9.83; N 19.52. Found: C, 55.83; H, 9.78; N, 19.47%.

4-Methyl-4-hydroxylaminopentan-2-one 2-thiobenzoylhydrazone (2c). (60%), m.p. 144–146°C. ^{1}H NMR ($CDCl_3$) δ: **A** form, (10%): 1.15 (s, 6H, $2CH_3C_{(3)}$), 1.53 (s, 3H, $CH_3C_{(5)}$), 1.81, 2.08 (AB-system, J_{AB} = 12 Hz, 2H, H-4), *E*-**B** form, (60%), 1.28 (s, 6H, $2CH_3$), 1.98 (s, 3H, CH_3C=N), 2.45 (s, 2H, CH_2), 8.33 (br. s, 2H, NHOH), 10.11 (br. s, 1H, NHCO), *Z*-**B** form, (30%): 1.34 (s, 6H, $2CH_3C$–N), 1.97 (s, 3H, CH_3C=N), 2.58 (s, 2H, CH_2), 8.45 (br. s, 2H, NHOH), 7.38–7.74 (m, 5H, C_6H_5 of **A** and *E*,*Z*-**B** forms). ^{1}H NMR (CF_3COOD) δ: *E*-**B** form, (65%): 1.56 (s, 6H, $2CH_3C$–N), 2.29 (s, 3H, CH_3C=N), 3.03 (s, 2H, CH_2), *Z*-**B** form, (35%), 1.61 (s, 6H, $2CH_3C$–N), 2.20 (s, 3H, CH_3C=N), 3.23 (s, 2H, CH_2), 7.35–7.78 (m, 5H, C_6H_5 of *E*-**B** and *Z*-**B** forms). ^{13}C NMR (CF_3COOD) δC *E*-**B** form, 16.5 (CH_3C=N), 22.1 ($2CH_3C$–N), 41.6 (CH_2), 65.5 (C–N), 163.2 (C=N), 202.1 (C=S). *Z*-**B** form: 20.7 (CH_3C=N), 22.4 ($2CH_3$), 38.3 (CH_2), 67.4 (C–N), 127.3–137.7 (C_6H_5 of *E*-**B** and *Z*-**B** forms), 163.9 (C=N), 201.5 (C=S). ^{13}C NMR (solid phase) δC, *E*-**B** form, (100%): 18.6 (CH_3C=N), 23.9, 25.4 ($2CH_3C$–N), 44.4 (CH_2), 59.7 (C–N), 124.2–138.3 (C_6H_5), 157.3 (C=N), 195.2 (C=S). Anal. Calcd for $C_{13}H_{19}N_3OS$ (265.38): C, 58.84; H, 7.22; N, 15.83. Found: C, 58.80; H, 7.27; N, 15.78%.

5-(2-Mercaptoacetylhydrazinyl)-3,3,5-trimethylisoxazolidine (2d). (50%), viscous oil, R_f = 0.31 (Silufol UV 254, benzene–acetone, 2:1), ^{1}H NMR (DMSO-d_6) δ: *Z*'-**A** form, (70%); 1.08, 1.16 (2s, 6H, $2CH_3C_{(3)}$), 1.77 (s, 3H, $CH_3C_{(5)}$), 1.78; 2.03 (AB-system, J_{AB} = 12 Hz, 2H, H-4), 2.23 (br. s, 1H, SH), 3.09 (s, 2H, CH_2S), 5.42 (br. s, 1H, NH), 9.28 (br. s, 1H, NHCO); *E*-**B** form, (20%); 1.15 (s, 3H, $2CH_3$), 1.90 (s, 3H, CH_3C=N), 2.40 (s, 2H, CH_2), 3.21 (s, 2H, CH_2S), 5.82 (br. s, 1H, N*H*OH), 10.14 (br. s, 1H, NHCO); **D** form, (10%), 1.01 (s, 3H, $2CH_3$), 1.48 (s, 3H, $CH_3C_{(2)}$), 2.21 (s, 2H, CH_2), 3.40; 3.51 (AB-system, J_{AB} = 13 Hz, 2H, H-6). ^{13}C NMR (DMSO-d_6) δ_C: *Z*'-**A** form: 22.3, 24.3 ($2CH_3C_{(3)}$), 28.3 ($CH_3C_{(5)}$), 45.5 (CH_2S), 52.4 ($C_{(4)}$), 61.2 ($C_{(3)}$), 99.4 ($C_{(5)}$), 169.3 (C=O), *E*-**B** form, 16.0 (CH_3C=N), 22.1; 25.7 ($2CH_3$), 28.0 (CH_2S), 43.1 (CH_2), 57.5 (C–N), 153.9 (C=N), 168.2 (C=O), **D** form, 21.7, 23.6 ($2CH_3$), 30.6 ($CH_3C_{(2)}$), 31.6 ($C_{(6)}$), 41.6 (CH_2), 62.5 (C–N), 69.7 ($C_{(2)}$), 173.6 ($C_{(5)}$). Anal. Calcd for $C_8H_{17}N_3O_2S$ (219.31): C, 43.81; H, 7.81; N, 19.16. Found: C, 47.78; H, 7.75; N 19.22%.

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