Three-ring tautomerism of the Δ^2-isoxazoline - Δ^2-pyrazoline - 1,3,4-thiadiazine system

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Abstract

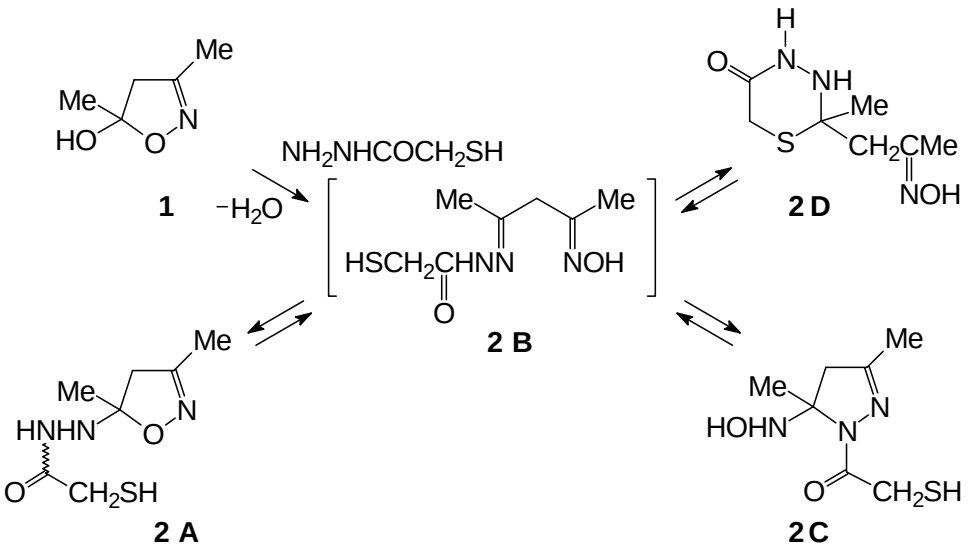
The tendency to tautomeric equilibria of 5-(2-mercaptoacetylhydrazine)-3,5-dimethyl-Δ^2-isoxazoline in solutions with the participation of not only the isoxazoline ring but also of Δ^2-pyrazoline and 1,3,4-thiadiazin-5(6*H*)-one forms was confirmed by ^{1}H and ^{13}C NMR spectroscopy. A new type of tautomeric transformations involving three different rings was found.

Keywords: Δ^2-Isoxazoline, Δ^2-pyrazoline, 1,3,4-thiadiazin-5(6*H*)-one, three-ring tautomerism

Introduction

We have shown earlier that the competition between two ring–chain transformations in solutions of the acetylacetone 1,3-alkanoylhydrazone oximes series gives rise to the implementation of a more complex variant of the equilibrium with the participation of two cyclic forms – ring–ring tautomerism of the 5-hydrazine-Δ^2-isoxazoline – 5-hydroxyamine-Δ^2-pyrazoline type.[1] On the other hand, ring–chain tautomerism of acetone mercaptoacetylhydrazone with participation of a six-membered tetrahydro-1,3,4-thiadiazine ring in the equilibrium has been investigated recently.[2] It is evident, that the possibility of occurrence of the equilibrium between three cyclic forms: Δ^2-isoxazoline **A** – Δ^2-pyrazoline **C** – tetrahydro-1,3,4-thiadiazine **D** (ring–ring–ring or three-ring tautomerism) in a solution could be expected in the case of acetylacetone 1,3-mercaptoacetylhydrazone oxime **2**.

The purpose of this study was to obtain previously unknown acetylacetone 1,3-mercapto-acetylhydrazone oxime and to investigate its tendency to tautomeric interconversions in solutions by ^{1}H and ^{13}C NMR spectroscopy (Scheme 1).



Scheme 1

Results and Discussion

It was found that compound **2** was obtained in high yield by the nucleophilic substitution of the hemiacetal OH group of 5-hydroxy-3,5-dimethyl-Δ^2-isoxazoline **1** upon the action of mercaptoacetic acid hydrazide in methanol at room temperature.

In the crystalline state compound **2** was found to exist as isoxazoline **A**. This proves to be true because the signal of sp^3-hybrid atom $C_{(5)}$ at 99.4 ppm (N,O-environment) is present in its ^{13}C NMR spectrum recorded in the solid phase (Table 1). Immediately after the dissolution of compound **2** in $CDCl_3$, a doubling of individual signals of the isoxazoline form **A** is observed in ^1H NMR spectrum. This may be caused by the effect of restricted amide rotation in the hydrazine fragment with respect to the C–N bond (Tables 1 and 2). This is confirmed by the coalescence of the signals when the ^1H NMR spectrum is recorded at 100°C in DMF-d_7. One day after compound **2** had been dissolved in $CDCl_3$, in addition to two asymmetrical doublets forming a typical *AB* pattern at 2.82 and 3.02 ppm (protons H–4) in ^1H NMR spectrum, the second *AB* pattern at 2.69 and 3.28 ppm caused by presence of one more cyclic form appeared. Comparison of its spectral characteristics in the ^1H and ^{13}C NMR spectra with those of model compounds of the acetylacetone 1,3-alkanoylhydrazone oximes series[1] shows that the former has the pyrazoline **C** structure. The transition from weakly polar $CDCl_3$ to strongly polar basic solvents (pyridine-d_5, DMSO-d_6, DMF-d_7) leads to the slightly increasing content of the pyrazoline **C** form. Three days after the dissolution of compound **2** in DMF-d_7, the signal of methyl protons at 1.78 ppm as well as two singlet signals of methylene protons appeared at 3.38 and 3.69 ppm. All these signals correspond to one more cyclic form. The coexistence in the solution of the third cyclic form is

also proved by ^{13}C NMR spectra. Subsequently spectrum of compound **2** did not undergo any changes. This indicates that final equilibrium is established in the solution.

Table 1. ^{13}C NMR spectra of compound 2 (δ_C, ppm)

Solvent	Form	CH_3-3 or $\underline{C}H_3C$=N	CH_3-5 or CH_3-2	CH_2S or C-6	C-3 or C=N	C-4 or $\underline{C}H_2C$-2	C-5 or C-2	C=O
Solid phase	**A**	13.3	24.2	39.6	158.7	45.9	99.4	168.4
DMSO-d_6	**A**[a]	13.3	23.3	40.3	155.5	45.5	98.2	167.4
		13.0	22.0	[b]	155.7	45.0	97.6	172.5
	C	16.0	23.1	[b]	155.6	46.9	83.3	166.1
Pyridine-d_5	**A**[a]	13.2	23.5	41.6	155.7	46.0	98.9	168.6
		13.1	22.1	41.4	155.6	45.5	98.3	173.7
	C	15.7	23.0	43.5	155.8	47.4	84.1	168.5
DMF-d_7	**A**[a]	13.1	23.3	41.2	155.8	45.9	98.6	167.3
		12.8	21.8	41.7	155.3	45.3	98.2	173.1
	C	15.7	22.8	43.4	156.2	47.2	84.0	166.3
	D	11.7	25.3	[b]	152.4	42.2	73.3	171.0

[a] Doubling of the signals of isoxazoline form **A** due to effect of the amide rotation.
[b] Signals were not observed or closed by the solvent signals.

The appearance of the above signals cannot be attributed to such structural properties of isoxazoline **A** or pyrazoline **C** forms as the restricted rotation of the amide fragment, since the high temperature record of the ^1H NMR spectrum of compound **2** in DMF-d_7 does not result in the coalescence of the double signals, and the signal at 73.3 ppm in the ^{13}C NMR spectrum of the third cyclic form shifts considerably upfield. This is not consistent either with the structure of 5-acylhydrazine-Δ^2-isoxazoline, or with that of 5-hydroxyamine-Δ^2-pyrazoline.

Table 2. Tautomeric composition and PMR spectra of compound 2 (δ, ppm, J, Hz)

Solvent	Tautomeric composition, (%)	CH_3-3 or CH_3C=N, s	CH_3-5 or CH_3-2, s	H-4 or CH_2 *AB* pattern	CH_2S or H-6, s	NH, OH, SH, br. s
$CDCl_3$	**A**[a] (83)	1.96	1.60	2.82; 3.02 (18)	3.52	4.57; 7.60
	(9)	2.01	1.52	2.84 s	3.48	7.25
	C (8)	1.98	1.65	2.69; 3.28 (18)	3.59	9.21
D_2O	**A** (84)	2.18	1.79	3.07; 3.19 (16)	3.62	[b]
	C (16)	2.21	1.82	[b]	3.91	[b]

Table 2. Continued

DMSO-d_6	**A**[a] (72)	1.85	1.40	2.80 s	3.47	5.58; 9.17
	(10)	1.82	[b]	2.71 s	3.44	7.65
	C (18)	1.93	1.49	3.04 s	3.61	5.86; 10.21
Pyridine-d_5	**A**[a] (75)	1.89	1.71	2.85; 3.32 (18)	3.89	5.63; 10.61
	(10)	[b]	1.64	3.07 s	3.94	6.36
	C (15)	1.79	[b]	2.73; 3.54 (18)	4.33	7.17
DMF-d_7	**A**[a] (68)	1.90	1.48	2.94 s	3.59	5.64; 9.28
	(12)	[b]	1.55	3.02 s	3.92	5.96; 8.25
	C (13)	1.97	[b]	3.11 s	4.02	9.37
	D (7)	1.78	[b]	3.38 s	3.69	10.36

[a] Doubling of the signals of isoxazoline form **A** due to effect of the amide rotation.
[b] Signals were not observed or closed by the solvent signals.

This phenomenon can be attributed only to the three-ring tautomeric equilibrium between isoxazoline **A** form, pyrazoline **C** form, and tetrahydro-1,3,4-thiadiazine **D** form which is observed in solution. The ^{1}H and ^{13}C NMR spectra of tetrahydro-2,2-dimethyl-1,3,4-thiadiazin-5(6*H*)-one (acetone mercaptoacetylhydrazone),[2] that is the closest structural analog to form **D** of compound **2**, are completely consistent with the structure proposed.

The attempts to find out variants of three-ring tautomeric equilibrium were also undertaken by us earlier. Thus, acetylacetone 1,3-thiocarbonohydrazone oxime[3] and 1,3-thio-benzoylhydrazone oxime,[4] potentially capable of undergoing three-ring tautomerism exist in solutions as a ring–ring tautomeric systems of the Δ^2-isoxazoline – tetrahydro-1,2,4,5-tetrazine and Δ^2-isoxazoline – 1,3,4-Δ^2-thiadiazoline types, respectively. In both cases the formation of one more possible cyclic form (Δ^2-pyrazoline form) in a solution was not observed.

Hence, the phenomenon described here is a rare case of tautomerism of three different heterocycles and does not have any close literary analogues. It is also remarkable that the cyclic forms being in equilibrium are the result of intramolecular nucleophilic additions of functional fragments, which contain three different heteroatoms: the OH group (Δ^2-isoxazoline ring), the NH group (Δ^2-pyrazoline ring), and the SH group (1,3,4-thiadiazine ring).

Experimental Section

General Procedures. The ^{1}H and ^{13}C NMR spectra in solutions were recorded on a Bruker AC 200 and AM 500 spectrometers, and in solid phase on Bruker CXP 100 spectrometer (25 MHz) by the standard procedure using polarisation transfer and «magic angle» rotation at a frequency of 3 kHz. The quantitative composition of tautomeric forms was determined by integrating of the appropriate signals in the ^{1}H NMR spectra. A check of the reaction progress and of the purity of

the compound obtained was effected by TLC on Silufol UV-254 plates. The eluent was benzene–acetone, 2:1. Compound **1** was obtained by the known procedure.[5]

5-(2-Mercaptoacetylhydrazine)-3,5-dimethyl-Δ^2-isoxazoline (2A). A mixture of compound **1** (2.3 g, 0.02 mol), mercaptoacetyl hydrazine (1.1 g, 0.01 mol), and several drops of acetic acid in methanol (25 ml) was maintained at 25°C for three days. After the removal of the solvent under reduced pressure, the residue was washed with ether and recrystallized from a benzene–hexane 1:1 mixture. Yield – 1.5 g (75 %). Mp 149–151^{o}C. Found (%): C 41.40; H 6.39; N 20.71. $C_7H_{13}N_3O_2S$. Calculated (%): C 41.36; H 6.45; N 20.67.

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