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RING–RING TAUTOMERISM IN 1,3-ALKANOYLHYDRAZONOXIMES OF ACETYLACETONE

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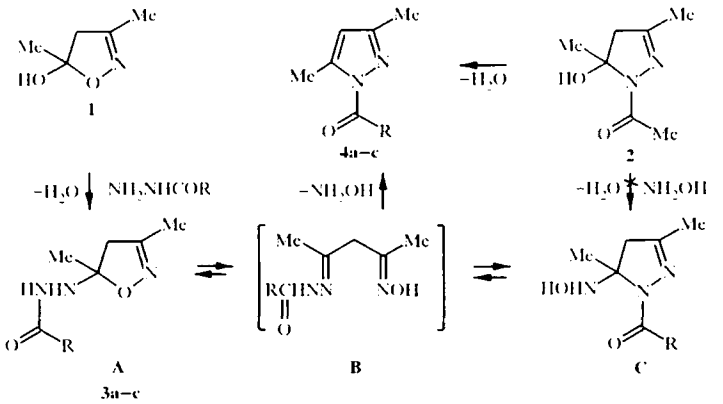
The coexistence in solution of tautomeric isoxazoline and pyrazoline forms of 1,3-alkanoylhydrazonoximes of acetylacetone has been detected and investigated by ^{1}H and ^{13}C NMR spectroscopic methods. The compounds indicated eliminate hydroxylamine under the action of acid catalysts, forming 1-acyl-3,5-dimethylpyrazoles.

Keywords: 5-hydrazino-Δ^2-isoxazolines, 5-hydroxyamino-Δ^2-pyrazolines, ring–ring tautomerism.

Compounds containing in their structures cyclic hemiacetal or hemiaminal fragments are characterized by an increased tendency towards ring–chain tautomeric conversion in solution [1,2]. This property is also observed in monooximes (monoacylhydrazones) of β-dicarbonyl compounds for which as a rule transformation into cyclic 5-hydroxy-Δ^2-isoxazoline **1** and 5-hydroxy-Δ^2-pyrazoline **2** forms respectively are preferred [3-5].



3, 4 a R = Me, b R = Et, c R = *i*-Pr

The simultaneous presence of oxime and hydrazone functions of 1,3-dioxo compounds may lead to competition between two ring–chain equilibria, and as a result, to the realization of a more complex variant of the equilibrium involving the two cyclic forms, *viz.* ring–ring tautomerism of the 5-hydrazino-Δ^2-isoxazoline – 5-hydroxyamino-Δ^2-pyrazoline type. The phenomenon described was previously only observed in the example of 1,3-alkylhydrazonoximes of α,α-dimethylacetyl-acetone [6], while 1,3-acylhydrazonoximes of other β-dicarbonyl compounds have predominantly an isoxazoline [7] or a pyrazoline [8] structure and do not display an tendency towards tautomeric conversion in solution.

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With the aim of continuing investigations of bifunctional derivatives of β-dicarbonyl compounds [6-13], we have studied the methods of synthesis and structure of a series of 1,3-alkanoylhydrazonoximes of acetylacetone.

It turned out that compounds **3a-c** may be obtained in high yield by the interaction of 5-hydroxy-3,5-dimethyl-Δ^2-isoxazoline **1** with the hydrazides of acetic, propionic, and isobutyric acids in methanol at room temperature (see Experimental and Table 1). An alternative method of obtaining compound **3a**, *viz.* the action of hydroxylamine on 1-acetyl-5-hydroxy-3,5-dimethyl-Δ^2-pyrazoline **2**, proved to be unsuccessful. In this case the dioxime of acetylacetone was isolated in high yield and was identified by us by physicochemical and spectral characteristics by comparison with a literature analog [11].

Compounds **3a,c** exist in the crystalline state in the cyclic isoxazoline form A. This was confirmed by the presence in their ^{13}C NMR spectra, taken in the solid phase (Table 1), of a signal of the sp^3-hybrid $C_{(5)}$ atom at 98 ppm (N,C,O-environment).

At once after dissolving compound **3a** in $CDCl_3$ a doubling of the individual signals of the isoxazoline form A is observed. This may be caused by restriction of amide rotation in the hydrazine fragment relative to the C–N bond (Table 2). This was confirmed by the coalescence of the signals on plotting the ^1H NMR spectra in DMF at 100°C. A day after dissolving compound **3a** in $CDCl_3$, in addition to two asymmetrical doublets forming a typical AB system at 2.74 and 2.89 ppm, there appeared in the spectra an additional AB system at 2.57 and 3.15 ppm caused by the presence in solution of a further cyclic form. The existence in solution of a second cyclic form was also confirmed by ^{13}C NMR spectra (see Fig. 1 and Table 1).

It is impossible to connect the appearance of the signals mentioned with such structural possibilities as restricted amide rotation of the isoxazoline form A, since the high temperature plotting of the ^1H NMR spectrum of compound **3a** in DMF-d_7 did not lead to coalescence of the doubled signals. The chemical shift of the $C_{(5)}$ atom of the second cyclic form in the ^{13}C NMR spectra was displaced significantly upfield (~15 ppm) which is not in agreement with the structure of 5-acylhydrazino-Δ^2-isoxazolines [7].

The phenomenon observed may only be connected with a ring–ring tautomeric equilibrium existing in solution between the isoxazoline form A and the pyrazoline form C. The signals in the ^1H and ^{13}C NMR spectra of the series of 1-acetyl-5-amino-3,5-dimethyl-Δ^2-pyrazolines, which are the closest structural analogs of form C of compound **3a** and were investigated by us in [13], are in full agreement with the structure proposed.

The tautomeric equilibrium, which is established in the course of several days, depends on steric factors and on the nature of the solvent (Table 2). The proportion of pyrazoline form C was reduced with an increase in the size of the N-acyl substituent. Its content in pyridine-d_5 was 30, 15, and 10% for compounds **3a-c** respectively. The change from polar basic solvents (pyridine-d_5, DMSO-d_6, DMF-d_7) to the low polarity $CDCl_3$ also leads to stabilization of the isoxazoline tautomer.

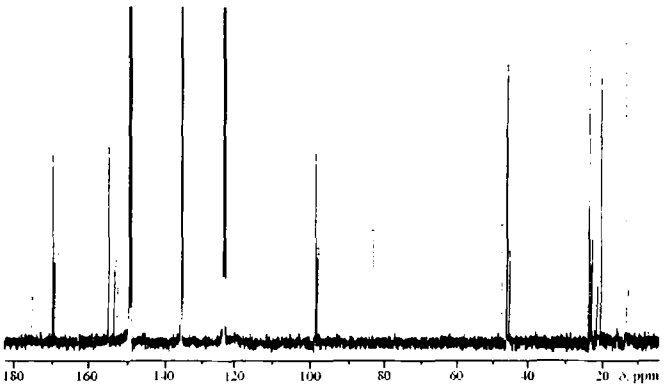

Fig. 1. The ^{13}C NMR spectrum of compound **3a** in pyridine-d_5: 1 denotes signals of form A; 2 denotes signals of form C.

TABLE 1. Physicochemical Characteristics and ^{13}C NMR Spectra of Compounds **3a-c**

Compound	mp, °C	Solvent	Form	^{13}C NMR spectrum, δ, ppm							Yield, %
				3-CH_3	5-CH_3	R	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	C=O	
3a	101-103	Solid phase	A	12.7	24.2	21.8, CH_3	159.1	46.6	99.8	174.9	55
		$CDCl_3$	A*	13.2	22.9	20.9, CH_3	156.2	45.6	98.3	169.8	
				13.3	23.0	19.6, CH_3	155.5	45.1	97.9	175.2	
			C	15.6	23.1	22.1, CH_3	154.7	47.2	83.4	169.7	
		Pyridine-d_5	A*	13.1	23.4	21.0, CH_3	155.6	46.1	98.9	169.7	
				12.8	22.8	19.6, CH_3	152.9	45.4	98.5	175.6	
			C	15.8	23.0	22.6, CH_3	154.2	47.6	83.6	169.6	
3b	Oil	Pyridine-d_5	A*	13.8	24.3	10.2, CH_3; 28.6, CH_2	155.6	45.9	98.9	173.8	40
				12.8	23.9	10.6, CH_3; 28.1, CH_2	156.7	45.4	98.4	178.9	
			C	16.7	23.4	9.1, CH_3; 29.1, CH_2	154.2	47.4	83.5	173.1	
3c	108-110	Solid phase	A	13.2	22.5	18.3; 21.4, $2CH_3$; 32.3, CH	159.8	45.4	98.7	175.1	60
		Pyridine-d_5	A*	12.8	23.3	19.4; 19.6, $2CH_3$; 33.2, CH	155.3	45.9	98.8	176.8	
				12.9	23.1	18.7; 19.0, $2CH_3$; 30.3, CH	155.5	45.5	98.5	178.6	
			C	15.7	22.4	18.8; 19.1, $2CH_3$; 32.0, CH	153.9	47.0	83.5	175.9	

* Doubling of signals of the isoxazoline form A due to restricted amide rotation.

TABLE 2. Data of Elemental Analysis and ^{1}H NMR Spectra of Compounds **3a-c**

Compound	Empirical formula	Found, % / Calculated, %			Solvent	Tautomeric composition, %	^{1}H NMR spectrum, δ, ppm, coupling constants (Hz)				
		C	H	N			3-CH_3, s	5-CH_3, s	R	4-H, AB-system	NH and OH, br. s
3a	$C_{11}H_{13}NO_2$	69.08 / 69.11	7.70 / 7.65	24.51 / 24.54	$CDCl_3$	A* (65)	1.87	1.50	1.87 s, CH_3	2.74; 2.89 (18)	4.52; 7.71
						(20)	1.96	1.48	2.02 s, CH_3	2.75 s	4.71; 7.22
						C (15)	1.66	1.56	2.20 s, CH_3	2.57; 3.15 (18)	6.63; 9.27
					Pyridine-d_5	A* (60)	1.81	1.66	2.04 s, CH_3	2.80; 3.23 (19)	5.38; 10.36
						(10)	1.86	1.58	2.26 s, CH_3	2.91 s	7.13; 10.75
						C (30)	1.84	1.73	2.41 s, CH_3	2.68; 3.41 (19)	6.67; 9.52
3b	$C_{13}H_{17}NO_2$	71.94 / 71.88	8.09 / 8.16	22.76 / 22.69	$CDCl_3$	A* (75)	1.88	1.50	0.96 t, CH_3; 2.02 m, CH_2	2.67; 2.89 (18)	4.66; 7.91
						(15)	1.90	1.48	1.05 t, CH_3; 2.25 m, CH_2	2.69 s	4.80; 7.24
						C (10)	1.69	1.54	1.03 t, CH_3; 2.12 m, CH_2	2.46; 3.06 (18)	5.61; 8.95
					Pyridine-d_5	A* (75)	1.81	1.63	1.13 t, CH_3; 2.29 m, CH_2	2.80; 3.20 (19)	5.45; 10.08
						(10)	1.76	1.57	1.21 t, CH_3; 2.29 m, CH_2	2.75 s	7.12; 10.49
						C (15)	1.86	1.71	1.20 t, CH_3; 2.39 m, CH_2	2.66; 3.37 (19)	6.45; 9.05
3c	$C_{14}H_{17}NO_2$	74.21 / 74.25	8.56 / 8.60	21.14 / 21.09	$CDCl_3$	A* (95)	1.86	1.51	1.06 d, $2CH_3$; 2.31 m, CH	2.72; 2.89 (18)	4.49; 7.44
						(5)	1.88	1.50	*[2]	2.72 s	4.62; 6.93
					Pyridine-d_5	A* (85)	1.83	1.64	1.17 d, $2CH_3$; 2.61 m, CH	2.80; 3.23 (19)	5.31; 10.12
						(5)	1.78	1.61	*[2]	2.93 s	7.17; 10.44
						C (10)	1.89	1.72	1.24 d, $2CH_3$; 2.63 m, CH	2.70; 3.40 (19)	6.62; 9.04

* Doubling of signals of the isoxazoline form A due to inhibition of amide rotation.

*[2] Closing of signals of the basic form.

It turned out that brief boiling of compounds **3a-c** in methanol in the presence of catalytic quantities of mineral acids leads to the quantitative formation of the 1-acylpyrazoles **4a-c**. We identified these compounds by physicochemical and spectral characteristics by comparison with literature analogs and in the case of compound **4a** by an alternate synthesis by the dehydration of 5-hydroxy-Δ^2-pyrazoline **2** (see Experimental).

The 1,3-alkanoylhydrazonoximes of acetylacetone are inclined towards ring–ring tautomeric conversion in solution with the participation of isoxazoline and pyrazoline forms, and in acidic media eliminate hydroxylamine being converted into 1-acyl-3,5-dimethyl-pyrazoles. The data obtained have extended ideas on reversible recyclizations in isoxazole derivatives, individual examples of which were investigated by us previously [6,14,15].

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker AC 200 spectrometer at a frequency of 200 MHz. The ^{13}C NMR spectra in solution were recorded on a Bruker AM 500 spectrometer at a frequency of 125 MHz, and in the solid state on a Bruker CXP 100 spectrometer at a frequency of 25 MHz by the 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 spectra. A check on the progress of reactions and the purity of the compounds obtained was effected by TLC on Silufol UV-254 plates. Chromatographic separation was carried out on a glass column (25 × 2.5 cm) packed with Chemapol L 100/160 silica gel. The eluent was benzene–acetone, 2 : 1. Compounds **1** and **2** were obtained by the known methods [3,5].

5-(2-Acylhydrazino)-3,5-dimethyl-Δ^2-isoxazolines (3a-c). A mixture of compound **1** (3.5 g, 0.03 mol), alkanoylhydrazine (0.025 mol), and several drops of acetic acid in methanol (25 ml) was maintained at 25°C for 3 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.

1-Acyl-3,5-dimethylpyrazoles (4a-c). A solution of compound **3a-c** (or **2**) (5 mmol) in methanol (30 ml) with several drops H_2SO_4 was boiled for 3 h. After removing the solvent in vacuum, the residue was extracted with a 1 : 1 ether–hexane mixture, dried over $CaCl_2$, the solvent evaporated, and compounds **4a-c** isolated (85-90% yield). These were then compared by physicochemical properties and spectral characteristics with literature analogs [16].

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