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SYNTHESIS AND STRUCTURE OF HYDRAZONES OBTAINED FROM HYDRAZIDES OF [5-(4-PYRIDYL)-1,3,4-OXADIAZOL-2-YLTHIO]ACETIC OR 2-[5-(4-PYRIDYL)-1,3,4-OXADIAZOL-2-YLTHIO]PROPIONIC ACIDS

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It has been shown by ^{1}H NMR spectroscopy that hydrazones obtained by the condensation of hydrazides of [5-4-pyridyl)-1,3,4-oxadiazol-2-ylthio]acetic or 2-[5-(2-pyridyl)-1,3,4-oxadiazol-2-ylthio]propionic acids with aldehydes, ketones, and β-dicarbonyl compounds exist in DMSO solution as a mixture of stereoisomeric forms.

Keywords: hydrazides, hydrazones, *Z,E*-isomers, 2-mercapto-5-(4-pyridyl)-1,3,4-oxadiazole.

Hydrazones obtained from the known isonicotinic acid hydrazide and also their complexes with metals are used as antibacterial and antitubercular preparations [1], analytical reagents [2], and dyestuffs [3]. However there are no literature data on hydrazones obtained from 2-mercapto-5-(4-pyridyl)-1,3,4-oxadiazole (**1**).

In the present work a method of synthesis of hydrazides is proposed from compound **1** using direct alkylation of monobromoacetic or 2-chloropropionic acid methyl esters in the presence of an alkaline component both in 2-propanol and in water under interphase catalysis conditions in the presence of triethylbenzylammonium chloride (TEBA) with the formation of the corresponding methyl esters **2,3**. These esters then condensed readily with hydrazine hydrate forming the hydrazides **4,5**. The latter condense with aldehydes and ketones giving the acylhydrazones **6a-i** (Scheme 1).

Conformational (rotating) isomerism due to hindered rotation around an N-CO double bond and geometric *syn,anti* isomerism relative to an N=C bond has already been studied by us in certain heterocyclic hydrazones [4,5]. We have established analogously to the data in the cited works that acylhydrazones **6a-i** in DMSO solution exist as a mixture of two stereoisomers, what follows from the doubling of the proton signals of the CH_2CO, CHCO, =CH, and NH groups in the ^{1}H NMR spectra. These signals coalesce on heating the solutions to 120°C. In agreement with the data of [4,5] the proton signals of the CH_2CO, CHCO, and NH groups of the *Z*-conformer of acylhydrazones **6a-i** are also found at higher field, but the proton signal of the =CH group is at lower field compared to the signal of the *E*-isomer. The reaction products of β-dicarbonyl compounds with acid hydrazides may form systems with hydrazone, enehydrazine, 5-hydroxypyrazoline, or pyrazole forms [4,6,7]. The interaction of acetylacetone with the hydrazides of (2-benzothiazolylthio)- and (2-benzoxazolylthio)acetic acids leads to the formation of a pyrazole system [4], however on studying the ^{1}H NMR spectrum of the condensation product of hydrazide **4** with acetylacetone a doublet was detected for the CH_2 group protons corresponding to a pyrazole ring with a chemical shift of 2.80 ppm and a singlet for a hydroxyl group proton at 6.41 ppm. An intense absorption

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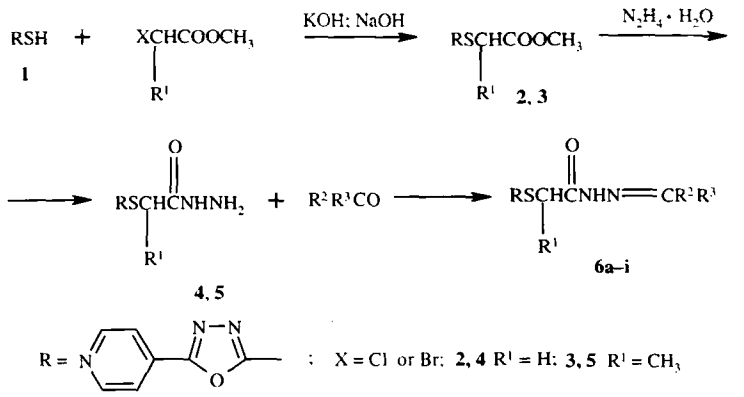
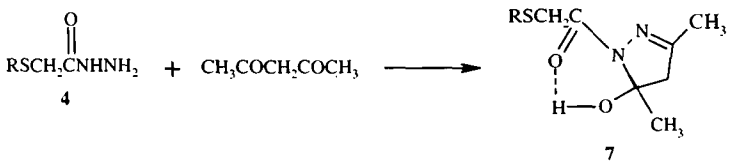
Scheme 1



2, **4**, **6a-f** R^1 = H; **3**, **5**, **6g-i** R^1 = CH_3; **6a-c,g** R^2 = H; **6e,h,i** R^2 = CH_3; **6a** R^3 = 3-Br-5-HOC_6H_3; **6b** R^3 = 4-$(CH_3)_2NC_6H_4$; **6c** R^3 = 4-$CH_3OC_6H_4$; **6d** R^2+R^3 = $(-CH_2-)_4$; **6e** R^2+R^3 = $(-CH_2-)_5$; **6f** R^3 = $CH_2C_6H_5$; **6g** R^3 = 2,3-$(CH_3O)_2C_6H_3$; **6h** R^3 = C_6H_5; **6i** R^3 = 3,4-$(OCH_2CH_2O)_2C_6H_3$

band was observed in the IR spectrum of the product at 1639 cm^{-1}, corresponding to the stretching vibration of the C=O bond in pyrazole compounds [8], with an intramolecular hydrogen bond (IMHB) to the hydroxyl group of the pyrazole ring. Weaker absorption bands at 1605 and 1580 cm^{-1} may belong to νC=N. The narrow band with center at 3490 cm^{-1} must be assigned to νOH. The initial hydrazide acts as an external base detaching one of the protons of the methylene group on splitting out water from the hydroxy-pyrazolines under the given conditions [7]. In our case hydrazide **4**, containing an electron-withdrawing 4-pyridyl group, possesses less basicity which impedes formation of the pyrazole ring, as a result of which the reaction stops at the stage of hydroxypyrazoline **7**. A singlet signal for the acyl radical CH_2 group protons and the strong displacement of the hydroxyl group signal (6.41 ppm) towards low field indicates the existence of hydroxypyrazoline **7** in DMSO solution exclusively in the *E*-stereoisomeric form. It is seen on spatially modeling compound **7** that only the *E*-isomer has a natural strongly conjugated IMHB. The solvent DMSO, which aids the formation of intermolecular hydrogen bonds, favors the *Z*-isomer, for which the capacity towards self-association is less. However, according to ^{1}H NMR (Table 2) compound **7** exists in DMSO solution only in one *E*-isomeric form. Probably the strongly conjugated IMHB excludes the possibility of forming the alternative *Z*-isomer.

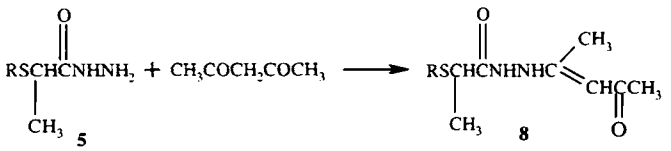


Study of the ^{1}H NMR and IR spectra of the condensation product of hydrazide **5** with acetylacetone shows the existence of the obtained hydrazide **8** in a tautomeric enehydrazide form. The stability of the cyclic form, and consequently of the position of the tautomeric equilibrium to a significant extent, is determined by the intensity of the conjugation including the unshared electron pair of the amino nitrogen atom and the C=N and C=O multiple bonds [9]. An increase in the bulk of the substituent in the N-acyl portion (in our case the introduction of a methyl group) impedes the attainment of the spatial structure of the hydrazone fragment necessary to achieve conjugation, and displaces the tautomeric equilibrium in the direction of the open enehydrazine form. In the ^{1}H NMR spectrum of pyrazole **8** the signal at 5.32 ppm corresponds to a typical signal of a vinylic proton of nitrogen derivatives of β-diketones with a conjugated enehydrazine structure [9]. The signal of the NHNH group protons is detected as two separate signals. As in the data of [10] the proton signal of the NH group linked with C=O is found at

TABLE 1. Characteristics of the Synthesized Compounds **2-8**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2	$C_{10}H_9N_3O_3S$	47.71 / 47.82	3.65 / 3.58	12.91 / 12.74	124-125	74
3	$C_{11}H_{11}N_3O_3S$	49.96 / 49.80	4.11 / 4.18	15.65 / 15.83	88-90	53
4	$C_9H_9N_5O_2S$	43.10 / 43.02	3.49 / 3.61	27.71 / 27.85	193-194 *i*-PrOH–H_2O	64
5	$C_{10}H_{11}N_5O_2S$	47.45 / 47.27	4.01 / 4.18	26.61 / 26.40	148-149	94
6a	$C_{16}H_{12}BrN_5O_3S$	44.41 / 44.25	2.88 / 2.79	16.30 / 16.12	215-217	69
6b	$C_{18}H_{18}N_6O_2S$	56.44 / 56.53	4.58 / 4.74	21.72 / 21.98	210-213	63
6c	$C_{17}H_{15}N_5O_3S$	50.03 / 50.14	4.33 / 4.20	23.21 / 23.39	180-182	76
6d	$C_{14}H_{15}N_5O_2S$	50.66 / 50.75	4.48 / 4.56	25.68 / 25.51	168-170	90
6e	$C_{15}H_{17}N_5O_2S$	52.26 / 52.17	4.81 / 4.95	24.22 / 24.34	169-71	87
6f	$C_{18}H_{17}N_5O_2S$	56.85 / 56.69	4.55 / 4.48	19.91 / 22.04	171-172 *i*-PrOH–dioxane	50
6g	$C_{19}H_{19}N_5O_4S$	55.36 / 55.20	4.51 / 4.63	16.81 / 16.93	95-97	73
6h	$C_{18}H_{17}N_5O_2S$	58.65 / 58.85	4.44 / 4.67	19.21 / 19.05	124-125	59
6i	$C_{20}H_{19}N_5O_4S$	56.40 / 56.46	4.32 / 4.50	16.25 / 16.46	151-152	43
7	$C_{14}H_{15}N_5O_3S$	50.22 / 50.44	4.67 / 4.53	21.20 / 21.01	152-153 *i*-PrOH	60
8	$C_{15}H_{17}N_5O_3S$	51.66 / 51.87	4.75 / 4.92	20.33 / 20.16	156-157	25

11.25 ppm, but the signal of the other NH group proton is at 11.20 ppm. An intense absorption band was observed in the IR spectrum of compound **8** at 1757 cm^{-1} corresponding to νC=O of an unconjugated bond belonging to the O=CNHNH grouping, and a very intense band at 1613 cm^{-1}, which must be assigned to the stretching vibration of a strongly conjugated C=O group [11]. There are two absorption bands in the νNH region at 3171 and 2993 cm^{-1}, the latter overlapping with the ν=CH band.



EXPERIMENTAL

The ^1H NMR spectra were obtained on a Hitachi R-22 (90 MHz) spectrometer, internal standard was HMDS, and solvent DMSO-d_6. Quantitative determinations were carried out using a five-fold integration of the signal of the methylene protons of CH_2CO or the methine proton of CHCO. The IR spectra were obtained on a UR 10 spectrometer for KBr disks.

TABLE 2. Data of ^{1}H NMR Spectra of Compounds **2-8** (solvent DMSO-d_6)

Compound	Chemical shifts, δ, ppm					*E*-Isomer, %
	CH_2C=O, s	CHC=O,q	=CH, s	NH, s	Other signals	
2	4.20	–	–	–	3.58 (3H, s, CH_3); 7.69 (2H, d, Ar); 8.65 (2H, d, Ar)	—
3	—	4.31	—	—	1.48 (3H, d, $\underline{CH_3}CH$);	—
4	3.60 (*Z*) 3.98 (*E*)	—	–	–	1.50 (3H, d, $\underline{CH_3}CH$); 7.73 (2H, d, Ar); 8.67 (2H, d, Ar)	93
5	—	4.17 (*Z*) 4.31 (*E*)	–	—	7.72 (2H, d, Ar); 8.72 (2H, d, Ar)	80
6a	4.13 (*Z*) 4.53 (*E*)	—	8.07 (*E*) 8.20 (*Z*)	11.51 (*Z*) 11.92 (*E*)	9.55 (1H, s, OH)	56
6b	4.12 (*Z*) 4.54 (*E*)	—	7.55 (*E*) 7.81 (*Z*)	10.95 (*Z*) 11.16 (*E*)	1.93 (6H, s, CH_3)	57
6c	4.13 (*Z*) 4.53 (*E*)	–	8.60 (*E*) 8.65 (*Z*)	11.58 (*Z*) 12.01 (*E*)	3.69 (3H, s, CH_3)	61
6d	4.07 (*Z*) 4.50 (*E*)	—	—	10.30 (*Z*) 10.48 (*E*)	7.89 (2H, d, Ar); 8.82 (2H, d, Ar)	54
6e	4.09 (*Z*) 4.40 (*E*)	—	—	10.61 (*Z*) 10.79 (*E*)	7.90 (2H, d, Ar); 8.81 (2H, d, Ar)	53
6f	4.09 (*Z*) 4.38 (*E*)	– –	—	10.44 (*Z*) 10.66 (*E*)	1.67 (3H, s, CH_3); 3.22 (2H, s, CH_2)	56
6g	—	4.29 (*E*)	8.12 (*E*) 8.27 (*Z*)	11.36 (*Z*) 11.54 (*E*)	1.51 (3H, d, CH_3); 3.65 (6H, d, CH_3O)	100
6h	– –	4.30 (*E*)	—	10.30 (*Z*) 10.59 (*E*)	1.52 (3H, d, $\underline{CH_3}CH$); 2.27 (3H, s, CH_3C=)	100
6i	—	4.30 (*E*)	—	10.19 (*Z,E*)	1.51 (3H, d, $\underline{CH_3}CH$); 2.22 (3H, s, CH_3C=O)	100
7	4.49 (*E*)	—	–	—	1.78 (3H, s, $\underline{H_3}COH$); 2.02 (3H, s, H_3C=N); 2.80 (2H, d, $\underline{H_2}COH$)	100
8	—	4.41 (*E*)	5.32	11.20 (1H, s, O=CNH$\underline{NH}$); 11.25 (1H, s, O=$\underline{CNH}$)	1.58 (3H, d, $\underline{CH_3}CH$); 2.03 (3H, s, CH_3C=O; 1.87 (3H, s, CH_3C=C)	100

The characteristics of the compounds synthesized are given in Table 1, and the ^{1}H NMR spectral data in Table 2.

2-Mercapto-5-(4-pyridyl)-1,3,4-oxadiazole (1). A mixture of isonicotinic acid hydrazide (10.96 g, 80 mmol), potassium ethyl dithiocarbonate (12.8 g, 80 mmol), 2-propanol (100 ml), and methanol (20 ml) was boiled for 4.5 h, the solution evaporated, diluted with water, filtered, and the solution neutralized with hydrochloric acid. The amorphous precipitate was filtered off, and washed with water. Compound **1** (10 g, 70%) of mp 271-272°C was obtained. Compound **1** obtained from isonicotinic acid hydrazide and carbon disulfide has reported mp 270°C [12].

[5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio]acetic Acid Methyl Ester (2). Oxadiazole **1** (5.38 g, 30 mmol) was added to a solution of NaOH (1.24 g, 31 mmol) in water (50 ml). The solution obtained was filtered and TEBA (0.2 g) was dissolved in it. Then monobromoacetic acid methyl ester (4.59 g, 2.84 ml, 30 mmol) was added dropwise with stirring. The mixture was then stirred for 0.5 h at room temperature. The crystals of precipitated product **2** were filtered off and washed many times with water.

2-[5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio]propionic Acid Methyl Ester (3). Oxadiazole **1** (8.95 g, 50 mmol) was added to a solution of KOH (3.3 g, 56 mmol) in 2-propanol (25 ml), methanol (20 ml), and water

(5 ml). 2-Chloropropionic acid methyl ester (6.13 g, 5.4 mmol) was added dropwise with stirring and heating to 55°C, and stirring and heating were continued for 2.5 h. The solution was evaporated, diluted with water, the crystals of ester **3** were filtered off, and washed with water.

[5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio]acetic Acid Hydrazide (4). Hydrazine hydrate (6 ml) was added with stirring to a solution of ester **2** (4.7 g, 20 mmol) in methanol (80 ml), prepared at 30°C. The solution was partially evaporated, the crystals of hydrazide **4** were filtered off, and washed with 2-propanol.

2-[5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio]propionic Acid Hydrazide (5) was obtained from ester **3** (6.65 g, 25 mmol) dissolved in methanol (100 ml), and hydrazine hydrate (8 ml) by the procedure for obtaining hydrazide **4**.

3-Bromo-5-hydroxybenzylidenehydrazide of [5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio]acetic Acid (6a). A mixture of hydrazide **4** (1.26 g, 5 mmol), 3-bromo-5-hydroxybenzaldehyde (1.05 g, 5 mmol), dioxane (40 ml), and water (2 ml) was stirred at 85°C for 2 h. The mixture was then filtered, the filtrate partially evaporated, and diluted with hexane. The precipitate of hydrazone **6a** was filtered off, and washed with hexane.

4-(Dimethylaminobenzylidenehydrazide of [5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio]acetic Acid (6b) was obtained from hydrazide **4** (1.26 g, 5 mmol) and 4-dimethylaminobenzaldehyde (0.75 g, 5 mmol) by the procedure for obtaining hydrazone **6a**.

4-Methoxybenzylidenehydrazide of [5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio]acetic Acid (6c) was obtained from hydrazide **4** (1.26 g, 5 mmol) and 4-methoxybenzaldehyde (0.68 g, 0.6 ml, 5 mmol) by the procedure for obtaining hydrazone **6a**.

Cyclopentylidenehydrazide of [5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio]acetic Acid (6d) was obtained from hydrazide **4** (1.26 g, 5 mmol) and cyclopentanone (0.42 g, 0.44 ml, 5 mmol) by the procedure for obtaining hydrazone **6a**.

Cyclohexylidenehydrazide of [5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio]acetic Acid (6e) was obtained from hydrazide **4** (1.26 g, 5 mmol) and cyclohexanone (0.49 g, 0.52 ml, 5 mmol) by the procedure for obtaining hydrazone **6a**.

Benzylethylidenehydrazide of [5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio]acetic Acid (6f) was obtained from hydrazide **4** (1.26 g, 5 mmol) and phenylacetone (0.67 g, 0.66 ml, 5 mmol) by the procedure for obtaining hydrazone **6a**.

2,3-Dimethoxybenzylidenehydrazide of 2-[5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio]propionic Acid (6g). A mixture of hydrazide **5** (1.59 g, 6 mmol), 2,3-dimethoxy-benzaldehyde (1 g, 6 mmol) and dioxane (40 ml) was stirred at 85°C for 2 h. The mixture was evaporated, the waxy product was triturated under diethyl ether, the crystals of hydrazone **6g** were filtered off, and washed with ether.

Phenylethylidenehydrazide of 2-[5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio]propionic Acid (6h) was obtained from hydrazide **5** (1.59 g, 6 mmol) and methyl phenyl ketone (0.72 g, 0.7 ml, 6 mmol) by the procedure for synthesizing compound **6g**. The waxy product was triturated under water, the crystals of hydrazone **6h** were filtered off, and washed with 2-propanol.

3,4-Ethylenedioxyphenylethylidenehydrazide of 2-[5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio]propionic Acid (6i) was obtained from hydrazide **5** (1.59 g, 6 mmol) and 3,4-ethylenedioxyphenyl methyl ketone (1.07 g, 6 mmol) by the procedure for **6g**. The waxy product was triturated under 2-propanol, the crystals of hydrazone **6i** were filtered off, and washed with 2-propanol.

2-[(5-Hydroxy-3,5-dimethyl-2-pyrazolinyl)-2-oxoethylthio]-5-(4-pyridyl)-1,3,4-oxadiazole (7). A solution of hydrazide **4** (1.26 g, 5 mmol) in acetylacetone (30 ml) was stirred at 105°C for 2 h. The reaction mixture was partially evaporated, diluted with hexane, the crystals of precipitated substance **7** were filtered off, and washed with hexane.

N-(4-Oxo-2-pentenyl)hydrazide of 2-[5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio]propionic Acid (8). Hydrazide **5** (1.59 g, 6 mmol) was dissolved in acetylacetone (30 ml), the solution was stirred at 105°C for 2 h, then partially evaporated. The precipitated oily product was dissolved in hot 2-propanol, the precipitated crystals of compound **8** were filtered off, and washed with ether.

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