Chemistry of Heterocyclic Compounds, Vol. 38, No. 7, 2002

$S_{(2)}$- OR $N_{(3)}$-SUBSTITUTED 2-MERCAPTO-5-(4-PYRIDYL)-1,3,4-OXADIAZOLES

A. Rutavicius and Z. Kuodis

New $S_{(2)}$- or $N_{(3)}$-substituted 2-mercapto-5-(4-pyridyl)-1,3,4-oxadiazoles have been obtained and characterized. The direction of substitution depends on the structure of the initial reactants and the reaction conditions. The synthesis of several thiosemicarbazides has been effected from isonicotinic acid hydrazide.

Keywords: isonicotinic acid hydrazide, 2-mercapto-5-(4-pyridyl)-1,3,4-oxadiazole, 5-(4-pyridyl)-1,3,4-thiadiazol-2-ylethylamine, thiosemicarbazides.

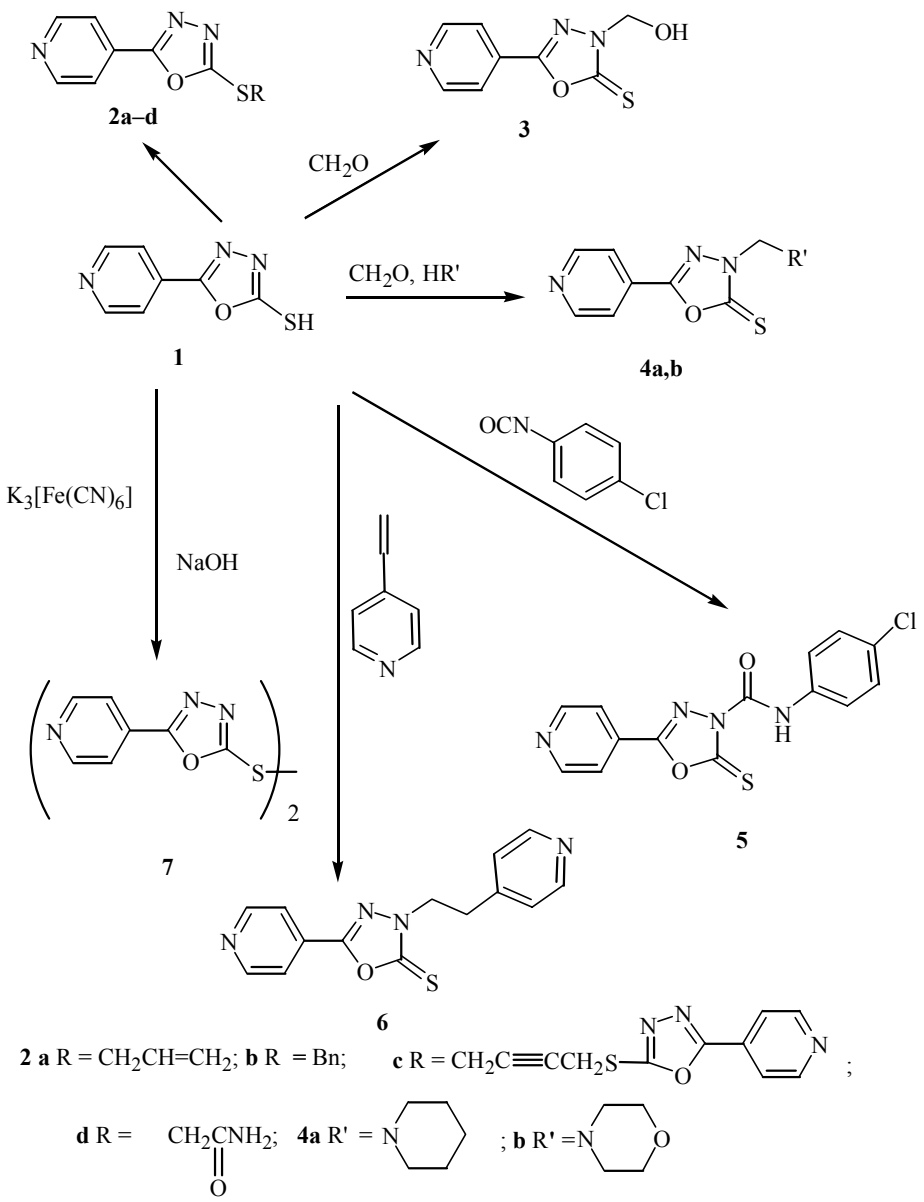
1,3,4-Oxadiazoles containing a pyridine fragment possess antibacterial, antitubercular, and tranquilizing properties [1].

2-Mercapto-5-(4-pyridyl)-1,3,4-oxadiazole exists in thione and thiol forms and this determines its ability to be substituted at sulfur or nitrogen. We [2] and others [3] previously carried out the alkylation of 1,3,4-oxadiazoline-2-thiones with alkyl halides in alkaline medium and obtained S-alkyl derivatives in this way. Oxadiazole **1** interacts with alkyl halides with the formation of thioethers **2a-d** in the presence of alkali in methanol or water under interphase catalysis conditions using triethylbenzylammonium chloride (TEBA) as catalyst. As might have been expected, absorption bands for the C=S bond were absent from the IR spectra of compounds **2a-d**. Two absorption bands were detected in the IR spectrum of thioether **2d** at 3170 and 3340 cm^{-1} corresponding to the stretching vibration of the NH group, also an absorption band for the C=O bond (amide I band) at 1685 cm^{-1}, and a band corresponding to the NH_2 deformation vibration (amide II band) at 1620 cm^{-1}.

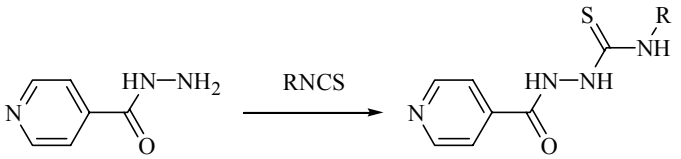
For the N-alkylation of compound **1** we chose several polar electrophilic reagents which interact with the ambident NH–C=S system only at the more electronegative nitrogen atom possessing the highest electron density [4]. On brief heating of compound **1** with formalin in a methanol–2-propanol mixture, the N-hydroxymethylated derivative **3** is formed, and under the conditions of the Mannich reaction oxadiazole **1** forms the aminomethylated derivatives **4a,b** with secondary amines. Heating compound **1** with 4-chlorophenyl isocyanate gives benzamide **5**, which was confirmed by the presence in the IR spectrum of an intense band for the stretching vibrations of the C=O bond at 1625 cm^{-1}, a band for the C=S bond (1538 cm^{-1}), and bands for the stretching vibrations of the NH group (3200 cm^{-1}). An absorption band for the C=S bond at 1534 cm^{-1} was also observed in the IR spectrum of compound **6**, synthesized by the addition of oxadiazole **1** to 4-vinylpyridine in acetic acid. Oxidation of compound **1** with potassium hexacyanoferriate leads to the disulfide **7**.

Institute of Chemistry, Vilnius LT-2600, Lithuania; e-mail: zenonas.kuodis@takas.lt. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 961-967, July, 2002. Original article submitted February 26, 2001.

 0009-3122/02/3807-0852$27.00

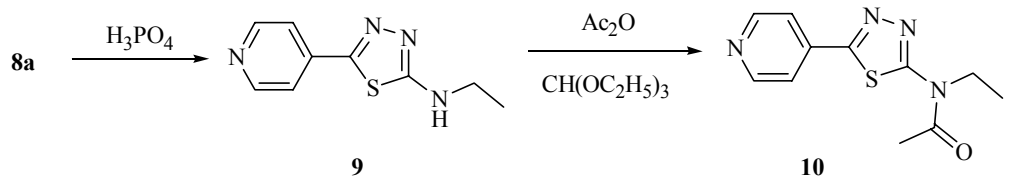


Isonicotinic acid hydrazide readily adds to the appropriate isothiocyanate and forms thiosemicarbazides **8a-c** (Table 1). Bands were observed in the IR spectrum of thiosemicarbazide **8b** for the stretching vibrations of the C=O bond at 1674 and for C=S at 1519 and 1315 cm^{-1} [5]. The formation of thiosemicarbazide **8b** is indicated by the appearance in its ^1H NMR spectrum (Table 2) of the characteristic multiplicity of the proton signals of CH_2 (4.76, d, J = 5 Hz), Ph (7.25, s), NHCH$_2$ (8.55, br. t), and HN-NH (9.41, s and 10.62 ppm, s) groups.



8 a R = Et; **b** R = Bn; **c** R = $CH_2OCH_2C{\equiv}CH$

On heating in anhydrous phosphoric acid thiosemicarbazide **8a** is cyclized into thiadiazole **9**, in the IR spectrum of which bands for the stretching vibrations of C=S and C=O bonds were missing, but an absorption band at 2950 cm^{-1} indicates the stretching vibration of the NH group.

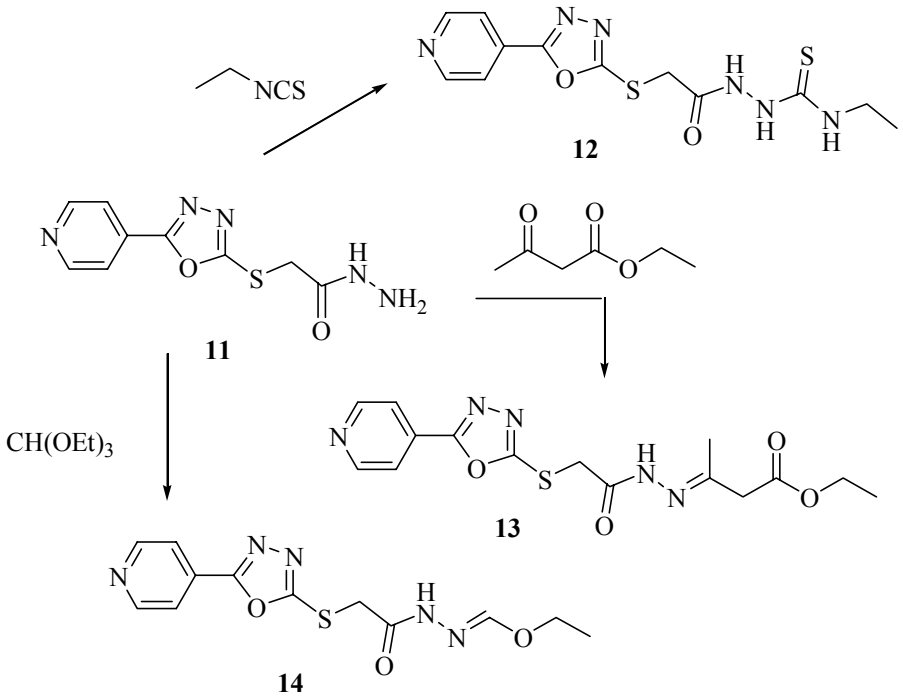


9 **10**

On heating thiadiazole **9** in a mixture of acetic anhydride and ethyl orthoformate the NH group is acetylated with the formation of amide **10**, in the ^1H NMR spectrum of which (Table 2) a triplet at 1.22 ppm corresponds to the methyl group protons in the C_2H_5 fragment, and a singlet at 1.80 ppm to the protons of the CH_3CO group. An intense band was observed in the IR spectrum for the stretching vibrations of the C=O bond at 1670 cm^{-1}.

The interaction of [5-(4-pyridyl)-1,3,4-oxadiazol-2-ylthio]acetic acid hydrazide (**11**) with ethyl isothiocyanate leads to thiosemicarbazide **12**.

We noted previously in [2] that the condensation of hydrazide **11** with acetylacetone leads to the formation of a pyrazole system. However on heating hydrazide **11** with other dicarbonyl compounds, such as ethyl acetoacetate, the linear hydrazone derivative **13** was obtained. An analogous ketohydrazone structure, also existing in the tautomeric enehydrazine form, was also detected when obtaining benzoylhydrazones from esters of 2,4-dioxobutanoic acid [6]. Analogously with the data of [6] an intense absorption band was observed at 1720 cm^{-1} in the IR spectrum of hydrazone **13**, indicating the presence of an ester grouping, and a band at 1675 cm^{-1} for the C=O bond of the amide group. An absorption was observed at 2950 cm^{-1} for the stretching vibrations of the NH group. The presence in the ^1H NMR spectrum of hydrazone **13** of characteristic signals for the protons of the $CH_2C=$ (3.43 ppm, s) and NH (10.64 ppm, s) groups point in its favor. However signals were absent from the spectrum of hydrazone **13** for the proton of the =CH group, distinctive for the enehydrazone form, which have been detected [6] at 4.60-4.80 ppm.



12 **11** **13** **14**

TABLE 1. Characteristics of the Synthesized Compounds **2-10** and **12-14**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, %
		C	H	N		
2a	$C_{10}H_9N_3OS$	54.85 / 54.76	4.21 / 4.14	19.32 / 19.17	57-58	56
2b	$C_{14}H_{11}N_3OS$	62.57 / 62.44	4.30 / 4.12	15.77 / 15.60	108-109	68
2c	$C_{18}H_{12}N_6O_2S_2$	52.88 / 52.94	2.99 / 2.96	20.67 / 20.57	149-150	65
2d	$C_9H_8N_4O_2S$	45.81 / 45.77	3.50 / 3.41	23.82 / 23.72	215-216	63
3	$C_8H_7N_3O_2S$	45.73 / 45.94	3.49 / 3.37	20.25 / 20.09	243-245	64
4a	$C_{13}H_{16}N_4OS$	56.59 / 56.50	5.91 / 5.83	20.40 / 20.28	110-112	47
4b	$C_{12}H_{14}N_4O_2S$	51.92 / 51.78	5.12 / 5.07	20.01 / 20.13	142-143	51
5	$C_{14}H_9ClN_4OS$	53.29 / 53.08	2.92 / 2.86	17.84 / 17.69	>250 (dec.)	71
6	$C_{14}H_{12}N_4OS$	59.22 / 59.13	4.30 / 4.26	19.61 / 19.71	123-124	81
7	$C_{14}H_8N_6O_2S_2$	47.35 / 47.18	2.29 / 2.26	23.45 / 23.59	236-238	70
8a	$C_9H_{12}N_4OS$	48.30 / 48.20	5.44 / 5.40	24.80 / 24.98	212-213	87
8b	$C_{14}H_{14}N_4OS$	58.77 / 58.71	5.01 / 4.92	19.75 / 19.57	216-217	85
8c	$C_{11}H_{12}N_4O_2S$	50.12 / 49.98	4.49 / 4.58	21.31 / 21.20	162-163 (dec.)	51
9	$C_9H_{10}N_4S$	52.44 / 52.40	4.99 / 4.89	27.25 / 27.16	160-162	66
10	$C_{11}H_{12}N_4OS$	53.37 / 53.21	4.99 / 4.87	22.45 / 22.57	186-187	88
12	$C_{12}H_{14}N_6O_2S_2$	42.66 / 42.59	4.22 / 4.17	24.99 / 24.84	152-153	90
13	$C_{15}H_{17}N_5O_4S$	49.73 / 49.58	4.81 / 4.72	19.41 / 19.27	107-108	61
14	$C_{12}H_{13}N_5O_3S$	46.81 / 46.90	4.33 / 4.26	22.90 / 22.79	150-152	68

* Compounds **2a-c** were recrystallized from a 2-propanol–octane mixture, compound **14** from 2-propanol.

On heating hydrazide **11** with ethyl orthoformate the ethoxymethylenehydrazide **14** was formed, in the ^{1}H NMR spectrum of which the signal at 1.36 ppm belongs to the proton of the methyl group, that at 6.95 to the proton of the =CH group, and the signal at 10.76 ppm to the NH group proton.

The antitubercular activity of some of the compounds synthesized in this work has been investigated. Initial investigations showed that compounds **4a,b** and **8a** at concn. 6.25 mg/ml displayed antitubercular activity in relation to *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294) (98-99%). The investigation was carried out under the program: the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) through a research and development contract with the U.S. National Institute of Allergy and Infectious Diseases.

TABLE 2. Data of ^{1}H NMR Spectra of Compounds **2-10**, **12-14**

Compound	^{1}H NMR spectrum, δ, ppm, *J* (Hz)*
2a	3.91 (2H, d, *J* = 7, SCH_2); 5.04 (1H, d, *J* = 7, =CH_2-*cis*); 5.21 (1H, d, *J* = 7, =CH_2-*trans*); 7.71 (2H, d, *J* = 6, 3-, 5-H); 8.64 (2H, d, *J* = 6, 2-, 6-H)
2b	4.51 (2H, s, SCH_2); 7.27 (5H, m, Ph); 7.71 (2H, d, *J* = 6, 3-, 5-H); 8.64 (2H, d, *J* = 6, 2-, 6-H)
2c	4.13 (4H, s, SCH_2); 7.69 (2H, d, *J* = 6, 3-, 5-H); 8.63 (2H, d, *J* = 6, 2-, 6-H)
2d	4.01 (2H, s, SCH_2); 7.68 (2H, d, *J* = 6, 3-, 5-H); 8.63 (2H, d, *J* = 6, 2-, 6-H)
3	5.22 (2H, s, NCH_2); 7.57 (2H, d, *J* = 6, 3-, 5-H); 8.58 (2H, d, *J* = 6, 2-, 6-H)
4a	1.36 (6H, m, $CH_2CH_2CH_2$); 2.62 (4H, m, CH_2NCH_2); 4.84 (2H, s, NCH_2N); 7.57 (2H, d, *J* = 6, 3-, 5-H); 8.56 (2H, d, *J* = 6, 2-, 6-H)
4b	2.62 (4H, m, CH_2OCH_2); 3.42 (4H, m, CH_2NCH_2); 4.89 (2H, s, NCH_2N); 7.60 (2H, d, *J* = 6, 3-, 5-H); 8.57 (2H, d, *J* = 6, 2-, 6-H)
5	7.38 (5H, m, Ph); 7.79 (2H, d, *J* = 6, 3-, 5-H); 8.79 (2H, d, *J* = 6, 2-, 6-H)
6	3.02 (2H, t, *J* = 7, CH_2); 4.24 (2H, t, *J* = 7, NCH_2); 7.07 (2H, d, *J* = 6, 3'-, 5'-H); 7.58 (2H, d, *J* = 6, 3-, 5-H); 8.27 (2H, d, *J* = 6, 3'-, 5'-H); 8.62 (2H, d, *J* = 6, 2-, 6-H)
7	7.53 (2H, d, *J* = 6, 3-, 5-H); 8.53 (2H, d, *J* = 6, 2-, 6-H)
8a	0.98 (3H, t, *J* = 7, CH_3); 3.24 (2H, m, CH_2); 7.58 (2H, d, *J* = 6, 3-, 5-H); 7.84 (1H, br. t, $\underline{NH}CH_2$); 8.53 (2H, d, *J* = 6, 2-, 6-H); 9.11 and 10.33 (1H, s and 1H, s, C(O)NHNH)
8b	4.76 (2H, d, *J* = 5, CH_2); 7.25 (5H, m, Ph); 7.80 (2H, d, *J* = 6, 3-, 5-H); 8.55 (1H, br. t, NH); 8.71 (2H, d, *J* = 6, 2-, 6-H); 9.41 and 10.62 (1H, s and 1H, s, C(O)NHNH)
8c	2.16 (1H, t, *J* = 3, ≡CH); 4.19 (2H, d, *J* = 3, CH_2C≡); 5.15 (2H, d, *J* = 6, $\underline{CH_2}NH$); 7.60 (1H, s, NH); 7.93 (2H, d, *J* = 6, 3-, 5-H); 8.80 (2H, d, *J* = 6, 2-, 6-H); 9.20 and 10.31 (1H, s and 1H, s, C(O)NHNH)
9	1.11 (3H, t, *J* = 7, CH_3); 3.29 (2H, m, CH_2); 7.49 (2H, d, *J* = 6, 3-, 5-H); 7.49 (1H, s, NH); 8.42 (2H, d, *J* = 6, 2-, 6-H)
10	1.22 (3H, t, *J* = 7, CH_3); 1.80 (3H, s, CH_3CO); 4.11 (2H, q, *J* = 7, CH_2); 7.60 (2H, d, *J* = 6, 3-, 5-H); 8.44 (2H, d, *J* = 6, 2-, 6-H)
12	0.98 (3H, t, *J* = 7, CH_3); 3.17 (2H, m, CH_2); 4.04 (2H, s, SCH_2); 7.67 (2H, d, *J* = 6, 3-, 5-H); 8.55 (2H, d, *J* = 6, 2-, 6-H); 9.04 (1H, s, NH); 9.51 (1H, s, NH); 9.95 (1H, s, NH)
13	1.21 (3H, t, *J* = 7, CH_3); 1.97 (3H, s, CH_3C=); 3.43 (2H, s, CH_2C=); 4.17 (2H, m, $\underline{CH_2}CH_3$); 4.58 (2H, s, SCH_2); 7.88 (2H, d, *J* = 6, 3-, 5-H); 8.88 (2H, d, *J* = 6, 2-, 6-H); 10.64 (1H, s, NH)
14	1.28 (3H, t, *J* = 7, CH_3); 4.15 (2H, m, CH_2CH_3); 4.55 (2H, s, SCH_2); 6.95 (1H, s, =CH); 7.90 (2H, d, *J* = 6, 3-, 5-H); 8.83 (2H, d, *J* = 6, 2-, 6-H); 10.76 (1H, s, NH)

* In DMSO-d_6.

EXPERIMENTAL

The ^{1}H NMR specra were measured on a Tesla BS 567 A (80 MHz) instrument, internal standard was HMDS, solvent was DMSO-d_6. The IR spectra were recorded on a UR 10 spectrometer in KBr disks.

The initial 2-mercapto-5-(4-pyridyl)-1,3,4-oxadiazole (**1**) and [5-(4-pyridyl)-1,3,4-oxadiazol-2-ylthio]-acetic acid (**11**) were obtained by the procedure of [2].

The physicochemical and spectral characteristics of the synthesized compounds are given in Tables 1 and 2.

2-(2-Propenyl)thio-5-(4-pyridyl)-1,3,4-oxadiazole (2a). Oxadiazole **1** (2.69 g, 15 mmol) was added to a solution of NaOH (0.6 g, 15 mmol) in water (30 ml), the solution obtained was filtered, TEBA (0.2 g) was dissolved in it, and allyl bromide (1.82 g, 15 mmol) was added dropwise with stirring. The mixture was stirred for 2 h at room temperature. The precipitated crystals of **2a** were filtered off and washed with water.

2-Benzylthio-5-(4-pyridyl)-1,3,4-oxadiazole (2b) was obtained from oxadiazole **1** (2.69 g, 15 mmol) and benzyl chloride (1.90 g, 15 mmol) analogously to thioether **2a**.

1,4-Di-[5-(4-pyridyl)-1,3,4-oxadiazol-2-ylthio]-2-butyne (2c) was obtained from oxadiazole **1** (2.69 g, 15 mmol) and 1,4-dichloro-2-butyne (0.95 g, 7.5 mmol) analogously to thioether **2a**.

[5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio]acetic Acid Amide (2d). Oxadiazole **1** (10.76 g, 60 mmol) and chloroacetamide (5.6 g, 60 mmol) were added to a solution of KOH (3.8 g, 68 mmol) in methanol (200 ml). The mixture was stirred for 3 h at 60°C, evaporated, and diluted with water. The crystals of amide **2d** were filtered off, and washed with water.

3-Hydroxymethyl-5-(4-pyridyl)-1,3,4-oxadiazole-2(3H)-thione (3). Formalin (25%) (6 ml) was added to the solution obtained by heating oxadiazole **1** (5.37 g, 30 mmol) in 2-propanol (100 ml), and methanol (10 ml) to 75°C. The mixture was stirred at room temperature for 3 h. The solution was partially evaporated, the precipitated crystals of compound **3** were filtered off, and washed with 2-propanol.

3-Piperidinomethyl-5-(4-pyridyl)-1,3,4-oxadiazole-2(3H)-thione (4a). Oxadiazole **1** (2.69 g, 15 mmol), methanol (30 ml), formalin (1.5 ml), and piperidine (1.28 g, 15 mmol) were mixed and heated to 40°C. The solution obtained was stored for 3 d, partially evaporated, the precipitated crystals of compound **4a** were filtered off, and washed with 2-propanol.

3-Morpholinomethyl-5-(4-pyridyl)-1,3,4-oxadiazole-2(3H)-thione (4b) was obtained from a mixture of oxadiazole **1** (2.69 g, 15 mmol), formalin (1.5 ml), and morpholine (1.3 g, 15 mmol) analogously to compound **4a**.

3-(4-Chlorophenyl)carbamoyl-5-(4-pyridyl)-1,3,4-oxadiazole-2(3H)-thione (5). A mixture of oxadiazole **1** (2.69 g, 15 mmol), 4-chlorophenyl isocyanate (2.3 g, 13.6 mmol), and dioxane (100 ml) was heated for 2 h at 90°C, and filtered. The filtrate was partially evaporated, and diluted with water. The precipitated crystals of amide **5** were filtered off, and washed with water.

3-(2-Ethyl-4-pyridyl)-5-(4-pyridyl)-1,3,4-oxadiazole-2(3H)-thione (6). A mixture of oxadiazole **1** (2.69 g, 15 mmol) , 4-vinylpyridine (1.57 g, 15 mmol), and glacial acetic acid (30 ml) was stirred for 2 h at 100°C, partially evaporated, and poured into cold 5% NaOH solution. The precipitated amorphous solid compound **6** was filtered off and washed with water.

Di-[5-(4-pyridyl)-1,3,4-oxadiazol-2-yl] Disulfide (7). A solution of potassium hexacyanoferriate (3.3 g, 10 mmol) in water (20 ml) was added to the solution obtained from NaOH (0.4 g, 10 mmol), water (20 ml), and oxadiazole **1** (1.79 g, 10 mmol). After 1 h the solution was filtered, partially evaporated, and diluted with acetone. The precipitated crystals of disulfide **7** were filtered off, and washed with acetone.

4-Ethyl-1-(4-pyridylcarbonyl)thiosemicarbazide (8a). A mixture of isonicotinic acid hydrazide (5.44 g, 40 mmol), dioxane (200 ml), and ethyl isothiocyanate (3.48 g, 40 mmol) was heated for 2 h at 90°C, the solution was partially evaporated, and diluted with diethyl ether. The crystals of thiosemicarbazide **8a** were filtered off, and washed with ether.

4-Benzyl-1-(4-pyridylcarbonyl)thiosemicarbazide (8b). Benzyl isothiocyanate (13.26 g, 100 mmol) was added to the solution obtained from isonicotinic acid hydrazide (13.7 g, 100 mmol) and dioxane (500 ml) at 60°C. The mixture was stirred for 30 min at 70°C. The precipitated crystals of thiosemicarbazide **8b** were filtered off, and washed with dioxane.

4-(2-Oxa-4-pentynyl)-1-(4-pyridylcarbonyl)thiosemicarbazide (8c) was obtained from isonicotinic acid hydrazide (6.85 g, 50 mmol), dioxane (200 ml), and 2-oxa-4-pentynyl isothiocyanate (6.35 g, 50 mmol) [7] analogously to compound **8b**.

2-Ethylamino-5-(4-pyridyl)-1,3,4-thiadiazole (9). A solution of thiosemicarbazide **8a** (1.8 g, 8 mmol) in anhydrous phosphoric acid (30 ml) was heated at 110°C for 1 h 30 min. The mixture was cooled, diluted with water (100 ml), and neutralized with aqueous ammonia. The precipitated thiadiazole **9** was filtered off, and washed with water.

2-(N-Acetylethylamino)-5-(4-pyridyl)-1,3,4-thiadiazole (10). Thiadiazole **9** (1.04 g, 5 mmol) was dissolved in ethyl orthoformate (20 ml) and acetic anhydride (15 ml). The mixture was heated for 2 h at 100°C, distilling off the volatile components through a fractionating column, and partially evaporated. The residue was diluted with diethyl ether, the precipitated crystals of thiadiazole **10** were filtered off, and washed with ether.

4-Ethyl-1-[5-(4-pyridyl)-1,3,4-oxadiazol-2-ylthioacetyl]thiosemicarbazide (12) was obtained from hydrazide **11** (1.26 g, 5 mmol), ethyl isothiocyanate (0.44 g, 5 mmol), and dioxane (40 ml) analogously to thiosemicarbazide **8a**.

[5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio]acetic Acid 4-Ethoxy-4-oxo-2-butylidenehydrazide (13). A solution of hydrazide **11** (1.26 g, 5 mmol) in ethyl acetoacetate (40 ml) was heated for 2 h at 105°C, distilling off the volatile components through a fractionating column, and partially evaporated. The precipitated crystals of hydrazide **13** were filtered off, and washed with ether.

[5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio]acetic Acid Ethoxymethylidenehydrazide (14). A solution of hydrazide **11** (1.26 g, 5 mmol) in ethyl orthoformate (40 ml) was heated at 105-110°C for 2 h, distilling off the volatile components through a fractionating column, and partially evaporated. The mixture was diluted with hexane, the precipitated crystals of hydrazide **14** were filtered off, and washed with hexane.

REFERENCES

1. H. Liszkiewicz, T. Glowiak, M. W. Kowalska, M. Rutkowska, A. Szelag, J. Barczynska, L. Kedzierska-Gozdzik, F. Blaszczyk, and W. Dziewiszek, *Pol. J. Chem.*, **73**, 321 (1999).
2. A. Rutavicius, S. Valyulene, and Z. Kuodis, *Khim. Geterotsikl. Soedin.*, 966 (2000).
3. V. Yakubkene and P. Vainilavicius, *Khim. Geterotsikl. Soedin.*, 1125 (1998).
4. S. I. Yakimovich, V. I. Nikolaev, and O. A. Afonina, *Zh. Org. Khim.*, **15**, 922 (1979).
5. A. Rutavicius and V. Mozolis, *Trud. Akad. Nauk LitSSR, Ser. B*, **5(126)**, 81 (1981).