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LETTERS TO THE EDITOR

Dedicated to the memory of Sh.S. Akhmedova

Thiosemicarbazides of Piperidylacetic Acid in the Synthesis of Bisheterocyclic Compounds

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Among the developed directions to search new medicines the most attention has been paid to derivatives of the nitrogen-containing heterocycles and first all to piperidine derivatives [1, 2].

In the course of the purposeful investigations [3–5] on the synthesis of biologically active compounds in the rank of nitrogen-contained heterocycles, the synthesis of thiosemicarbazides as the main starting compounds for preparing of biheterocyclic compounds was per-formed, and some of their reactions were investigated.

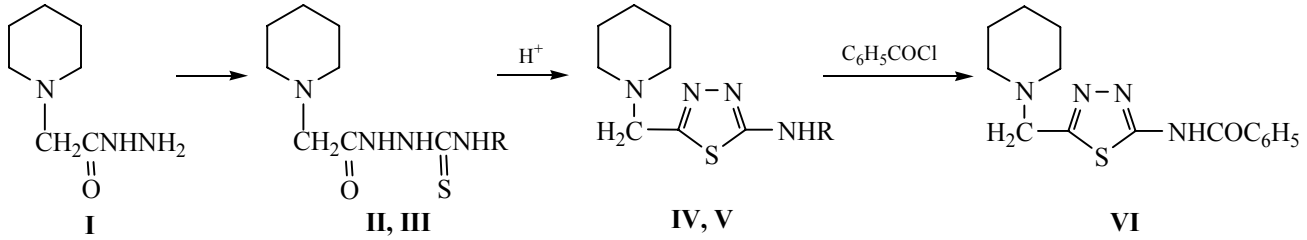
Thus, for preparation of 1,3,4-thiadiazoles **IV** and **V**, cyclization of thiosemicarbazides **II** and **III** obtained from 2-(piperidin-1-yl)acetohydrazine **I** was performed in acidic medium.

Acylation of compound **IV** with benzoyl chloride in benzene in the presence of trimethylamine afforded benzoic acid *N*-[5-(piperidin-1-ylmethyl)-1,2,4-thiadiazol-2-yl]amide **VI** (Scheme 1).

It was found that in the presence of concentrated alkaline compounds **II** and **III** converted to the thiolate form that was favorable for intramolecular cyclization [6, 7] due to an attack of the electron-deficient carbon atom of the carbonyl group by nucleophilic nitrogen atom with formation of stable compounds **VII** and **VIII**. Based on the spectral characteristics the prepared compounds occurred to be substituted 1,2,4-triazole-5-thiones. In the IR spectra of compounds **VII** and **VIII** absorption in the field 2600–2500 (S–H) and 900–850 cm^{-1} (C–S–H) was not registered, but there were two maxima at 1342 and 1320 cm^{-1} corresponded to the vibrations of C=S bond of 1,2,4-triazole-5-thione (Scheme 2).

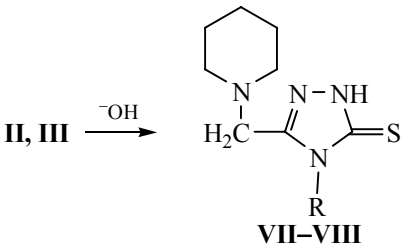
It is known that due to the thione–thiol tautomerism in the molecule of 1,3,4-triazoel-5-thiones there are

Scheme 1.



R = H (**II, IV**), Ph (**III, V**).

Scheme 2.



VII–VIII

R = H (**II, VII**), Ph (**III, VIII**).

two reaction sites, NH and SH, that gives an opportunity to prepare various derivatives. Alkylation and acylation of 4-phenyl-3-(piperidin-1-ylmethyl)-1*H*-1,2,4-triazole-5(4*H*)-thione **VIII** were done by us (Scheme 3).

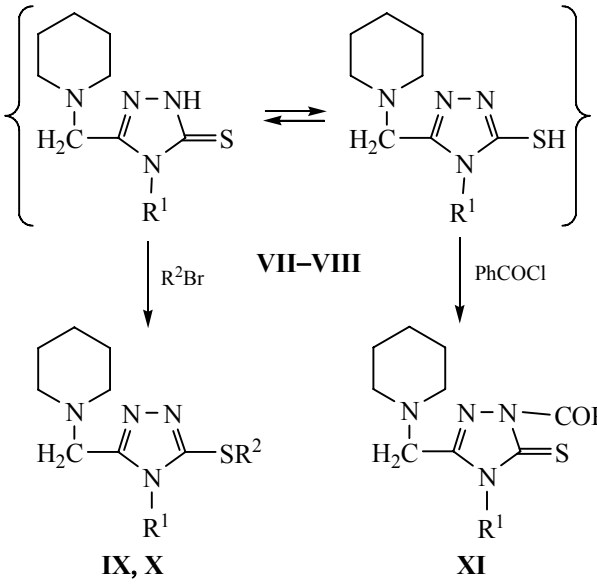
Using the procedure elaborated earlier [8] alkylation of 1,2,4-triazole-5-thione **VIII** with butyl bromide and ethyl bromoacetate provided compounds **IX** and **X**. Acylation of compound **VIII** with benzoyl chloride led to the formation of phenyl[4-phenyl-3-(piperidin-1-ylmethyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazole-1-yl]-ketone **XI**.

2-[2-(Piperidin-1-yl)acetyl]thiosemicarbazide (II). A mixture of 2-(piperidin-1-yl)acetohydrazine **I** (1.57 g, 0.01 mol), potassium rhodanide (1.1 g, 0.015 mol), 1.5 mL of hydrochloric acid, and 20 mL of water was stirred for 4 h at 95°C, and then left for 24 h at room temperature followed by alkalization up to pH 6–7. The formed precipitate was filtered and recrystallized from petroleum ether. Yield 1.38 g (64.0%), mp 226–228°C. IR spectrum, ν, cm^{-1}: 3305–3240 (NH_2), 3210 (CN), 1660 (C=O), 1270 (C=S). Found, %: C 44.42; H 7.46; N 25.90. $C_8H_{16}N_4OS$. Calculated, %: C 44.25; H 7.29; N 25.63.

***N*-Phenyl-2-[2-(piperidin-1-yl)acetyl]thiosemicarbazide (III)**. Phenyl isothiocyanate (1.35 g, 0.01 mol) was added to a solution of 2-(piperidin-1-yl)-acetohydrazine **I** (1.57 g, 0.01 mol) in 20 mL of ethanol. The reaction mixture was stirred for 5 h at 60–65°C. After removing of the solvent, the residue was recrystallized from petroleum ether. Yield 2.63 g (90.2%), mp 165–166°C. IR spectrum, ν, cm^{-1}: 3120–3220 (NH), 3040 (C=C, arom.), 1675 (C=O), 1450–1605 (C=C, arom.), 1250 (C=S), 690 (C=C, arom.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.41 m (2H, CH_2), 1.63 m (4H, 2-CH_2), 2.41 t (4H, 2-CH_2, *J* 4.44 Hz), 3.14 s (2H, NCH_2), 7.16–7.51 m (5H, ArH), 10.40 s (1H, NHC=O), 13.72 (1H, NHC=S). Found, %: C 57.53; H 6.85; N 19.18. $C_{14}H_{20}N_4OS$. Calculated, %: C 57.22; H 6.54; N 19.03.

The general procedure for the synthesis of 1,3,4-thiadiazoles (IV, V). Thiosemicarbazide **II** or **III** (0.01 mol) was dissolved in 5.2 mL of conc. sulfuric acid. The obtained solution was poured into 100 mL of cooled water. The formed white crystalline solid was

Scheme 3.



IX, X **XI**

R^1 = H (**VII**), Ph (**VIII**); R^2 = C_4H_9 (**IX**), $CH_2COOC_2H_5$ (**X**).

filtered off, washed with ethanol, and recrystallized from ethanol.

5-(Piperidin-1-ylmethyl)-1,3,4-thiadiazolyl-2-amine (IV). Yield 1.5 g (75.6%), mp 265–266°C. IR spectrum, ν, cm^{-1}: 3305–3255 (NH_2), 1605 (C=N), 1515–860 (thiadiazole). Found, %: C 48.46; H 7.12; N 28.26. $C_8H_{14}N_4S$. Calculated, %: C 48.25; H 7.16; N 28.13.

***N*-Phenyl-5-(piperidin-1-ylmethyl)-1,3,4-thiadiazolyl-2-amine (V)**. Yield 1.71 g (62.1%), mp 154–155°C. IR spectrum, ν, cm^{-1}: 3150 (NH), 1670 (C=N), 1440–1660 (C=C, arom.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.35 m (2H, CH_2), 1.50 m (4H, 2-CH_2), 2.10 t (4H, 2-CH_2, *J* 4.44 Hz), 2.44 s (2H, NCH_2), 7.10–7.65 m (5H, ArH). Found, %: C 61.06; H 6.95; N 20.34. $C_{14}H_{19}N_4S$. Calculated, %: C 60.82; H 6.62; N 20.61.

Benzoic acid *N*-[5-(piperidin-1-ylmethyl)-1,3,4-thiadiazol-2-yl]amide (VI). Benzoyl chloride (0.7 g, 0.0052 mol) was added to a mixture of 5-(piperidin-1-ylmethyl)-1,3,4-thiadiazolyl-2-amine **IV** (1.02 g, 0.005 mol) and triethylamine (0.52 g, 0.0052 mol) in 20 mL of benzene. The reaction mixture was heated for 2 h at 60–70°C; after the solvent removing, the residue was recrystallized from petroleum ether. Yield 1.1 g (72.5%), mp 248°C. IR spectrum, ν, cm^{-1}: 3220 (NH), 3030 (C=C, arom.), 1725 (C=O), 1620 (C=N), 1530–1590, (C=C, arom.), 660 (C=C, arom.). Found, %: C 59.58; H 6.00; N 18.53. $C_{15}H_{18}N_4OS$. Calculated, %: C 59.17; H 6.13; N 18.40.

The general procedure for the synthesis of substituted 1,2,4-triazole-5-thiones (VII, VIII). A mixture of thiosemicarbazide **II** or **III** (0.01 mol) and 10% potassium hydroxide (20 mL) was heated for 6 h at 80–85°C. After cooling the reaction mixture was acidified with hydrochloric acid up to pH 6–7. The formed precipitate was filtered off and recrystallized from acetone.

3-(Piperidin-1-ylmethyl)-1*H*-1,2,4-triazol-5(4*H*)-thione (VII). Yield 1.83 g (92.5%), mp 179–180°C. IR spectrum, ν, cm^{-1}: 3210 (NH), 1605 (C=N), 1320 (C=S). Found, %: C 48.16; H 7.12; N 28.26. $C_8H_{14}N_4S$. Calculated, %: C 48.13; H 7.02; N 28.17.

4-Phenyl-3-(piperidin-1-ylmethyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (VIII). Yield 2.62 g (95.7%), mp 183–184°C. IR spectrum, ν, cm^{-1}: 3100–3300 (NH), 3040 (C=C, arom.), 1590 (CN), 1450–1605 (C=C, arom.), 1380 (C=S), 685 (C=C, arom.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.30 m (2H, CH_2), 1.42 m (4H, 3-CH_2), 2.31 m (4H, 2-CH_2), 3.30 s (2H, NCH_2), 7.44–7.56 m (5H, ArH), 11.25 s (1H, NH). Found, %: C 61.31; H 6.59; N 20.43. $C_{14}H_{18}N_4S$. Calculated, %: C 61.16; H 6.87; N 20.03.

1-[(5-Butylthio)-4-phenyl-4H-1,2,4-triazol-3-yl-methyl]piperidine (IX). Butyl bromide (1.37 g, 0.01 mol) was added to a mixture of compound **VIII** (2.74 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol) in 20 mL of absolute ethanol. The reaction mixture was heated for 6 h at 70–75°C. After the reaction completed, ethanol was distilled off. The residue was washed with diethyl ether and recrystallized from ethanol. Yield 2.59 g (78.7%), mp 238–240°C. IR spectrum, ν, cm^{-1}: 3045 (C=C, arom.), 1605 (C=N), 1450–1590 (C=C, arom.). Found, %: C 65.45; H 7.90; N 16.97. $C_{18}H_{26}N_4S$. Calculated, %: C 64.72; H 7.74; N 16.82.

Ethyl 2-[4-phenyl-5-(piperidin-1-ylmethyl)-4*H*-1,2,4-triazol-3-yl]thioacetate (X). Freshly distilled ethyl bromoacetate (1.8 g, 0.11 mol) was added to a mixture of compound **VIII** (2.74 g, 0.01 mol) and potassium carbonate (2.1 g, 0.015 mol) in 50 mL of anhydrous acetone. The reaction mixture was heated at 55–60°C for 6 h. The precipitated potassium bromide was filtered off and washed with acetone. The filtrate was evaporated; the residue was acidified with solution of HCl in diethyl ether. The precipitate was filtered off and recrystallized from ethanol. Yield 2.71 g (68.4%), mp 254–255°C. IR spectrum, ν, cm^{-1}: 1735 (C=O), 1620 (C=N), 1235 (C–O–C), 940–1450 (C=C, arom.). Found, %: C 60.00; H 6.67; N 15.55. $C_{18}H_{24}N_4O_2S$. Calculated, %: C 59.83; H 6.85; N 15.32.

Phenyl[4-phenyl-3-(piperidin-1-ylmethyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]ketone (XI). Benzoyl chloride (1.40 g, 0.01 mol) was slowly added to a mixture of compound **VIII** (2.74 g, 0.01 mol) and triethylamine (1.0 g, 0.01 mol) in 25 mL of absolute benzene. The reaction mixture was heated for 2 h at 60–70°C. After cooling the precipitate was filtered off and recrystallized from ethanol. Yield 2.36 g (62.6%), mp 240°C. IR spectrum, ν, cm^{-1}: 3080 (C=C, arom.), 1665 (C=C), 1650 (C=N), 1450–1590 (C=C, arom.), 1330 (C=S), 690 (C=C, arom.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.54 m (2H, CH_2), 1.71 m (4H, 3-CH_2), 2.10 t (4H, 2-CH_2, *J* 4.4 Hz), 4.36 s (2H, NCH_2), 7.32–7.67 m (10H, ArH). Found, %: C 66.64; H 5.86; N 14.80. $C_{21}H_{22}N_4OS$. Calculated, %: C 66.34; H 5.56; N 14.35.

The reaction progress was monitored by the means of TLC on Silufol UV-254 plates developing with

iodine vapors. IR spectra were registered on a Specord 75 IR spectrometer. ^{1}H NMR spectra were recorded on a Bruker WM 250 and Bruker DRX 500 instruments.

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