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Synthesis and Spatial Structure of 4-(2-Hydroxyethyl)-5-(2-hydroxyphenyl)-2*H*-1,2,4-triazolo-3(4*H*)-thione

A. S. Alimbayeva[a], O. A. Nurkenov[a], A. Kh. Zhakina[a], I. V. Kulakov[a], D. M. Turdybekov[b], and K. M. Turdybekov[b]

[a] *Institute of Organic Synthesis and Coal Chemistry of Republic of Kazakhstan, ul. Alikhanova 1, Karaganda, 100008 Kazakhstan*
e-mail: kulakov_iv@mail.ru

[b] *Phytochemistry Scientific Production Centre, Karaganda, Kazakhstan*

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Abstract—By reaction of 2-vinyloxyethyl isothiocyanate with salicylic acid hydrazide a synthesis of the corresponding thiosemicarbazide was performed. Alkaline hydrolysis of the latter led to an intramolecular heterocyclization into 1,2,4-triazole derivative. When cyclization was carried out in the water-alkali medium, 2-vinyloxyethyl fragment was shown to be hydrolyzed to form 4-(2-hydroxyethyl)-5-(2-hydroxyphenyl)-2*H*-1,2,4-triazolo-3(4*H*)-thione, whose spatial structure was established by XRD analysis.

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Salicylic acid is abundant in nature. Its derivatives, in which it is predominantly bound to a glucose residue, are contained in willow leaves and also in essential oils of various plants. Salicylic acid is widely used in medicine. It possesses antirheumatic, anti-inflammatory, febrifugal, antimicrobial, antibacterial, and antimycotic actions. Since 1876 *o*-oxybenzoic acid derivatives (salicylates) has been introduces into the clinic practice and are used everywhere to this day. Sodium salicylate, salicylamide and acetylsalicylic acid (aspirin) are employed as febrifugal, antirheumatic, anti-inflammatory and analgesic agents, and phenyl salicylate is used as antiseptic, *p*-aminosalicylic acid (PASK) and calcium *p*-benzoylaminosalicylate (BEPASK), as tuberculocidal agents [1].

Of particular interest is the synthesis of hydrazine-containing derivatives of the salicylic acid since many of hydrazine derivatives have a broad spectrum of biological activity: analgesic, cardiovascular, anticonvulsive, antiviral, antimicrobial, tuberculocidal, etc. [2–5]. It is also known that many of the thiosemicarbaside and thioamide derivatives such as thioacetazone, *p*-aminobenzaldehyde thiosemicarbazone, α-methylbenzylthiourea possess bacteriostatic and antiviral activity [6, 7].

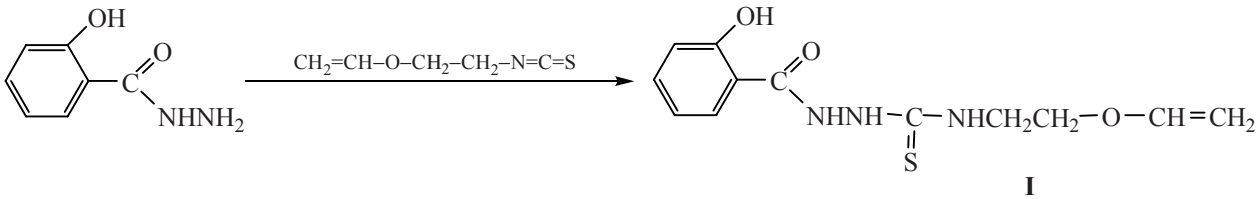
The published data indicate that reaction of isothicyanates with amines and hydrazides is the main synthesic approach to thioureas and thiosemicarbazides. In this connection we attempted to prepare a new thiosemicarbazide derivative proceeding from the salicylic acid hydrazide and 2-vinyloxyethyl isothiocyanate. 2-Vinyloxyethyl isocyanate is of special interest among isocyanates as a starting object. It is a highly active bifunctional synthon combining unique synthetic possibility of vinyl ethers and isothiocyanates. From 2-vinyloxyethyl isothiocyanate, isonicotinic acid hydrazide and anabasine thiourea derivatives were synthesized showing high antifungal activity [8, 9].

Condensation of 2-vinyloxyethyl isothiocyanate with salicylic acid hydrazide was carried out in alcohol using equimolar reagents ratio.

Reaction proceeds under mild conditions with product **I** yield of 70%. The prepared compound **I** is crystalline and well soluble in polar organic solvents.

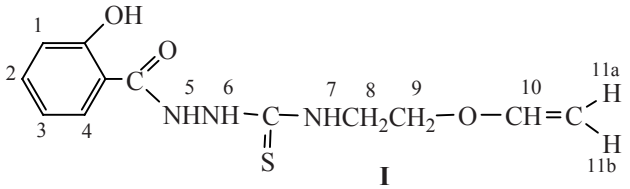
In the IR spectrum of **I** there is an absorption band in the region of 1310 cm^{-1} characteristic of NH-CS moiety of the thiosemicarbazide fragment. The absorption bands of amide C(O)NH and NH groups appear at 1675 and 3390 cm^{-1} respectively.

In the ^1H NMR spectrum of **I** the signals of aromatic ring protons are observed. Thus, signals of



I

H^1–H^4 protons are registered in the downfield region: a doublet at δ 6.97 (H^1), a triplet at 7.45 (H^2), a triplet at 6.92 (H^3), and a doublet at 7.87 ppm (H^4). Two triplets at δ 3.70 and 3.80 ppm belong to the four methylene protons H^8 and H^9 of the oxyethyl fragment. The vinyl methine proton H^{10} is observed at δ 6.50 ppm as a doublet of doublets. Methylene protons H^{11a} and H^{11b} of the vinyl fragment appear at δ 4.00 and 4.21 ppm. Aromatic hydroxyl proton gives a singlet at δ 8.30 ppm. Amide and thioamide N–H protons appear as three singlets at δ 11.92 (H^5), 10.58 (H^6), and 9.55 ppm (H^7).



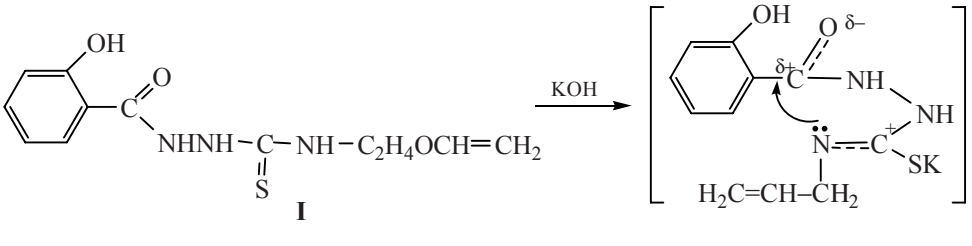
I

In the mass-spectrum of compound **I** there are some peaks with *m/z* values and relative intensities I_{rel} (%) that belong to molecular ion 281 $[M]^+$ (27%) and fragment ions 248 (17%), 144 (28%), 121 (100%) and 86 (48%).

Thiosemicarbazides are known to be widely used in organic chemistry as starting synthons for synthesis of the nitrogen-containing heterocyclic compounds.

The prepared salicylic acid thiosemicarbazide derivative **I** was subjected to an intramolecular cyclization aiming at the preparation of new biologically active substances. The promising in respect to antibacterial properties are the derivatives of 1,2,4-triazole-3-thione, many of which are used in pharmacology [10, 11] and agriculture [12–14].

The cyclization of salicylic acid thiosemicarbazide derivative was carried out in the water-alkali medium under heating the reaction mixture to 80–85ºC. In the presence of alkali compound **I** transforms into a thiolate. On further acidifying of the latter formed 5-(2-hydroxyphenyl)-4-vinyloxyethyl-1,2,4-triazole-3-thione **II**.



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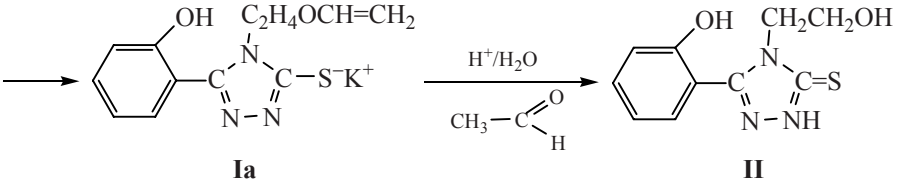
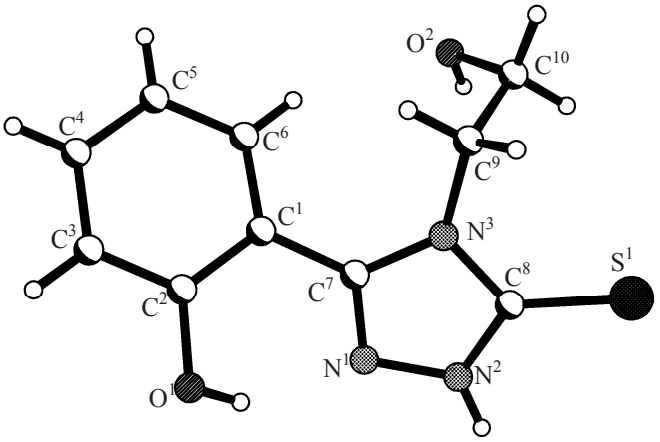


Ia **II**

Thioureas and thiosemicarbazides are weak SH-acids. However, in a solution thione form prepredominants, and the SH-form is present in a negligible amount incapable to affect the further reaction course. The alkali effect is based on the fact that these compounds transform fully into thiolates at the high alkali concentration resulting in a shift of the electronic equilibrium and formation of conditions for intramo-



General view of the molecule of 4-(2-hydroxy-ethyl)-5-(2-hydroxyphenyl)-2*H*-1,2,4-triazolo-3(4*H*)-thione **II.**

lecular cycle closure due to nucleophilic attack of the nitrogen atom on the electron-deficient carbonyl carbon giving a stable heterocyclic system.

However, on carrying out the intramolecular heterocyclization we isolated not the expected compound **Ia**, but its hydrolysis product, 4-(2-hydroxyethyl)-5-(2-hydroxyphenyl)-2*H*-1,2,4-triazolo-3-(4*H*)-thione **II**. The prepared compound **II** is a white crystalline substance soluble in the polar organic solvents. Formation of the derivative **II** was unambiguously confirmed using mass-spectrometry, IR, and ^{1}H NMR spectroscopy. In the IR spectrum of **II** we observed absorption bands of hydroxy group in the range of 3370 cm^{-1}. C=S group vibrations are observed at 1265 cm^{-1}.

Peaks of molecular ion 237 $[M]^+$ (51%) and ions 194 (59%), 193 (100%) and 120 (31%) were detected in the mass-spectrum of **II**.

In the ^{1}H NMR spectrum of **II** as distinct from compound **I** some shift of aromatic H^4 proton is observed. Thus, H^4 proton doublet is shifted upfield from δ 7.87 (in compound **I** with adjacent carbonyl group) to 7.31 ppm. There are a triplet of H^2 at δ 7.40, a doublet of H^1 at 7.00, and a triplet of H^3 at 6.94 ppm. Four methylene H^6 and H^7 and oxyethyl fragment protons give two triplets at δ 3.49 and 3.90 ppm. Aromatic and oxyethyl hydroxy protons appear as a singlet at δ 10.25 ppm and as a broad singlet at δ 4.74 ppm respectively. Thioamide N–H proton of triazole cycle gives a narrow singlet in the downfield region at δ 13.80 ppm.

The X-ray diffraction analysis was carried out to establish the spatial structure of 4-(2-hydroxyethyl)-5-(2-hydroxyphenyl)-2*H*-1,2,4-triazolo-3(4*H*)-thione **II** (see figure).

Bond lengths and bond angles are close to the standard values (Tables 1, 2) [15].

The five-membered triazole cycle $N^1N^2N^3C^7C^8$ is planar within 0.0028 Å. The deviation of the sulfur

Table 1. Bond lengths (*d,* Å) in molecule **II**

Bond	*d*	Bond	*d*
S^1–C^8	1.6821(15)	C^1–C^2	1.404(2)
O^2–C^{10}	1.4266(19)	C^1–C^7	1.4669(19)
N^3–C^8	1.3744(17)	C^{10}–C^9	1.513(2)
N^3–C^7	1.382118)	C^2–O^1	1.356(2)
N^3–C^9	1.4709(17)	C^2–C^3	1.384(2)
N^1–C^7	1.3110(18)	C^3–C^4	1.371(3)
N^1–N^2	1.3685(18)	C^4–C^5	1.383(3)
N^2–C^8	1.3344(19)	C^5–C^6	1.380(2)
C^1–C^6	1.393(2)		

Table 2. Bond angles (ω, deg) in structure **II**

Angle	ω	Angle	ω
$C^8N^3C^7$	107.58(12)	$N^1C^7C^1$	121.56(13)
$C^8N^3C^9$	123.16(12)	$N^3C^7C^1$	127.99(12)
$C^7N^3C^9$	128.46(12)	$O^2C^{10}C^9$	112.72(12)
$C^7N^1N^2$	104.77(12)	$O^1C^2C^3$	116.78(15)
$C^8N^2N^1$	112.99(12)	$O^1C^2C^1$	122.72(15)
$C^6C^1C^2$	118.12(14)	$C^3C^2C^1$	120.50(15)
$C^6C^1C^7$	123.25(13)	$N^3C^9C^{10}$	113.64(12)
$C^2C^1C^7$	118.62(13)	$C^4C^3C^2$	120.09(15)
$N^2C^8N^3$	104.35(12)	$C^3C^4C^5$	120.35(16)
$N^2C^8S^1$	128.25(11)	$C^6C^5C^4$	119.96(16)
$N^3C^8S^1$	127.36(11)	$C^5C^6C^1$	120.86(15)
$N^1C^7N^3$	110.31(12)		

Table 3. Torsion angles (τ, deg) in molecule **II**

Angle	τ	Angle	τ
$C^7N^1N^2C^8$	0.48(18)	$C^2C^1C^7N^3$	–142.35(16)
$N^1N^2C^8N^3$	–0.74(17)	$C^6C^1C^2O^1$	176.63(17)
$N^1N^2C^8S^1$	176.88(11)	$C^7C^1C^2O^1$	–2.1(3)
$C^7N^3C^8N^2$	0.69(16)	$C^6C^1C^2C^3$	–3.8(2)
$C^9N^3C^8N^2$	171.24(12)	$C^7C^1C^2C^3$	177.46(14)
$C^7N^3C^8S^1$	–176.95(11)	$C^8N^3C^9C^{10}$	77.39(17)
$C^9N^3C^8S^1$	–6.4(2)	$C^7N^3C^9C^{10}$	–114.14(16)
$N^2N^1C^7N^3$	0.00(16)	$O^2C^{10}C^9N^3$	66.15(16)
$N^2N^1C^7C^1$	–175.99(13)	$O^1C^2C^3C^4$	–177.93(18)
$C^8N^3C^7N^1$	–0.44(17)	$C^1C^2C^3C^4$	2.5(3)
$C^9N^3C^7N^1$	–170.33(13)	$C^2C^3C^4C^5$	0.6(3)
$C^8N^3C^7C^1$	175.22(14)	$C^3C^4C^5C^6$	–2.2(3)
$C^9N^3C^7C^1$	5.3(2)	$C^4C^5C^6C^1$	0.8(3)
$C^6C^1C^7N^1$	–145.82(17)	$C^2C^1C^6C^5$	2.2(3)
$C^2C^1C^7N^1$	32.9(2)	$C^7C^1C^6C^5$	–179.14(17)
$C^6C^1C^7N^3$	39.0(2)		

Table 4. Atomic coordinates ($\times10^4$, $\times10^3$ for H) in **II**

Atom	*x*	*y*	*z*
S^1	3585(1)	2350(1)	317(1)
O^2	9256(1)	844(2)	–1566(1)
N^3	5661(2)	2472(2)	–2231(1)
N^1	3767(2)	1476(2)	–3449(1)
N^2	2965(2)	1456(2)	–2110(1)
C^1	6682(2)	2439(2)	–4809(2)
C^8	4061(2)	2062(2)	–1342(2)
C^7	5414(2)	2100(2)	–3506(2)
C^{10}	8302(2)	2231(2)	–929(2)
C^2	5976(2)	3012(2)	–6047(2)
C^9	7184(2)	3426(2)	–1879(2)
C^3	7130(2)	3415(2)	–7293(2)
C^4	8973(2)	3191(3)	–7336(2)
C^5	9691(2)	2548(3)	–6139(2)
C^6	8556(2)	2185(3)	–4886(2)
O^1	4166(2)	3211(3)	–6092(2)
HO^1	364(4)	27(4)	–538(3)
HO^2	865(3)	–9(3)	–127(2)

atom from this plane is +0.079 Å. We believe that the flattening of this cycle is due to the conjugation between electron density of double bonds N^1=N^2 and C^8=S^1. The benzene ring atoms are planar within 0.0012 Å, and the deviation of the atom O^1 from this plane is –0.074 Å. The phenyl plane is turned equatorially relative to the triazole cycle. The corresponding torsion angle $N^1C^7C^1C^2$ is 32.84º (Table 3). In this molecule the intramolecular hydrogen bond $O^1HO^1\cdots N^1$ is observed. The parameters of the hydrogen bond are as follows: $O^1H\cdots N^1$ 2.694 Å, O^1–$HO^1\cdots N^1$ 1.991 Å, $\angle O^1$–$HO^1\cdots N^1$ 147.62º that influence considerably the turn of benzene ring relative to the five-membered cycle. The todsion angle $N^1C^7C^1C^2$ is 32.84º. The bulky substituent at the N^3 atom is equatorially oriented (torsion angle $N^2C^8N^3C^9$ = 171.07º).

EXERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker DRX500 spectrometer (500 MHz) in DMSO-d_6 solution relative to internal TMS. The mass-spectra were measured on a FINNIGAN MAT.INCOS 50 device (70 eV). Melting points were determined on a Boetius device. TLC analysis was accomplished on a Sorbfil plates using iodine vapor as a detecting agent.

Single crystal X-ray diffraction analysis. The unit cell parameters and intensities of 2564 reflections were measured on a BrukerP4 automatic four-circle diffractometer (λMoK_α radiation, graphite monochromator, θ/2θ scanning). The crystals are triclinic, $2\theta \le 56.9º$, *a* 7.4320(4), *b* 7.4873(3), *c* 9.9304(4) Å, α 79.959(3), β 81.189(4), γ 88.543(4), *V* 537.70(4) Å^3, *Z* 2($C_{12}H_{13}N_3O_2S$), d_{calc} 1.626 g cm^{-3}, space group *P*1.

In the calculation we used 2358 independent reflections with $I > 2\sigma$. The structure was solved by the direct method and refined by the least-squares method in the full-matrix anisotropic approximation for nonhydrogen atoms. All the H atoms were geometrically placed on the "rider" model, except for the hydroxy hydrogen atoms at the O^1 and O^2 atoms, which were revealed and refined in the anisotropic

approximation. The final values of the divergence factors are R 0.0359 and wR_2 0.0985. The atomic coordinates are given in Table 4. All the calculations were performed using the SHELX-97 program package.

Salicylic acid *N*-2-vinyloxyethylthiosemicarbazide (I). To a solution of 1.52 g (0.01 mol) of salicylic acid hydrazide in 25 ml of isopropyl alcohol was added dropwise 1.29 g (0.01 mol) of 2-vinyloxyethyl isothiocyanate dissolved in 5 ml of isopropyl alcohol at room temperature. A mixture was stirred at 40–45ºC for 2 h and then it was cooled. The white crystalline precipitate was filtered off, dried and recrystalled from anhydrous isopropyl alcohol. Yield 70%, mp 163–165ºC.

4-(2-Hydroxyethyl)-5-(2-hydroxyphenyl)-2*H*-1,2,4-triazolo-3(4*H*)-thione (II). To a water-alkali solution of 0.56 g (0.01 mol) of KOH in 30 ml of the distilled water was added 2.81 g (0.01 mol) of salicylic acid *N*-(2-vinyloxyethyl)thiosemicarbazide **I**. The reaction mixture was refluxed at 85ºC for 1 h, whereupon it was cooled and acidified with hydrochloric acid to pH 3–4. The precipitate was filtered off and recrystalled from 70% water ethanol. Yield 69%, mp 184–186ºC.

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