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Synthesis and Structure of New 1,2,4-Triazoles Derived from *p*-Hydroxybenzoic Acid Hydrazide

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Abstract—Hydrolysis of thiosemicarbazides obtained by reacting *p*-hydroxybenzoic acid hydrazide with alkyl isocyanates occurs via intramolecular heterocyclization affording substituted 4-3-(4-hydroxyphenyl)-1*H*-1,2,4-triazole-5(4*H*)-thiones in a high yield.

Keywords: hydrazides, thiosemicarbazides, triazole

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1,2,4-Triazole derivatives are promising synthons for the preparation of new effective medicines. A number of 1,2,4-triazole derivatives are successfully used in medicine for treating fungal (fluconazole, itraconazole, terconazole) and viral infections (ribavirin, magaunos), mental disorders (trazodone, nefazodone, alprazolam, triazolam), breast cancer (letrozole, anastrozole), cardiovascular diseases (thiotriazoline, kardiotril) [1]. Some 1,2,4-triazole derivatives have been shown to possess antimicrobial [2, 3], anti-inflammatory [4], fungicidal [5], and other activities. This causes increased interest in the synthesis [6, 7] and studying the properties of 1,2,4-triazole derivatives [8, 9].

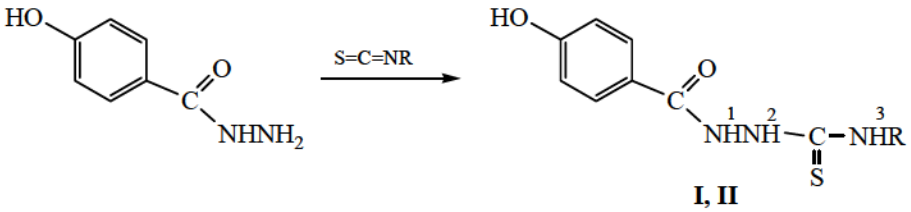
Previously we have synthesized allylthiosemicarbazide derivatives [10] based on *o*- and *p*-hydroxylbenzoic acids, which showed high antimicrobial activity towards gram-positive (*Staphylococcus aureus, Bacillus subtilis*) strains. Thiosemicarbazides are polyfunctional compounds and can be used to synthesize on their basis various heterocyclic systems.

Further developing our previous studies on the chemistry of 1,2,4-triazole, we report here a convenient synthesis of new triazole derivatives from *p*-hydroxybenzoic acid hydrazide.

The reaction of *p*-hydroxybenzoic acid hydrazide with ethyl and phenyl isothiocyanates in an alcohol medium at equimolar ratios of the reactants led to the formation of new thiosemicarbazides **I** and **II** (Scheme 1).

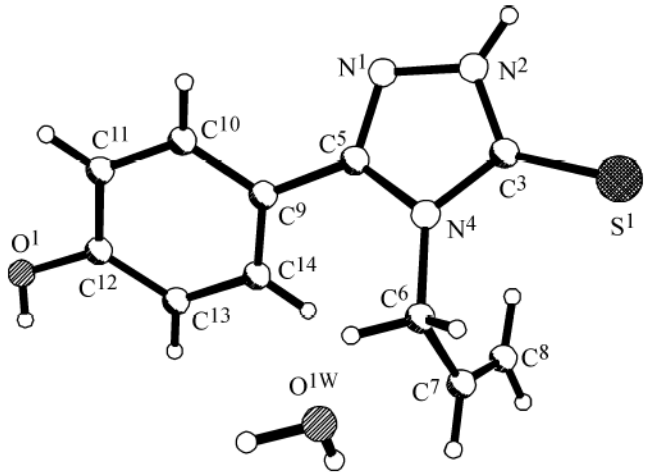
Boiling the latter with *N*-allyl-2-(4-hydroxybenzoyl)hydrazinocarbothioamide **III** [10] in an

Scheme 1.



I, II

R = CH_2CH_3 (**I**), C_6H_5 (**II**).



General view of the molecule of 4-allyl-3-(4-hydroxyphenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (**VI**).

aqueous potassium hydroxide solution for 2 h followed by acidification with acetic acid gave rise to new 4-alkyl-3-(4-hydroxyphenyl)-1*H*-1,2,4-triazole-5(4*H*)-thiones **IV**–**VI** (Scheme 2).

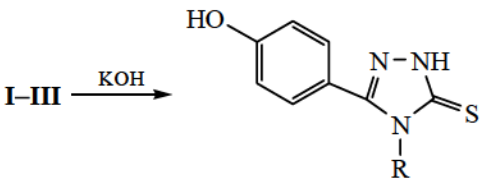
The synthesized compounds **IV**–**VI** were white crystalline substances readily soluble in polar organic solvents. IR spectra of compounds **I** and **II** contained absorption bands in the ranges of 1672–1665 and 3390–3385 cm^{-1} belonging to C(O)NH and NH groups.

In the ^1H NMR spectrum of *p*-hydroxybenzoic acid ethylthiosemicarbazide **I** the signals of α- and β-protons of aromatic ring appeared as doublet signals at 7.78 ($H_α$, $J_{αβ}$ 8.7 Hz) and 6.81 ppm ($H_β$, $J_{αβ}$ 8.7 Hz). The proton of OH group at the aromatic ring resonated

Table 1. Bond lengths in the molecule of compound **VI**

Bond	*d*, Å	Bond	*d*, Å
S^1–C^3	1.689(2)	C^6–C^7	1.500(3)
O^1–C^{12}	1.357(3)	C^7–C^8	1.294(4)
N^1–C^5	1.308(3)	C^9–C^{14}	1.389(3)
N^1–N^2	1.365(2)	C^9–C^{10}	1.393(3)
N^2–C^3	1.331(3)	C^{10}–C^{11}	1.379(3)
C^3–N^4	1.368(3)	C^{11}–C^{12}	1.387(3)
N^4–C^5	1.377(3)	C^{12}–C^{13}	1.388(3)
N^4–C^6	1.462(3)	C^{13}–C^{14}	1.376(3)
C^5–C^9	1.467(3)		

Scheme 2.



IV–VI

R = CH_2CH_3 (**I, IV**), C_6H_5 (**II, V**), CH_2=$CHCH_2$ (**III, VI**).

at 10.04 ppm. The signals of amide and thioamide protons were also observed in the weak field at 10.06 (H^2), 9.13 (H^1) and 8.02 ppm (H^3).

IR spectra of triazoles **IV**–**VI** contained no absorption band characteristic of the amide carbonyl group. Absorption at 1272 cm^{-1} corresponded to a thiocarbonyl group. In the ^1H NMR spectra of **IV**–**VI** there were the signals of all the structural fragments.

X-ray diffraction data of a single crystal of 4-allyl-3-(4-hydroxyphenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione hydrate **VI** confirmed unambiguously the formation of triazoles **IV**–**VI** (see Figure). The bond lengths and angles coincided with those typically found in similar compounds (Tables 1, 2) [11].

The triazole ring is flat to within ±0.005 Å; the allyl group is turned perpendicularly to the plane (torsion angle $C^5N^4C^6C^7$ 98.5°). *p*-Hydroxyphenyl substituent is deviated from this plane by –42.7° (torsion angle $N^1C^5C^9C^{10}$). A similar reversal of the phenyl ring was observed in the molecule of 4-amino-3-(4-ethoxyphenyl)-1,2,4-triazole-3-thione (torsion angle $N^1C^5C^9C^{10}$ –41.5°) [12]. However, it should be noted that the rotation angle of the phenyl substituent in the crystal can vary considerably. For example, in the molecule of 3-phenyl-4,5-dihydro-1,2,4-triazole-3-thione the torsion angle $N^1C^5C^9C^{10}$ is –7.9° [13], and in the molecule of 4-allyl-5-(2-hydroxyphenyl)-2,4-dihydro-1,2,4-triazole-3-thione **VI** this angle is –78.8° [14].

In the crystal, the molecules are bound by intermolecular hydrogen bonds N^2–H (x, y, z)···O^{1W} (1 – x, –y, 1 – z) (N···O 2.69 Å, H···O 1.86 Å, angle NH···O 159°), O^1H (x, y, z)···N^1 (–0.5 + x, y, 1.5 – z) (O···N 2.89 Å, H···N 2.12 Å, angle NH···O 179°) to form flat bands along the axis c, which are connected by hydrogen bonds O^{1W}–H (x, y, z)···S^1 (–0.5 – x, 0.5 – y, 1 – z) (O···S 3.30 E, H···S 2.57 E, angle NH···O 168°) and O^{1W}–H (x, y, z)···S^1 (0.5 – x, –0.5 + y, z) (O···O 3.31 Å, H···S 2.47 Å, angle NH···O 163°).

Yields, melting points, and elemental analysis data of the synthesized thiosemicarbazides **I**, **II** and triazoles **IV**–**VI** are listed in Table 3.

In summary, hydrazides and thiosemicarbazides of *p*-hydroxybenzoic acid are suitable synthons for the synthesis of new classes of potentially bioactive compounds based on 1,2,4-triazole.

EXPERIMENTAL

IR spectra were recorded on a Nicolet Avatar-320 Fourier spectrometer from KBr pellets. ^{1}H NMR spectra were registered on a Bruker DRX500 spectrometer (500 MHz, DMSO-d_6), internal reference TMS. Melting points were determined on a Boetius instrument (measurement error ±0.1°C). TLC analysis was performed on a Sorbfil plates, detecting with iodine vapor.

N-Allyl-2-(4-hydroxybenzoyl)hydrazinocarbothioamide **III** was synthesized as described in [10].

4-Ethyl-2-(4-hydroxybenzoyl)thiosemicarbazide (I). To a stirred solution of 1.52 g (0.01 mol) of *p*-hydroxybenzoic acid hydrazide in 20 mL of ethanol was added dropwise 0.95 g (0.011 mol) of ethyl isothiocyanate. The mixture was stirred for 10 h at 50–60°C. The reaction progress was monitored by TLC. After cooling, the resulting fine crystalline precipitate was filtered off, washed with a small amount of cold ethanol, and recrystallized from 2-propanol. Yield 1.81 g (76%), mp 220–221°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.05 t (3H, CH_3, J_{HH} 7.1), 2.50 q (2H, CH_2), 6.81 d (1H, CH_{arom}), 7.78 d (1H, CH_{arom}, J_{HH} 8.7), 8.02 s (1H, NH^3), 10.06 s (1H, NH^2), 9.13 s (1H, NH^1), 10.04 s (1H, OH).

***N*-Phenyl-2-(4-hydroxybenzoyl)hydrazinocarbothioamide (II)** was prepared similarly. Yield 2.09 g (52.3%), mp 190–191°C (2-propanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.11 d (1H, CH_{arom}, J_{HH} 8.6), 7.09 d (1H, CH_{arom}, J_{HH} 8.6), 6.42 t (1H, CH_{arom}, J_{HH} 7.8), 6.59 t (1H, CH_{arom}, J_{HH} 7.4), 6.72 t (1H, CH_{arom}, J_{HH} 7.3), 8.89 s (1H, NH^3), 9.04 s (1H, NH^2), 9.55 s (1H, NH^1), 9.35 s (1H, OH).

Table 2. Bond angles in the molecule of compound **VI**

Angle	ω, deg	Angle	ω, deg
$C^5N^1N^2$	104.5(2)	$C^8C^7C^6$	127.2(2)
$C^3N^2N^1$	113.3(2)	$C^{14}C^9C^{10}$	118.7(2)
$N^2C^3N^4$	104.0(2)	$C^{14}C^9C^5$	121.8(2)
$N^2C^3S^1$	127.1(2)	$C^{10}C^9C^5$	119.4(2)
$N^4C^3S^1$	128.9(2)	$C^{11}C^{10}C^9$	120.5(2)
$C^3N^4C^5$	107.9(2)	$C^{10}C^{11}C^{12}$	120.3(2)
$C^3N^4C^6$	124.3(2)	$O^1C^{12}C^{11}$	118.3(2)
$C^5N^4C^6$	127.5(2)	$O^1C^{12}C^{13}$	122.2(2)
$N^1C^5N^4$	110.3(2)	$C^{11}C^{12}C^{13}$	119.5(2)
$N^1C^5C^9$	123.6(2)	$C^{14}C^{13}C^{12}$	120.0(2)
$N^4C^5C^9$	126.1(2)	$C^{13}C^{14}C^9$	121.0(2)
$N^4C^6C^7$	114.2(2)		

4-Ethyl-3-(4-hydroxyphenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (IV). To a solution of 0.40 g (0.01 mol) of NaOH in 30 mL of distilled water was added 2.39 g (0.01 mol) of **I**. The reaction mixture was heated at 85°C for 2 h, then cooled and neutralized with hydrochloric acid to pH 7. The formed precipitate was filtered off and recrystallized from 2-propanol. Yield 1.62 g (73.3%), mp 210–212°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15 t (3H, CH_3, J_{HH} 7.1), 4.01 q (2H, CH_2), 6.93 d (1H, CH_{arom}), 7.48 d (1H, CH_{arom}, J_{HH} 8.6), 10.09 br.s (1H, OH), 13.79 br. s (1H, NH).

Table 3. Yields, melting points, and elemental analysis data of compounds **I**, **II**, **IV**–**VI**

Comp. no.	Yield, %	mp, °C	Found, %		Formula	Calculated, %	
			C	H		C	H
I	76	220–221	50.47	5.69	$C_{10}H_{13}N_3O_2S$	50.19	5.48
II	52.3	190–191	58.64	4.73	$C_{14}H_{13}N_3O_2S$	58.52	4.56
IV	73.3	210–212	54.43	5.34	$C_{10}H_{11}N_3OS$	54.28	5.01
V	93	292–293	62.64	4.26	$C_{14}H_{11}N_3OS$	62.44	4.12
VI	90	162–163	56.78	4.86	$C_{11}H_{11}N_3OS$	56.63	4.75

4-Phenyl-3-(4-hydroxyphenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (V) was prepared similarly. Yield 2.5 g (93%), mp 292–293°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.59 d (1H, CH^1_{arom}, J_{HH} 8.7), 6.39 d (1H, CH^2_{arom}, J_{HH} 8.6), 6.55–6.79 m (5H, C_6H_5), 9.25 s (1H, NH).

4-Allyl-3-(4-hydroxyphenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (VI) was prepared similarly. Yield 2.09 g (90%), mp 162–163°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.9 d (1H, CH_2CH=, J_{HH} 1.5), 4.03–4.41 d.d (1H, CH=CH_2), 5.0–5.12 m (1H, CH_2CH=), 6.12 d (1H, CH^1_{arom}, J_{HH} 8.7), 6.73 d (1H, CH^2_{arom}, J_{HH} 8.6), 9.32 s (1H, NH).

X-ray diffraction analysis of compound VI. Unit cell parameters and intensities of 2192 independent reflections were measured on a Xcalibur diffractometer (CuK_α-irradiation, graphite monochromator, θ/2θ-scanning, $2\theta \leq 134°$) at 293 K. The crystals are orthorhombic, parameters of the unit cell ar as follows: *a* 12.0992(9), *b* 9.5076(5), *c* 21.540(1) Å; space group *Pbca*, d_{calc} 1.347 g/cm, *V* 2477.9(3) Å^3, *Z* 8, $C_{11}H_{11}N_3OS \cdot H_2O$, μ 0.290 mm^{-1}. The structure was solved by the direct method. Positions of non-hydrogen atoms were refined in an anisotropic full-matrix approximation. The hydrogen atoms of the hydroxy group and hydrated water were revealed by the difference synthesis; their positions were refined in isotropic approximation. The other hydrogen atoms were placed in geometrically calculated positions and refined using a *rider* model. In calculation 1782 reflections with $I \geq 2\sigma(I)$ (R_{int} 0.0236) were used. The final divergence factors areas follows: R_1 0.0383, wR_2 0.1059, *GOF* 1.063. The structure was solved and refined with the use of SHELXS-97 [15] and SHELXL-97 [16] software. Atomic coordinates were deposited in the Cambridge Crystallographic Data Centre (CCDC 1,003,460).

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