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SYNTHESIS AND CRYSTAL STRUCTURE OF β-N-(5-METHYL-4-OXO-5,6-DIHYDRO-4H-1,3-THIAZIN-2-YL)ISONICOTINO-HYDRAZIDE

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In the presence of amines under mild conditions, β-N-(methacryloylcarbamoythioyl)isonicotino-hydrazide underwent intramolecular heterocyclization to give β-N-(5-methyl-4-oxo-5,6-dihydro-4H-1,3-thiazin-2-yl)isonicotinohydrazide, the spatial structure was confirmed by X-ray crystallography.

Keywords: methacryloylthiosemicarbazide of isonicotinic acid, intramolecular heterocyclization, X-ray crystallography.

Previously the synthesis was reported of β-N-(methacryloylcarbamothioyl)isonicotinohydrazide (**1**) which, on boiling in 2-propanol for 10-16 h, underwent intramolecular cyclization to give β-N-(5-methyl-4-oxo-5,6-dihydro-4H-1,3-thiazin-2-yl)isonicotinohydrazide (**2**) [1]. The objective of the present work includes the study of the reaction of thiosemicarbazide **1** with a series of amines with the aim of obtaining the corresponding products of nucleophilic addition at the activated C=C bond.

However mixing compound **1** with equimolar quantities of cyclic secondary amines (morpholine, piperidine) or alkaloids (anabasine, cytosine) in ethanol or 2-propanol solutions at about 30°C gave not the expected addition products **3** but the product of heterocyclization of compound **1** – the substituted 5,6-dihydro-1,3-thiazin-4-one **2** in 82% yield. Under these conditions cyclization of compound **1** occurred considerably faster (~1 h) than the same reaction in boiling 2-propanol reported previously [1]. The yield of product **2** did not depend on either the structure or the basicity of the amine and alkaloid starting materials.

It is probable that the presence of base in the reaction medium facilitates the formation of the thiol form of compound **1** which is necessary for its cyclization. The ^{1}H NMR and IR spectra of samples of compound **2** obtained by using various amines or on boiling in 2-propanol [1] were identical.

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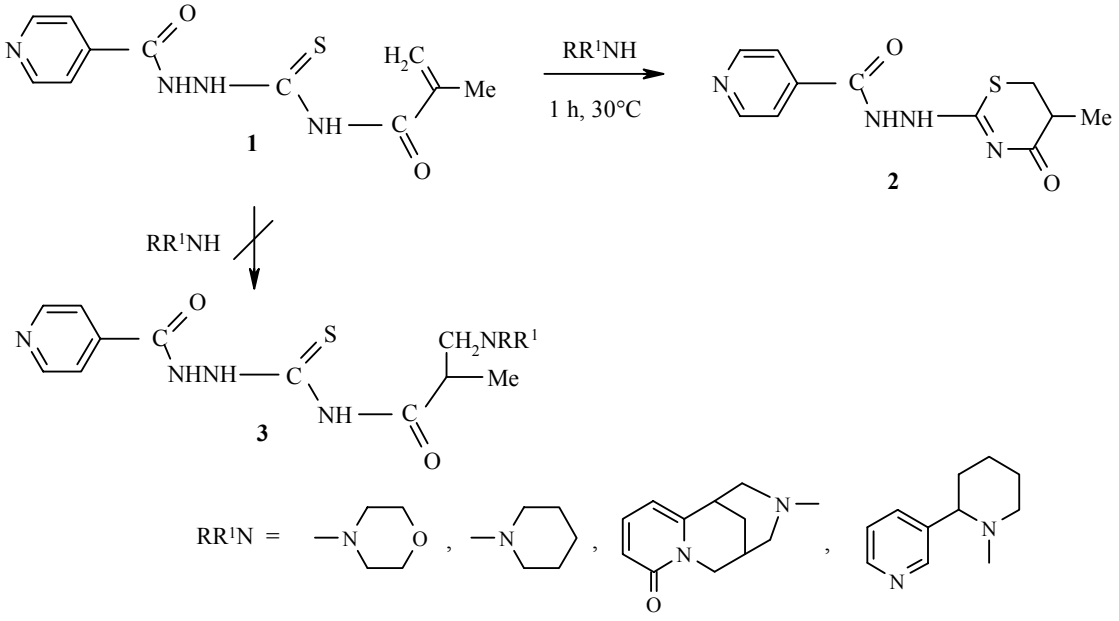
To establish the spatial structure compound **2** was investigated by X-ray crystallography (Fig. 1).



It was established that the bond lengths and valence angles in the structure of compound **2** (Tables 1 and 2) were close to normal [2].

The pyridine ring is planar with a precision of 0.017 Å . The bulky substituent relative to the pyridine is equatorial (C(6)C(1)C(5)C(4) = -175.17°). The atoms C(6), N(2), N(3), and O(1) lie in the plane of the pyridine ring with departure from it by 0.139, 0.538, 0.639, and -0.058 Å respectively.

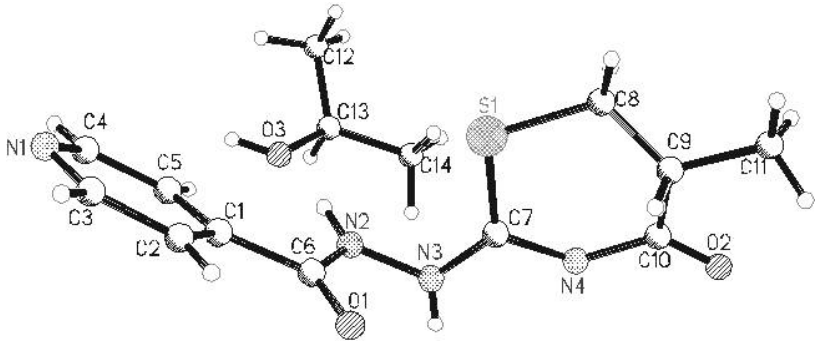


Fig. 1. Three-dimensional structure of the solvate of compound **2**.

The thiazine ring C(7)S(1)C(8)(C9)C(10)N(4) in compound **2** has the 8,9-*half-chair* conformation (ΔC_s9 = 22.76°). The atoms S(1), C(7), N(4), and C(10) of the six-membered ring are coplanar within the limits of ±0.0471 Å, while the displacement of atoms C(8) and C(9) from the mean plane of the atoms S(1), C(7), N(4), and C(10) were 0.256 and -0.388 Å respectively.

It was also established that a molecule of the solvent (2-propanol), used in the recrystallization of compound **2** was present in the crystal. The formation of this solvate is explained by the presence of strong hydrogen bond N(2)H(2a)···O(3) (*x, y, z*) at a distance equal to 2.125 Å and a valence angle N(2)H(2a)O(3) -158.45°.

Table 1. Bond Lengths (*d*) in Molecule **2**

Bond	*d*, Å	Bond	*d*, Å
S(1)–C(7)	1.744(3)	O(2)–C(10)	1.218(4)
S(1)–C(8)	1.764(5)	O(3)–C(13)	1.442(5)
C(1)–C(2)	1.374(4)	N(3)–C(7)	1.267(4)
C(1)–C(5)	1.376(5)	N(4)–C(10)	1.359(5)
C(1)–C(6)	1.503(4)	N(4)–C(7)	1.391(4)
N(1)–C(3)	1.299(5)	C(4)–C(5)	1.376(4)
N(1)–C(4)	1.330(4)	C(8)–C(9)	1.426(7)
O(1)–C(6)	1.222(4)	C(9)–C(11)	1.497(7)
N(2)–C(6)	1.340(4)	C(9)–C(10)	1.515(6)
N(2)–N(3)	1.414(3)	C(12)–C(13)	1.429(8)
C(2)–C(3)	1.379(5)	C(13)–C(14)	1.465(7)

Table 2. Valence Angles (ω) in Molecule **2**

Angle	ω, deg	Angle	ω, deg
C(7)–S(1)–C(8)	100.82(18)	N(2)–C(6)–C(1)	115.8(3)
C(2)–C(1)–C(5)	116.6(3)	N(3)–C(7)–N(4)	116.3(3)
C(2)–C(1)–C(6)	118.2(3)	N(3)–C(7)–S(1)	123.3(2)
C(5)–C(1)–C(6)	125.3(3)	N(4)–C(7)–S(1)	120.4(2)
C(3)–N(1)–C(4)	117.0(3)	C(9)–C(8)–S(1)	118.5(4)
C(6)–N(2)–N(3)	120.0(3)	C(8)–C(9)–C(11)	120.4(5)
C(1)–C(2)–C(3)	119.7(3)	C(8)–C(9)–C(10)	112.3(5)
C(7)–N(3)–N(2)	112.7(3)	C(11)–C(9)–C(10)	112.8(4)
N(1)–C(3)–C(2)	123.7(3)	O(2)–C(10)–N(4)	118.8(3)
C(10)–N(4)–C(7)	128.3(3)	O(2)–C(10)–C(9)	123.1(4)
N(1)–C(4)–C(5)	123.3(3)	N(4)–C(10)–C(9)	118.1(3)
C(1)–C(5)–C(4)	119.5(3)	C(12)–C(13)–O(3)	112.2(4)
O(1)–C(6)–N(2)	123.1(3)	C(12)–C(13)–C(14)	118.5(6)
O(1)–C(6)–C(1)	121.0(3)	O(3)–C(13)–C(14)	109.0(4)

Table 3. Torsion Angles (τ) in Molecule **2**

Angle	τ, deg	Angle	τ, deg
C(5)–C(1)–C(2)–C(3)	-4.7(6)	N(2)–N(3)–C(7)–N(4)	-177.4(3)
C(6)–C(1)–C(2)–C(3)	174.2(4)	N(2)–N(3)–C(7)–S(1)	-0.1(4)
C(6)–N(2)–N(3)–C(7)	-90.0(4)	C(10)–N(4)–C(7)–N(3)	-166.1(3)
C(4)–N(1)–C(3)–C(2)	2.3(7)	C(10)–N(4)–C(7)–S(1)	16.5(5)
C(1)–C(2)–C(3)–N(1)	1.7(8)	C(8)–S(1)–C(7)–N(3)	-177.9(4)
C(3)–N(1)–C(4)–C(5)	-3.4(7)	C(8)–S(1)–C(7)–N(4)	-0.7(4)
C(2)–C(1)–C(5)–C(4)	3.7(6)	C(7)–S(1)–C(8)–C(9)	-35.0(6)
C(6)–C(1)–C(5)–C(4)	-175.1(4)	S(1)–C(8)–C(9)–C(11)	-167.4(5)
N(1)–C(4)–C(5)–C(1)	0.3(7)	S(1)–C(8)–C(9)–C(10)	56.1(8)
N(3)–N(2)–C(6)–O(1)	5.2(5)	C(7)–N(4)–C(10)–O(2)	-179.8(4)
N(3)–N(2)–C(6)–C(1)	-178.2(3)	C(7)–N(4)–C(10)–C(9)	2.5(6)
C(2)–C(1)–C(6)–O(1)	13.8(5)	C(8)–C(9)–C(10)–O(2)	143.0(5)
C(5)–C(1)–C(6)–O(1)	-167.5(4)	C(11)–C(9)–C(10)–O(2)	3.1(8)
C(2)–C(1)–C(6)–N(2)	-162.8(4)	C(8)–C(9)–C(10)–N(4)	-39.4(8)
C(5)–C(1)–C(6)–N(2)	15.9(5)	C(11)–C(9)–C(10)–N(4)	-179.3(5)

EXPERIMENTAL

^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded with a Bruker DRX500 (500 MHz) spectrometer. IR spectra of KBr discs were recorded on an "AVATAR-320" Fourier transform spectrometer.

X-ray Structure Investigation. Cell parameters and the intensities of 2906 independent reflections for compound **2** were measured at 20°C on a Bruker P4 automatic four-circle diffractometer with a graphite monochromator and MoKα radiation (θ/2θ scanning, 2θ < 53°). Crystals were rhombic, a = 13.924(12), b = 12.852 (15), c = 18.771(3), V = 3359.1(8) Å^3, d_{calc} = 1.089 g/cm^3, Z = 8 ($C_{11}H_{23}N_4O_2S$). Space group *Pbca*. In the calculations 2401 reflections with intensities $I>2\sigma(I)$ were used. The structure was solved by direct methods using the Sir-2002 program [3] and refined by the full matrix least squares method in the anisotropic approximation for all non-hydrogen atoms. The H atoms were determined geometrically and fixed as the "riding" type. The final divergence factors were R = 0.0728 and wR_2 = 0.2016. Refinement of the geometry was carried out with the SHELXL-97 program [4]. Atomic coordinates have been deposited in the Cambridge Structural Data Bank (CCDC 692505).

β-N-(5-Methyl-4-oxo-5,6-dihydro-4H-1,3-thiazin-2-yl)isonicotinohydrazide (2). The corresponding amine (5.0 mmol) was added with stirring to a suspension of compound **1** (1.32 g, 5.0 mmol) in 2-propanol (15 ml) at 30°C. After 1 h the precipitate was filtered off to give a white crystalline substance (1.08 g, 82%), mp 104-107°C (solvate of composition $C_{11}H_{12}N_4O_2S\cdot C_3H_8O$), which decomposed on drying at about 115°C into a white crystalline powder, mp 179-180°C. IR spectrum, ν, cm^{-1}: 2971 (NH); 1706 (C=O); 1646 (C=O amide); 1576 (C=N); 1300 (C–N). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.21 (3H, d, J = 6.9, CHC<u>H</u>$_3$); 2.81 (1H, m, C<u>H</u>CH$_3$); 3.02, 3.16 (2H, dd, J_1 = 10.1, J_2 = 4.1, SCH$_2$); 7.74 (2H, d, J = 6.0, 2β-H pyridine); 8.74 (2H, d, J = 6.0, 2α-H pyridine); 10.92 (1H, s, NHN<u>H</u>–NCO); 11.20 (1H, s, N<u>H</u>NH–NCO).

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