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Synthesis and Structure of (Thio)semicarbazonocyclohexane-dicarboxylates. Crystalline and Molecular Structure of Diethyl 4-Hydroxy-4-methyl-2-phenyl-6-thiosemicarbazonocyclohexane-1,3-dicarboxylate

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Abstract—Diethyl 2-aryl-4-hydroxy-4-methyl-6-(thio)semicarbazonocyclohexane-1,3-dicarboxylates were synthesized, and their structure was determined by ^{1}H and ^{13}C NMR spectroscopy, including the HSQC technique. The molecular and crystalline structure of diethyl 4-hydroxy-4-methyl-6-thiosemicarbazono-2-phenylcyclohexane-1,3-dicarboxylate was determined by X-ray analysis.

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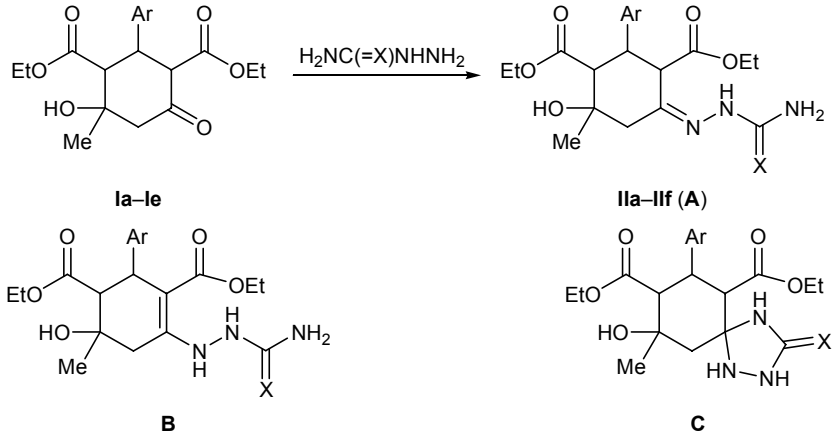
Polycarbonyl compounds of the dialkyl 2-aryl-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate series (β-keto esters) are used as model structures for stereochemical studies and keto–enol transformations, as well as intermediate products in the synthesis of carbo- and heterocyclic systems [1–3]. Their reactions with nitrogen-centered nucleophiles have been well documented; depending on the nucleophile structure, these reactions lead to the formation of enamines, oximes, fused heterocycles, and heterocyclic spiro compounds whose structure was determined by spectral methods and X-ray analysis [4–7].

Reactions of such β-keto esters with thiosemicarbazides have been studied in the recent years [3, 8]; however, the available spectral data (IR, ^{1}H NMR) are clearly insufficient to unambiguously assign the struc-

Scheme 1.



Ia, **IIa**, **IIb**, Ar = Ph; **Ib**, **IIc**, Ar = 4-MeOC$_6$H$_4$; **Ic**, **IId**, Ar = 3-O$_2$NC$_6$H$_4$; **Id**, **IIe**, Ar = 4-HO-3-MeOC$_6$H$_3$; **Ie**, **IIf**, Ar = 2-thienyl; X = S (**a**), O (**b**–**f**).

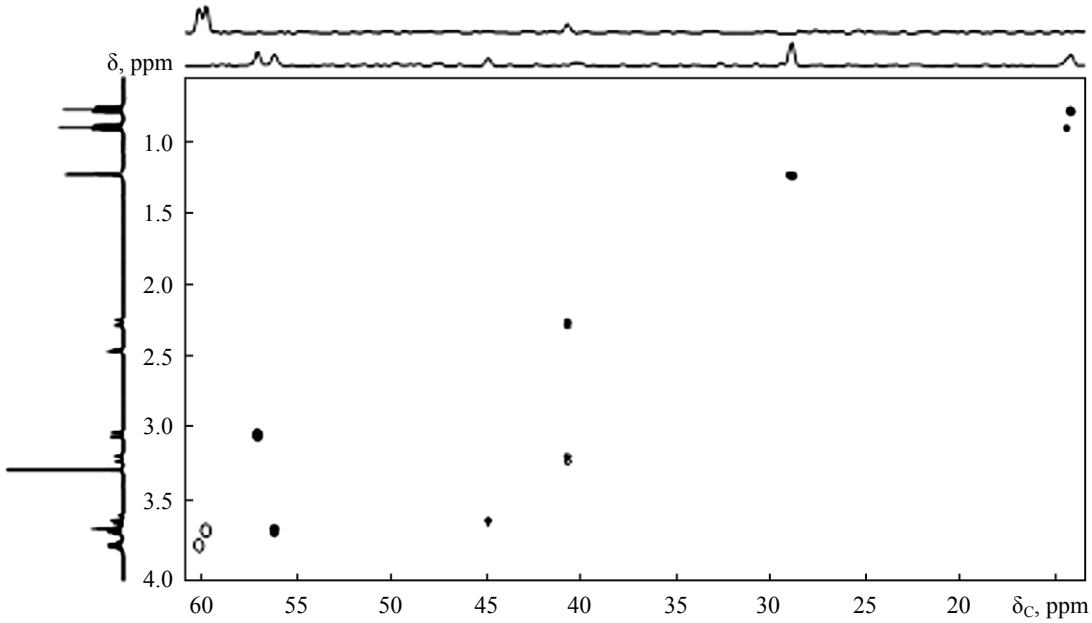


Fig. 1. A fragment of the HSQC spectrum of diethyl 4-hydroxy-4-methyl-2-phenyl-6-thiosemicarbazonocyclohexane-1,3-dicarboxylate (**IIa**).

ture of the reaction products (thiosemicarbazone **A**, thiosemicarbazide **B**, or spirane **C**). Therefore, additional studies using ^{13}C NMR spectroscopy (including double resonance techniques) and X-ray analysis are necessary.

In the present article we present new data on the structure of the reaction product of diethyl 4-hydroxy-4-methyl-6-oxo-2-phenylcyclohexane-1,3-dicarboxylate (**Ia**) with thiosemicarbazide, as well as on reactions of β-keto esters **I** with semicarbazide, which were not reported previously. Diethyl 4-hydroxy-4-methyl-6-thiosemicarbazono-2-phenylcyclohexane-1,3-dicarboxylate (**IIa**) was obtained in 79% yield by reaction of keto diester **Ia** with thiosemicarbazide according to the known procedure [8] (heating in boiling ethanol using 1.5 equiv of the nucleophile), and its structure was determined on the basis of the ^1H and ^{13}C NMR, HSQC, and X-ray diffraction data.

The ^1H NMR spectrum of **IIa** (DMSO-d_6) contained singlets from three NH protons at δ 6.71, 8.20, and 10.4 ppm and hydroxy proton at δ 4.61 ppm; methylene protons on C^5 resonated as doublets at δ 2.26 and 3.22 ppm with a coupling constant ^2J of 14 Hz, and the 2-H signal was a doublet at δ 3.05 ppm with a coupling constant J of 12 Hz; and the 1-H and 3-H protons together with OCH_2 protons in the ester moiety give rise to a multiplet at δ 3.61–3.75 ppm. The presence of a signal from 1-H rules out one of the possible structures, thiosemicarbazide **B**, but we still cannot distinguish between thiosemicarbazone **A** and spiro structure **C**. Valuable information was obtained from the ^{13}C NMR spectrum (DMSO-d_6) which contained 10 signals from sp^3-hybridized carbon atoms and one signal assignable to sp^2-carbon atom (C^6, δ_C 151 ppm); this spectral pattern is consistent with thiosemicarbazone structure **A** and excludes isomeric structures **B** and **C** where 9 and 11 sp^3-carbon atoms are present, respectively. Detailed signal assignment was made on the basis of the two-dimensional HSQC spectrum (Fig. 1). It contained the following cross peaks: 1-H/C^1 (δ 3.63/δ_C 56.3 ppm), 2-H/C^2 (3.05/57.1), 3-H/C^3 (3.73/44.6), 5-H_{ax}/C^5 (2.26/41.0),

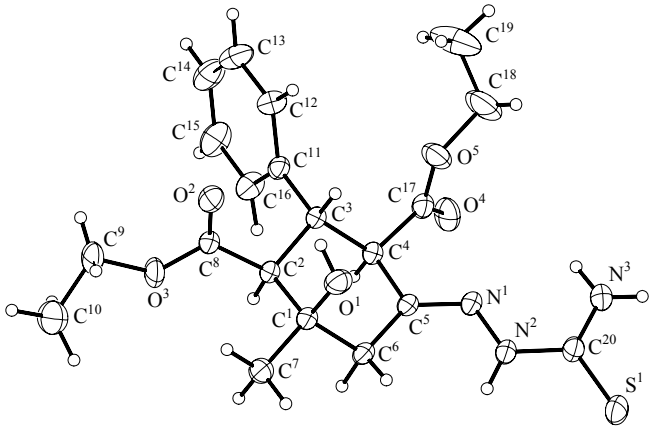


Fig. 2. Structure of the molecule of diethyl 4-hydroxy-4-methyl-2-phenyl-6-thiosemicarbazonocyclohexane-1,3-dicarboxylate (**IIa**) according to the X-ray diffraction data.

and 5-H_{eq}/C^5 (3.22/41.0). Thus the above data indicated that compound **IIa** in DMSO-d_6 has thiosemicarbazone structure **A**.

Thiosemicarbazone **IIa** crystallized to form well-defined crystals, and its molecular conformation was determined on the basis of the X-ray diffraction data (Fig. 2). The C^5 atom (for atom numbering, see Fig. 2) has sp^2-hybridization: the bond angle $N^1C^5C^4$ is 116°, and the C^5–N^1 bond length is 1.28 Å. The thiosemicarbazone fragment is almost planar: the torsion angle $C^5N^1N^2C^{20}$ is –178.2°. The cyclohexane ring adopts a distorted *chair* conformation, and the torsion angles $C^6C^1C^2C^3$ (–61.6°) and $C^1C^2C^3C^4$ (61.4°) approach those in analogous cyclohexane conformer.

All substituents in the cyclohexane ring, except for the hydroxy group, occupy equatorial positions. The hydrogen atoms on C^2 and C^3, as well as on C^3 and C^4, occupy axial positions and are arranged *trans* with respect to each others. This follows from the torsion angles between the corresponding ester fragment and phenyl substituent: $C^8C^2C^3C^{11}$ –51.8°, $C^{11}C^3C^4C^{17}$ 56.5°. Molecules **IIa** in crystal are characterized by weak intramolecular hydrogen bond O^1–$H^1\cdots O^2$ ($O^2\cdots H^1$ 2.47, $O^1\cdots O^2$ 3.09 Å) and intermolecular hydrogen bonds N^2–$H^2\cdots O^{2'}$ ($O^{2'}\cdots H^2$ 2.25, $N^2\cdots O^{2'}$ 3.08 Å) and N^3–$H^3\cdots O^{4'}$ ($O^{4'}\cdots H^3$ 2.23, $N^3\cdots O^{4'}$ 3.03 Å). Intermolecular hydrogen bonds give rise to a three-dimensional network. Thus compound **IIa** has thiosemicarbazone structure **A** both in solution in DMSO-d_6 and in the crystalline state.

The reactions of β-keto esters **Ia**–**Ie** with semicarbazide were carried out following a modified procedure. Taking into account instability of semicarbazide as free base, it was used as hydrochloride, and the free base was generated by adding potassium hydroxide. As a result, we isolated the corresponding semicarbazones **IIb**–**IIe** in high yield (81–90%).

The spectral parameters of semicarbazones **IIb**–**IIe** were similar to those of thiosemicarbazone **IIa**. Their IR spectra contained absorption bands at 1703–1726 cm^{-1}, belonging to stretching vibrations of unconjugated ester carbonyl groups, two bands due to primary amino group (3082–3206 cm^{-1}), and a band corresponding to secondary amino group (3314–3364 cm^{-1}). In the ^1H NMR spectra of compounds **IIb**–**IIe** in DMSO-d_6 we observed doublets from axial and equatorial qprotons on C^5 (δ 2.11–2.22 and 2.49–3.11 ppm, J = 14–15 Hz), signals from 2-H (δ 2.90–3.17 ppm), 1-H, and 3-H (δ 3.49–3.83 and 3.49–3.80 ppm), a singlet from the NH proton (δ 9.21–9.25 ppm), a diffuse doublet from the NH_2 group (δ 5.53–6.28 ppm), and a singlet from the hydroxy proton (δ 4.34–4.55 ppm). Compound **IIb** displayed in the ^{13}C NMR spectrum (DMSO-d_6) 10 signals from sp^3-hybridized carbon atoms. The C^6 atom resonated at δ_C 147 ppm. The HSQC spectrum of **IIb** (DMSO-d_6) revealed the following cross peaks formed by directly coupled ^1H and ^{13}C nuclei: 1-H/C^1 (δ 3.64/δ_C 56.1 ppm), 2-H/C^2 (3.00/57.2), 3-H/C^3 (3.64/44.8), 5-H_{ax}/C^5 (2.16/40.0), 5-H_{eq}/C^5 (3.07/40.0).

We can conclude that products of the reactions of β-keto diesters **I** with thiosemicarbazide and semicarbazide have (thio)semicarbazone structure.

EXPERIMENTAL

The IR spectra were recorded in KBr on an FSM-1201 spectrometer with Fourier transform. The ^1H and ^{13}C NMR spectra, and two-dimensional HSQC spectra were recorded on Bruker AM-200 (200 MHz), Bruker MSL-400 (400 MHz), and Varian 400 spectrometers using DMSO-d_6 as solvent and tetramethylsilane as internal reference.

The X-ray diffraction data for a 0.18×0.14×0.12-mm single crystal of compound **IIa** were acquired at room temperature on a Bruker Nonius X8 Apex automatic diffractometer equipped with a two-dimensional CCD detector (λMoK_α irradiation, graphite monochromator, φ-scanning through a step of 0.5°, Bragg angle range 2.50° ≤ θ ≤ 27.50°). Total of 16745 reflection intensities were measured over one half of the reciprocal space sphere; among these, 5031 reflections were independent (R_{int} = 0.0195). Monoclinic crystal system; $C_{20}H_{27}N_3O_5S$; M 421.51; space group $P2_1/n$; unit cell parameters: a = 9.5131(4), b = 16.8601(6), c = 12.1904(4) Å; β = 101.748(1)°, V = 2195.78(14) $Å^3$; Z = 4; d_{calc} = 1.275 g/cm^3. No correction for absorption was introduced, taking into account small value of the linear absorption coefficient (μ = 0.182 mm^{-1}).

The structure was solved by the direct method using SHELXS-97 software [9] and was refined by full-matrix least-squares procedure in anisotropic approximation for non-hydrogen atoms using SHELXL-97 software package [10]. All hydrogen atoms were localized by the Fourier difference syntheses, and their positions were refined with isotropic thermal parameters. The final divergence factors were R = 0.0450, wR_2 = 0.1195 for 3857 reflections with $F \geq 4\sigma(F)$ (with respect to F_{hkl}; 371 varied parameters) and R = 0.0636, wR_2 = 0.1379 for all independent reflections (5031); goodness of fit S = 1.058.

Diethyl 4-hydroxy-4-methyl-2-phenyl-6-thiosemicarbazonocyclohexane-1,3-dicarboxylate (IIa) was synthesized according to the procedure described in [8]. Yield 79%, colorless crystals, mp 160–161°C [8]. Single crystals suitable for X-ray analysis were obtained by slowly cooling a solution of **IIa** in ethanol. ^{1}H NMR spectrum, δ, ppm: 0.78 t and 0.90 t (3H each, $CH_2C\mathbf{H}_3$, J = 7.0 Hz), 1.23 s (3H, 4-CH_3), 2.26 d (1H, 5-H_{ax}, J = 14 Hz), 3.05 d (1H, 2-H, J = 12 Hz), 3.22 d (1H, 5-H_{eq}, J = 14 Hz), 3.61–3.75 m (4H, 1-H, 3-H, OCH_2), 3.79–3.87 m (2H, OCH_2), 4.61 s (1H, OH), 6.71 s (1H, NH), 7.12–7.26 m (5H, Ph), 8.20 s (1H, NH), 10.4 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.6 and 13.8 ($CH_2\mathbf{C}H_3$), 28.3 (4-CH_3), 44.6 (C^3), 55.6 (C^1), 56.6 (C^2), 59.2 and 59.5 (OCH_2), 71.1 (C^4); 127, 128, 129, 140 (C_{arom}); 151 (C^6), 169 and 170 (C=O), 179 (C=S). HSQC spectrum, δ, ppm/δ_C, ppm: 0.78/14.0 ($CH_2C\mathbf{H}_3$), 0.90/14.5 ($CH_2C\mathbf{H}_3$), 1.23/28.6 (4-CH_3), 2.26/41.0 (5-H_{ax}/C^5), 3.05/57.1 (2-H/C^2), 3.22/41.0 (5-H_{eq}/C^5), 3.63/44.6 (3-H/C^3), 3.73/56.3 (H^1/C^1), 3.63/59.9 (OCH_2), 3.73/60.1 (OCH_2); 7.13/127, 7.20/128, 7.23/129 (CH_{arom}).

Diethyl 4-hydroxy-4-methyl-2-phenyl-6-semicarbazonocyclohexane-1,3-dicarboxylate (IIb). A solution of 0.97 g (8.7 mmol) of semicarbazide hydrochloride and 0.49 g (8.7 mmol) of potassium hydroxide in 2 ml of water was added to a solution of 2 g (5.8 mmol) of compound **Ia** in 50 ml of ethanol, and the mixture was heated for 1 h under reflux. After cooling, the precipitate was filtered off, washed with water, propan-2-ol, and diethyl ether, and dried under reduced pressure. Yield 1.97 g (85%), colorless crystals, mp 201–203°C (from EtOH). IR spectrum, ν, cm^{-1}: 3501 (OH); 3353 (NH); 3088, 3183 (NH_2); 1713, 1719 (C=O, ester); 1676 (C=O, amide); 1560 (C=N). ^{1}H NMR spectrum, δ, ppm: 0.83 t and 0.97 t (3H each, $CH_2C\mathbf{H}_3$, J = 6.8 Hz), 1.25 s (3H, 4-CH_3), 2.16 d (1H, 5-H_{ax}, J = 14 Hz), 2.99–3.04 m (1H, 2-H), 3.10 d (1H, 5-H_{eq}, J = 15 Hz), 3.62–3.68 m (2H, 1-H, 3-H), 3.75 q (2H, OCH_2, J = 6.8 Hz), 3.82–3.92 m (2H, OCH_2), 4.36 s (1H, OH), 5.53–6.19 br.d (NH_2), 7.13–7.25 m (5H, Ph), 9.25 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.7 and 14.0 ($CH_2C\mathbf{H}_3$), 28.5 (4-CH_3), 44.4 (C^3), 55.8 (C^1), 56.8 (C^2), 59.3 and 59.5 (OCH_2), 71.0 (C^4); 127, 128, 129, 141 (C_{arom}); 147 (C^6), 157 (C=O, amide), 169 and 171 (C=O, ester). HSQC spectrum, δ, ppm/δ_C, ppm: 0.80/14.1 ($CH_2C\mathbf{H}_3$), 0.93/14.5 ($CH_2C\mathbf{H}_3$), 1.20/29.2 (4-CH_3), 2.16/40.0 (5-H_{ax}/C^5), 3.00/57.2 (2-H/C^2), 3.07/40.0 (5-H_{eq}/C^5), 3.64/44.8 (3-H/C^3), 3.64/56.1 (1-H/C^1), 3.81/59.4 (OCH_2), 3.82/60.0 (CH_2); 7.16/127, 7.17/128, 7.20/129 (CH_{arom}). Found, %: C 59.38; H 6.72; N 9.76. $C_{20}H_{27}N_3O_6$. Calculated, %: C59.25; H 6.71; N 10.36.

Compounds **IIc**–**IIf** were synthesized in a similar way.

Diethyl 4-hydroxy-2-(4-methoxyphenyl)-4-methyl-6-semicarbazonocyclohexane-1,3-dicarboxylate (IIc). Yield 90%, colorless crystals, mp 211–212°C (from EtOH). IR spectrum (KBr), ν, cm^{-1}: 3497 (OH); 3363 (NH); 3088, 3182 (NH_2); 1715 (C=O, ester); 1672 (C=O, amide); 1561 (C=N). ^{1}H NMR spectrum, δ, ppm: 0.87 t and 1.00 t (3H each, $CH_2C\mathbf{H}_3$, J = 6.8 Hz), 1.23 s (3H, 4-CH_3), 2.13 d (1H, 5-H_{ax}, J = 14 Hz), 2.90–2.95 m (1H, 2-H), 3.08 d (1H, 5-H_{eq}, J = 14 Hz), 3.51–3.58 m (2H, 1-H, 3-H), 3.69 s (3H, OCH_3), 3.76 q (2H, OCH_2, J = 7.2Hz), 3.82–3.90 m (2H, OCH_2), 4.34 s (1H, OH), 5.66–6.22 br.d (NH_2), 6.75 d and 7.15 d (2H each, C_6H_4), 9.22 s (1H, NH). Found, %: C 58.60; H 6.74; N 9.77. $C_{21}H_{29}N_3O_7$. Calculated, %: C 58.49; H 7.26; N 9.34.

Diethyl 4-hydroxy-4-methyl-2-(3-nitrophenyl)-6-semicarbazonocyclohexane-1,3-dicarboxylate (IId). Yield 89%, colorless crystals, mp 207–210°C (from EtOH). IR spectrum, ν, cm^{-1}: 3477 (OH); 3314 (NH); 3150, 3206 (NH_2); 1715–1730 (C=O); 153 (C=N). ^{1}H NMR spectrum, δ, ppm: 0.85 t (3H, $CH_2C\mathbf{H}_3$, J = 6.8 Hz), 0.98 t (3H, $CH_2C\mathbf{H}_3$, J = 7.4 Hz), 1.27 s (3H, 4-CH_3), 2.22 d (1H, 5-H_{ax}, J = 14 Hz), 3.11 d (1H, 5-H_{eq}, J = 14 Hz), 3.14–3.17 m (1H, 2-H), 3.75–3.83 m (3H, 1-H, OCH_2), 3.85–3.93 m (3H, 3-H, OCH_2), 4.55 s (1H, OH), 5.62–6.16 br.d (NH_2); 7.55 t, 7.73 d, 8.04 d, and 8.20 s (4H, C_6H_4); 9.25 s (1H, NH). Found, %: C 53.84; H 5.72; N 12.32. $C_{20}H_{26}N_4O_8$. Calculated, %: C 55.05; H 5.69; N 12.84.

Diethyl 4-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4-methyl-6-semicarbazonocyclohexane-1,3-dicarboxylate (IIe). Yield 90%, colorless crystals, mp 186–187°C (from EtOH). IR spectrum, ν, cm^{-1}: 3480 (OH); 3441 (OH_{arom}); 3320 (NH); 3150, 3206 (NH_2); 1726 (C=O), 1545 (C=N). ^{1}H NMR spectrum, δ, ppm: 0.89 t and 1.02 t (3H each, $CH_2C\mathbf{H}_3$, J = 6.8 Hz), 1.23 s (3H, 4-CH_3), 2.11 d (1H, 5-H_{ax}, J = 15 Hz), 2.95 d (1H, 2-H, J = 10 Hz), 3.07 d (1H, 5-H_{eq}, J = 15 Hz), 3.49–3.59 m (2H, 1-H, 3-H), 3.72 s (3H, OCH_3), 3.79 q (2H, OCH_2, J = 7.2 Hz), 3.86–3.92 m (2H, OCH_2), 4.30 s (1H, OH), 5.58–6.28 br.d (NH_2), 6.56–6.60 m and 6.78 s (3H, H_{arom}), 8.60 s (1H, OH_{arom}), 9.21 s (1H, NH). Found, %: C 55.41; H 6.58; N 9.61. $C_{21}H_{29}N_3O_8$. Calculated, %: C 55.88; H 6.43; N 9.31.

Diethyl 4-hydroxy-4-methyl-6-semicarbazono-2-(2-thienyl)cyclohexane-1,3-dicarboxylate (IIf). Yield

81%, colorless crystals, mp 194°C (from EtOH). IR spectrum, ν, cm^{-1}: 3502 (OH); 3352 (NH); 3082, 3182 (NH_2); 1703, 1722 (C=O, ester); 1680 (C=O, amide); 1557 (C=N). ^1H NMR spectrum, δ, ppm: 0.96 t and 1.06 t (3H each, $CH_2C\mathbf{H}_3$, J = 6.8 Hz), 1.24 s (3H, 4-CH_3), 2.15 d (1H, 5-H_{ax}, J = 14 Hz), 2.95 d (1H, 2-H, J = 12Hz), 3.08 d (1H, 5-H_{eq}, J = 15 Hz), 3.55 d (1H, 1-H, J = 12 Hz), 3.86 q (2H, OCH_2, J = 7.2 Hz), 3.92–3.98 m (3H, 3-H, OCH_2), 4.45 s (1H, OH), 5.58–6.27 br.d (NH_2), 6.86–6.88 m and 7.24 d (3H, C_4H_3S), 9.24 s (1H, NH). Found, %: C 52.55; H 6.08; N 10.22. $C_{18}H_{25}N_3O_6S$. Calculated, %: C 52.70; H 5.72; N 10.58.

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