UDC 547.94; 547.917/.918

Obtaining New Biologically Active Compounds from 2-Vinyloxyethylisothiocyanate

O. A. NURKENOV, I. V. KULAKOV, S. D. FAZYLOV and A. ZH. SARSENBEKOVA

Institute of Organic Synthesis and Coal Chemistry, NAS of Kazakhstan, Ul. Alikhanova 1, Karaganda 100008 (Kazakhstan)

E-mail: kulakov_iv@mail.ru

(Received February 20, 2012; revised May 17, 2012)

Abstract

Via the reaction of alkaloid cytisine, *l*-ephedrine, *d*-pseudoephedrine as well as glucosylbenzylamine and xylosylbenzylamine aminoglycosides with vinyloxyethylisothiocyanate and its acetal derivatives, we synthesized and characterized novel 2-vinyl-, *N*-1-propargyl-, 1-*N*-phenyloxyethoxyethylo-*N*'-aminothiourea species. By the example of the *N*-vinylethoxythiocarbamoyl derivatives of *l*-ephedrine and *d*-pseudoephedrine is demonstrated that the mentioned thiourea species could quite readily undergo hydrolyzing in the presence of acids. On the basis of salicylic acid hydrazide we have synthesized and studied the acidic hydrolysis of corresponding vinyloxyethylthiosemicarbazide. The composition and the structure of the thiourea derivatives synthesized were confirmed by IR spectroscopy, ^{1}H NMR, ^{13}C NMR and mass spectrometry as well as by XRD structural analysis.

Key words: vinyloxyethylisothiocyanate, alkaloids, cytisine, anabasine, *l*-ephedrine, *d*-pseudoephedrine, XRD structural analysis

INTRODUCTION

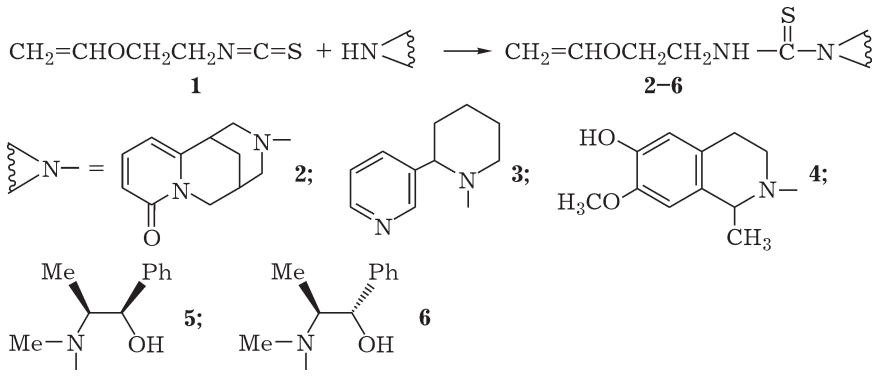
Thioamides represent one of the most important classes of chemical compounds those have found wide application in organic synthesis, as well as in industry, agriculture and medicine [1, 2]. The most common method for the synthesis of the thiourea derivatives is based on the reaction between isothiocyanates and amines. Among the isothiocyanates, of particular interest as an initial object is 2-vinyloxyethylisothiocyanate **1** that represents a highly active bifunctional synthone with unique synthetic capabilities inherent in both vinyl ethers and isothiocyanates, which opens access to many isothiocyanate derivatives unknown earlier.

The introduction of the thioamide moiety into the structure of alkaloids could extend the borders of the structural modification of these naturally occurring compounds to initiate new types of biological activity [3, 4].

In order to search for novel biologically active compounds we carried out the condensation reaction between 2-vinyloxyethylisothiocyanate **1** and alkaloids cytisine, anabasine, salsoline, *l*-ephedrine and *d*-pseudoephedrine. The reactions was performed at an equimolar ratio between the reactants in an alcohol medium at the reaction temperature ranging within (0±5) °C, followed by heating up to 40 °C. Compounds **2–6** represent well crystallizing colourless substances (Scheme 1).

The IR spectra of compounds **2–6** exhibit characteristic absorption bands corresponding to the vibrations of the functional groups such as NH–, NH–CS, CH_2=CH, and –C=S within the regions of 3460–3440, 1510–1500, 1645–1621 and 1220–1200 cm^{-1}, respectively.

In order to determine the spatial structure of the synthesized thiourea derivatives of monoethanolamine vinyl ether **2–6** there was XRD structural investigation [5] performed concern-



Scheme 1.

ing the molecule of anabasinovinylhydroxyethylaminothiourea **3**. The general view of the molecule **3** is demonstrated in Fig. 1. It was demonstrated that the piperidine ring exhibits the chair conformation ($\Delta C_s^8 = 2.2$ Å). The pyridine ring is planar to within ±0.009 Å. The pyridine ring is oriented axially (C3C7C8C9 torsion angle is equal to 72.4°) with respect to the piperidine ring.

It should be noted that there is almost no data available from the literature concerning the hydrolysis of the thiourea derivatives of ephedrine-based alkaloids.

In order to study the reactivity of thioamides synthesized containing a substituted hydroxyethyl group, by the example of *N*-vinylethoxythiocarbamoyl derivatives of *l*-ephedrine **5** and *d*-pseudoephedrine **6**, we studied the reaction of acidic hydrolysis in the presence of concentrated hydrochloric acid at a room temperature

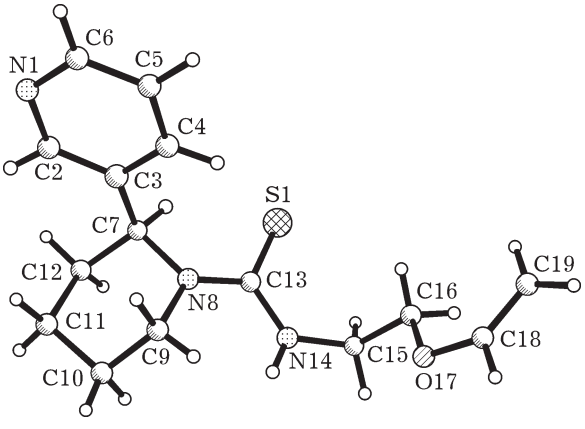
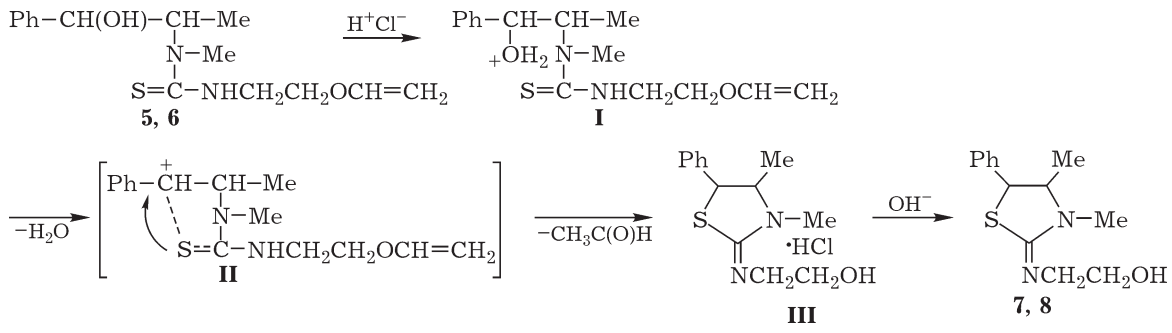


Fig. 1. Spatial molecular structure of compound **3**.

[6]. It was established that the acidic hydrolysis resulted in the formation of five-membered sulphur-containing heterocyclic compounds such as 2-imino-1,3-thiazolidines **7**, **8**. To all appearance, the process occurs through the stage consisting in the protonation of the hydroxyl group of thiourea **I** with the further formation of a carbocation **II**, which carbocation undergoes intramolecular heterocyclization to convert into thiazolidine **III** resulting from the nucleophilic attack of positively charged carbon atom by sulphur atom. In this case, there is also the hydrolysis of the vinyl group is observed. Free bases **7** and **8** were isolated by means of the action of alkali on hydrochlorides **III** (Scheme 2).

The IR spectra of compounds **7** and **8** exhibit a strong absorption band at 1680–1650 cm^{-1}, characteristic of the C=N bond, and the absorption band of the hydroxyl group at 3500–3250 cm^{-1}.

The ^{1}H NMR spectrum of compound **8** demonstrate the methine proton CH–S to be registered within the region of 4.31 ppm as a doublet with a coupling constant J = 7.6 Hz. The doublet at 0.58 ppm with the coupling constant J = 8.8 Hz could be attributed to the protons of the methyl group CH_3–CH, whereas the three methyl protons at the nitrogen atom of the cycle N–CH_3 are observed as a singlet within the region 1.88 ppm. The multiplet at 2.16–2.35 ppm could be attributed to the methine proton CH–CH_3. The aromatic ring protons are observed within the range of 7.00–7.15 ppm in the form a multiplet. Methylene protons NCH_2 exhibit splitting in the form of a triplet within the region of 2.64 ppm. Two methylene pro-



Scheme 2.

tons of $\underline{CH_2}OH$ are observed as a doublet within a 2.90 ppm region.

In order to establish the absolute configuration and the stereochemistry of molecule (4*S*,5*R*)-3,4-dimethyl-5-phenyl-2-hydroxyethylimino-1,3-thiazolidine **7**, we performed the XRD structural investigation of this compound [7]. The molecular structure of **7** is presented in Fig. 2. It can be seen that the thiazolidine cycle exhibits the conformation of a slightly distorted 4β-envelope (ΔC_s^4 = 9.57 Å). Atom C4 is ±0.49 Å out of the plane of the remaining atoms of the ring, atoms S1, C2, N3, C5 are coplanar to within ±0.05 Å. Being in the 4β-envelope conformation, the methyl group at C4 atom and the phenyl group at the C5 atom are oriented axially (torsion angles C10C4N3C2 = −91.72°, C11C5C2N3 = 88.54°). The methyl and hydroxyethylamine groups at atoms N^3 and C^2 exhibit equatorial orientation (C5C4N3C9 = −169.49°, C4N3C2N6 = 167.0°).

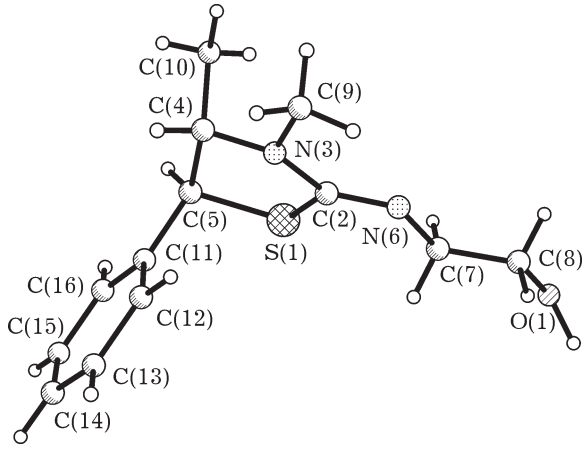


Fig. 2. Spatial structure of molecule **7**.

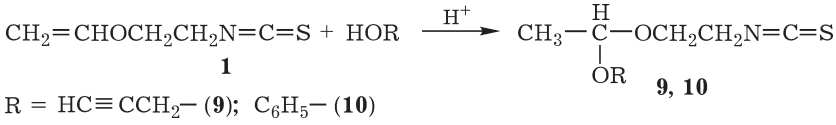
Owing to the presence of substituents at C4, C5, N3 atoms in the oxazolidine derivatives of *l*-ephedrine and *d*-pseudoephedrine, another efficient conformation of the cycle represents 3α-envelope, wherein the methyl group at N^3 demonstrates equatorial orientation, whereas the other two substituent s at the mentioned atoms have pseudo-equatorial orientation. Just such a conformation is exhibited by the most of the oxazolidine derivatives of pseudoephedrine such as (2*S*,4*S*,5*S*)-3,4-dimethyl-5-phenyl-2-phenylethynyl-1,3-oxazolidine [8].

A high affinity of the double bond activated by a conjugated oxygen atom with respect to the electrophilic addition of functions with labile hydrogen atom represents the most typical and basic chemical property of vinyl esters that determines a wide use thereof in organic synthesis and in practice [9–11]. Among the varieties of electrophilic addition to the vinyl ethers, the most important reaction consists in the addition of alcohols as a simple method for the synthesis of acetals.

In terms of creating novel biologically active compounds, of great interest is the synthesis of isothiocyanate derivatives containing complicated acetal fragments, since it gives access to the synthesis of much more complicated thiourea derivatives of alkaloids.

In this connection it is appropriate to carry out the synthesis of the acetals of isothiocyanatoethanol **9** and **10** *via* the interaction of propargyl alcohol and phenol with 2-vinyloxyethylisothiocyanate **1**. The reaction catalyst is presented by perfluorobutyric acid or trifluoroacetic acid, the technique is described in [12] (Scheme 3).

It was found that at the equimolecular ratio the 2-vinyloxyethylisothiocyanate **1** can add the



Scheme 3.

mentioned alcohols in a regioselective manner with respect to the vinyloxy group to form the propargyl- and phenyl(2-isothiocyanatoethyl) acetals of acetaldehyde with almost quantitative yields.

Further, resulting from the obtained acetal isothiocyanates **9**, **10**, it would be interesting to synthesize thiourea derivatives based on physiologically active alkaloids cytosine, *l*-ephedrine and *d*-pseudoephedrine [13, 14]. The synthesis was carried out in an alcoholic medium *via* direct adding the alkaloids to 1-propargyloxyethoxyethylisothiocyanate **9** and 1-phenyloxyethoxyethylisothiocyanate **10** (Scheme 4).

The addition of alkaloids to compounds **9** and **10** those belong to heterocumulenes occurs through a well-known mechanism of nucleophilic addition.

The synthesized compounds **11**–**16** represent crystalline and oily white compounds, moderately soluble in organic solvents.

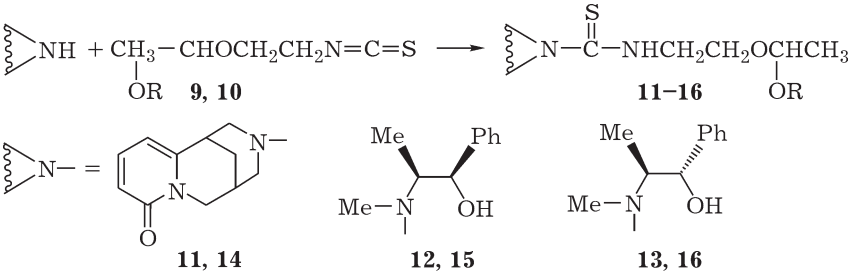
The IR spectra of compounds **11**–**16** within the region of 1530–1500 cm^{-1} correspond to the absorption band of thioamide group. The IR spectra of compounds **11**, **14** exhibit an intense signal of the amide group (N–C=O) of alkaloid cytisine within the region of 1651 cm^{-1}, whereas compounds **12**, **13**, **15**, **16** within the region of 3348–3416 cm^{-1} exhibits hydroxyl stretching vibrations.

In the course of analyzing the mass spectra of compounds **11**, **15** we revealed molecular ions and fragments produced in the decay of the molecule by electron impact.

The ^1H NMR spectra of compounds **11**–**16**, besides the protons of the alkaloid moiety, exhibited also the protons of the thioamide component. So, the ^1H NMR spectrum of compound **15**, demonstrate the methyl group protons to resonate at 0.97 ppm as a doublet with the coupling constant J = 5.1 Hz. Within the strong field region of the spectrum at 1.4 ppm (J_{HH} = 4.0 Hz) one can also observe the protons of the methyl group inherent in CH_3–CHO fragment. The three-proton singlet can be attributed to the protons of the methyl group attached to the nitrogen atom at 2.85 ppm (3H, N–C$\underline{H}_3$). The methine proton of CHN fragment manifests as a multiplet within 2.50 ppm region. Another methine proton inherent in the fragment CHO of ephedrine exhibits resonance at 4.75 ppm as a doublet with a coupling constant J = 3.5 Hz. The next methine group of CH_3–C$\underline{H}$O fragment manifests as a quartet within the region of 5.43 ppm. Within the weak field range of the spectrum 7.30–7.40 ppm one can observe the signals of the ten protons of two phenyl rings in the form of a complex multiplet. The integral curve corresponds to the number of protons.

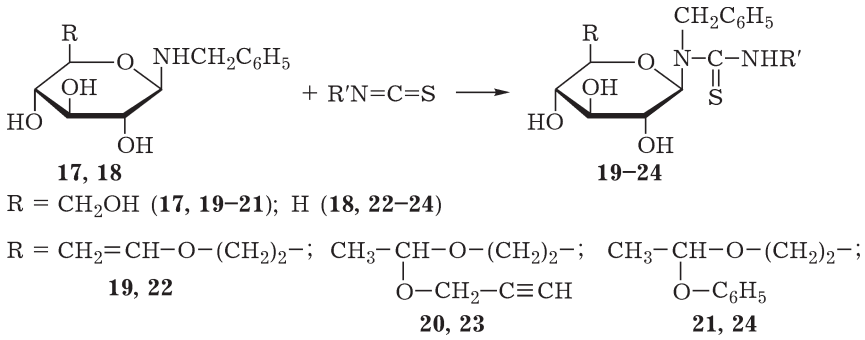
In order to conclusively confirm the structure of the compound **11** we performed ^{13}C NMR spectrometric investigation [14].

To obtain analogous thiourea derivatives based on *N*-aminoglycosides we performed the



R = HC≡C–CH_2– **(9, 11–13);** C_6H_5– **(10, 14–16)**

Scheme 4.



Scheme 5.

interaction of glucosylbenzylamine **17** and xylosylbenzylamine **18** with compounds **1**, **9**, **10** synthesized according to well-known methods; we obtained corresponding *N*-substituted glucosyl- and xylosyl-thiourea species **19–24** [15] (Scheme 5).

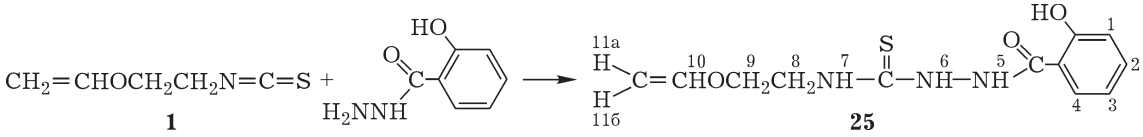
The reaction was carried out in an alcoholic medium at a room temperature. The compounds **19–24** synthesized represent white crystalline solids readily soluble in water and in ethanol.

The IR spectra of compounds **19–24** exhibit the absorption band of thiocarbonyl group (C=S) within the range of 1128–1150 cm^{-1}. The IR spectra of compounds **19**, **22** at 1190–1236 cm^{-1} demonstrate the absorption band of vinyl ether fragment =C–O–C.

When analyzing the ^1H NMR spectrum of compound **22** we revealed the protons of two methylene groups inherent in NH–C$\underline{H}_2$–C$\underline{H}_2$, appearing as a multiplet within the range of 3.84–3.97 ppm. The methylene non-equivalent protons of the vinyl group are registered in the form of two doublets of doublets within the region centred at 4.20 ppm, whereas the methine proton within 6.25 ppm region is exhibited as a doublet of doublet. Protons H(2)–H(5) inherent in xylopyranose ring are registered as a multiplet within 3.15–3.70 ppm region. The anomeric protons H(1) of the carbohydrate moiety is observed as a doublet at 4.50 ppm with the coupling constant J = 6.4 Hz, inherent in β anomer. The protons of the methylene group of the benzyl moiety demonstrate a singlet at 3.83 ppm. Within the range of 4.80–5.00 ppm there are three doublets of the hydroxyl protons of the pyranose ring of xylose. Within the range of 7.12–7.29 ppm there are the signals observed corresponding to aromatic ring protons.

Continuing the studies on the synthesis of novel biologically active substances based on 1 vinyloxyethylisothiocyanate **1** we performed the reaction of the latter with salicylic acid hydrazide in alcoholic medium at equimolar ratio between the reagents. [16] The reaction occurs under mild conditions for the synthesis with a 70 % yield of the target product **25** (Scheme 6).

The ^1H NMR spectrum of compound **25** demonstrated the signals inherent in the protons of the aromatic ring. Thus, the signals from aromatic protons H_1–H_4 are observed within the range of weak field: doublet H_1 at 6.97 ppm, triplet H_2 at 7.45 ppm, triplet H_3 at 6.92 ppm, doublet H_4 at 7.87 ppm. The signals from four methylene protons H_8, H_9 of hydroxyethyl moiety exhibit two triplets within the range of 3.70 and 3.80 ppm. The methane proton H_{10} of the vinyl moiety is observed as a doublet of doublets within the region of 6.50 ppm. The methylene protons H_{11a} and H_{11b} of the same vinyl moiety are observed as two doublets within the range of 4.00 and 4.21 ppm.



Scheme 6.

The proton of aromatic hydroxyl is observed as a singlet at 8.30 ppm. The amide and thioamide N–H protons are registered in the form of three singlets at 11.92 (H_5), 10.58 (H_6) and 9.55 ppm (H_7).

The mass spectrum of compound **25** demonstrated the peaks with the following m/z and relative intensity values (I_{rel}, %): molecular ion $[M]^+$ 281 (27 %), the molecule fragmentation products 248 (17 %), 144 (28 %), 121 (100 %), 86 (48 %).

It is known that thiosemicarbazides are widely used in the organic chemistry as starting synthones for the synthesis of many nitrogen-containing heterocyclic compounds. In this regard, it seems to be promising to search for the antibacterial properties of 1,2,4-triazole-3-thione derivatives, many among those are used in pharmacology [17, 18] and agriculture [19–21].

In order to extend searching for novel biologically active substances, the obtained thiosemicarbazide derivative of salicylic acid **25** was further subjected to intramolecular cyclization in an aqueous alkaline medium by means of heating the reaction mixture to 80–85 °C. In the presence of alkali, the compound **25** is converted into the thiolate ion, whereas the further acidification results in the formation of 4-vinyloxyethyl-5-(2-hydroxyphenyl)-2*H*-1,2,4-triazole-3(4*H*)-thione **26**.

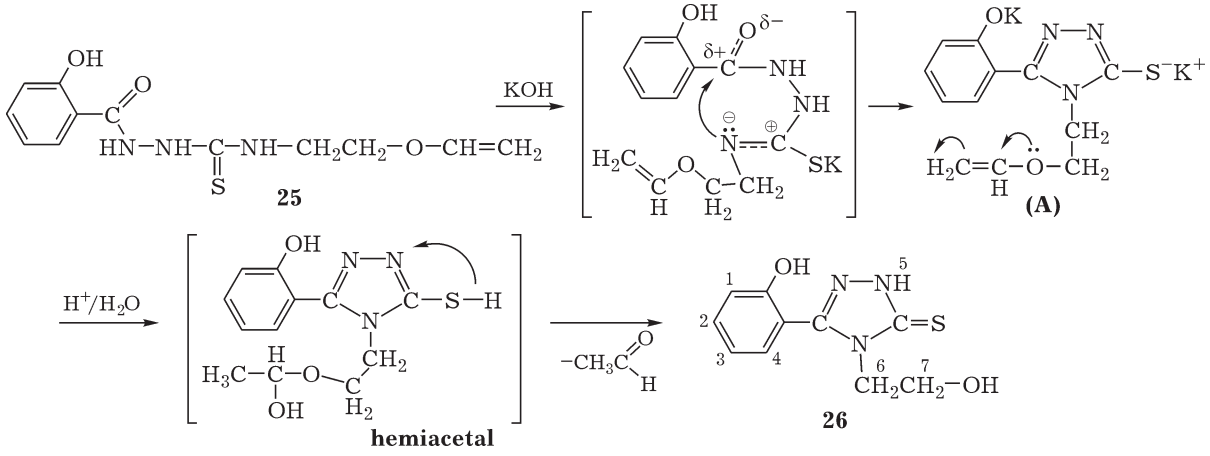
The thiourea species and thiosemicarbazides represent weak SH acids, but the solution contains predominantly the form of thione. The proportion of SH acid form is insignificant and it is not able to influence the further course of the reaction. The action of alkali is based on the fact that at high concentration values these compounds can be almost completely transformed into thiolates. As a result, the electronic balance is shifted to provide the conditions for intramolecular cyclization caused by the nucleophilic attack of the electron deficient carbon atom of the carbonyl group by the nitrogen atom with the formation of a stable heterocyclic ring system (Scheme 7).

However, in the course of performing the intramolecular heterocyclization, we have unexpectedly isolated compound **A**, whose hydrolysis product is presented by 4-(2-hydroxyethyl)-5-(2-hydroxyphenyl)-2*H*-1,2,4-triazole-3(4*H*)-thione **26**. Thus, upon acidification, alongside with the cyclization, one can observe the acidic hydrolysis the vinyl moiety *via* the formation of unstable intermediate hemiacetal that can readily decompose to produce acetaldehyde and corresponding alcohol.

The formation of derivative **26** is unambiguously proven by ^{1}H NMR and mass spectrometry, IR spectroscopy and XRD structural analysis.

The analysis of the mass spectrum of compound **26** revealed the peaks with the following m/z values and relative intensity (I_{rel}, %): molecular ion $[M]^+$ 237 (51 %), the fragments resulted from the molecule destruction 194 (59 %), 193 (100 %), 120 (31%).

The ^{1}H NMR spectrum of compound **26**, as against the compound **25**, there is some shifting observed for the signal of aromatic proton H_4. So, the H_4 proton doublet is shifted towards the stronger field region with 7.87 ppm (for com-



Scheme 7.

pound **25** the corresponding value is equal to 7.31 ppm). Triplet H_2 is exhibited at 7.40 ppm, doublet H_1 at 7.00 ppm, triplet H_3 at 6.94 ppm. The signals of four methylene protons H_6 and H_7 inherent to the hydroxyethyl fragment are also manifested in the form of two triplets within the region of 3.49 and 3.90 ppm. The aromatic hydroxyl proton exhibits a singlet at 10.25 ppm, whereas the proton of the hydroxyethyl hydroxyl H_9 demonstrates a broadened singlet at 4.74 ppm. The thioamide proton N–H inherent in triazole ring exhibits a fairly narrow singlet within a rather downfield region of the spectrum at 13.80 ppm. The integral intensity ratio corresponds to the structure of compound **26**.

In order to determine the spatial structure of 4-(2-hydroxyethyl)-5-(2-hydroxyphenyl)-2*H*-1,2,4-triazole-3(4*H*)-thione **26** we performed the XRD structural investigation thereof [16]. The general view of the molecule **26** is presented in Fig. 3.

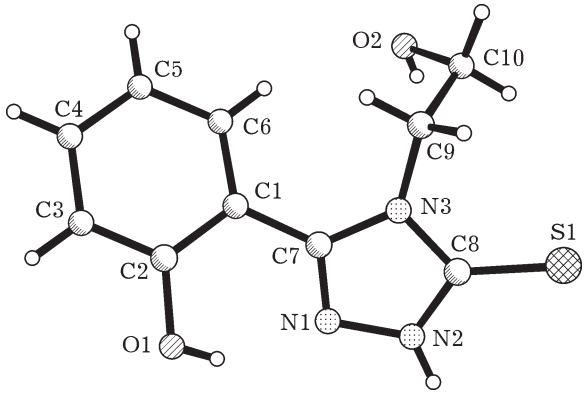


Fig. 3. Spatial molecular structure of compound **26**.

EXPERIMENTAL

The IR spectra were registered by means of an Avatar-20 IR spectrometer using tablets with KBr, The ^{1}H NMR spectra were registered by means of a Bruker DRX 500 NMR spectrometer at 500 MHz in DMSO-d_6 solution, with respect to TMS as an internal reference. Mass spectra were registered using a Finnigan MAT.INCOS 50 mass spectrometer *via* direct sample injection, with the ionization energy of 70 eV. The TLC analysis was performed using Sorbfil plates, the molar ratio in the system of isopropyl alcohol/benzene/ammonia amounting to 10 : 5: 2, with the visualization by means of iodine vapour.

2-Vinyloxyethylisothiocyanate (1). To 8.7 g (0.1 M) of vinyloxyethylamine was added 10.12 g (0.1 M) of triethylamine in 20 mL of chloroform under stirring, followed by dropwise adding of 7.61 g (0.1 M) of carbon disulfide. The mixture was stirred during 10–15 min, to add another 10.12 g (0.1 M) of triethylamine, and added dropwise 14.0 g (0.1 M) of benzoyl chloride. Further, the reaction mixture was stirred at a room temperature during 1 h and washed thrice with water. The chloroform layer was allowed to stand overnight above K_2CO_3, then the solvent was distilled off. The residue was distilled under oil-pump vacuum. B. p. = 67–68 °C (3 mmHg). The yield is equal to 10 g (78 %) of transparent liquid with n_D^{20} = 1.5324.

***N*-(*N*-Vinyloxyethylthiocarbamoyl)cytisine (2).** To a solution of 1.90 g (0.01 M) of cytisine in 20 mL of benzene was slowly added under stirring 1.29 g (0.01 M) of 2-vinyloxyethylisothiocyanate dissolved in 5 mL of benzene. The reaction mixture was then stirred at a room temperature during 1 h, then at the temperature of 39–40 °C during 2 h. After the completion of the reaction, the solvent was distilled off under reduced pressure. The reaction mixture was allowed to stand overnight; the precipitated crystals were filtered and washed with benzene. The yield is equal to 2.55 g (89 %), m. p. 167–168 °C.

***N*-(*N*-Vinyloxyethyltiocarbamoil)anabasine (3)** was prepared in a similar manner as compound **2** from 1.62 g (0.01 M) of anabasine and 1.29 g (0.01 M) of 2-vinyloxyethylisothiocyanate. A white crystalline substance was obtained. The yield is equal to 2.9 g (80 %), m. p. 84–85 °C.

***N*-(*N*-Vinyloxyethylthiocarbamoyl)salsoline (4)** was prepared in a similar manner as compound **2** from 1.93 g (0.01 M) of salsoline and 1.29 g (0.01 M) of 2-vinyloxyethylisothiocyanate. A white crystalline substance was obtained. The yield is equal to 2.35 g (73 %), m. p. 153–154 °C.

***l*-*N*-(*N*′-2-vinyloxyethylthiocarbamoyl)-ephedrine (5).** To 2 g (0.012 M) of *l*-ephedrine dissolved in 5 mL of ethanol was added 1.5 g (0.012 M) vinyloxyethylisothiocyanate to stir at a room temperature for 20–30 min, then 1/3 of the solvent was distilled off to hold during 12 h. A crystalline product precipitated was fil-

tered and washed with ether. The yield is equal to 2.9 g (86 %) of compound **I**, m. p. 96–97 °C. Found, %: C 61.27, H 7.36. $C_{15}H_{22}O_2N_2S$. Calculated %: C 61.22, H 7.48. IR spectrum, ν, cm^{-1}: 1530–1500 (NH–C(S)–), 3400–3200 (OH). ^1H NMR spectrum, δ, ppm: 0.86 d ($\underline{CH}_3CH$), J_{HH} 8.4 Hz, 2.01 s (CH_3N), 2.34–2.52 m ($\underline{CH}–CH_3$), 4.43 d (CH–O), J_{HH} 10.6 Hz, 7.10–7.24 m (C_6H_5), 3.06–3.40 dd (CH_2), 6.44 d (CH=C), 3.50 d ($C=CH_2$).

(4*S*,5*R*)-3,4-Dimethyl-5-phenyl-2-hydroxyethylimino-1,3-thiazolidine (7). To 1.5 g (0.009 mol) of *l*-N-(N′-2-vinyloxyethylthiocarbamoyl)-ephedrine **5** at a room temperature was added dropwise 10 mL of concentrated hydrochloric acid. Stirring was performed for 3 h, then was added a six fold amount of water; water was distilled off in vacuum. To the residue was added a 40 % aqueous solution of NaOH. The product was extracted with benzene, the organic layer was dried with Na_2SO_4, and the solvent was removed. The yield is equal to 0.76 g (60 %) of crystalline product with m. p. 108–109 °C. Found, %: C 62.35, H 7.12. $C_{13}H_{18}ON_2S$. Calculated, %: C 62.40, H 7.20. IR spectrum, ν, cm^{-1}: 1680–1650 (C=N), 3500–3000 (OH). ^1H NMR spectrum, δ, ppm: 0.92 d ($\underline{CH}_3CH$), J_{HH} 8.6 Hz, 2.10 s (CH_3N), 2.30–2.50 m ($\underline{CH}–CH_3$), 4.93 d (CH–S), J_{HH} 10.6 Hz, 7.00–7.15 m (C_6H_5), 3.20 d ($N–CH_2$), 3.40 d ($CH_2–\underline{CH}_2$).

Cytisino-*N*-(1-propargyloxyethoxyethyl)-thiocarbamide (11). To 1.85 g (0.01 mol) of 1-propargyloxyethoxyethylisothiocyanate was added 1.9 g (0.01 M) of cytisine, dissolved in 10 mL of absolute benzene. The mixture was stirred during 4 h at a room temperature. The solution with a precipitate formed was cooled and filtered. The yield is equal to 3.41 g (91 %) of a white crystalline solid, m. p. 120–121 °C (benzene). Found, %: C 60.78, H 6.65, N 11.19, $C_{19}H_{25}N_3O_3S$. Calculated, %: C 60.42, H 6.65, N 10.69. Mass spectrum (EI, 70 eV), m/z (I_{rel}, %): 375 (M^+ (7), 189 (51), 276 (55), 233 (40), 130 (56), 146 (67), 39 (100). ^1H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, *J*, Hz): 1.18 (3H, d, H-16, $J_{16,15}$ = 7.0), 1.90 (2H, m, H-7), 3.08 (1H, br. d, H-8), 3.16 (2H, m, H-10), 3.32 (1H, m, H-6), 3.40 (4H, m, H-13, H-14), 3.45 (2H, m, H-11), 3.65 (1H, m, H-9a), 3.97 (1H, d, H-9e, $J_{9e,9a}$ = 15.0), 4.13 (1H, q, H-15, $J_{15,16}$ = 7.1), 4.73 (2H, m, H-17), 4.86 (1H, t, H-19, *J* = 10.3), 6.12 (1H, d, H-4, $J_{4,3}$ = 7.0), 6.20 (1H, d, H-2, $J_{2,3}$ = 8,8), 7.31 (1H, dd, H-3, $J_{3,4}$ = 6.9), 7.61 (1H, br. s, N–H). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): 163.29 (C-1), 117.53 (C-2), 138.83 (C-3), 105.52 (C-4), 148.33 (C-5), 34.85 (C-6), 26.00 (C-7), 27.87 (C-8), 53.16 d (C-9), 54.67 (C-10), 48.82 (C-11), 183.76 (C-12), 46.04 (C-13), 74.46 (C-14), 99.40 (C-15), 19.65 (C-16), 63.97 (C-17), 79.54 (C-18), 77.06 (C-19).

***N*-1-propargyloxyethoxyethyl-*N′*-ephedrinothiourea (12).** To 1.85 g (0.01 M) of 1-propargyloxyethoxyethylisothiocyanate was added 1.65 g (0.01 M) of *l*-ephedrine dissolved in 5 mL of absolute benzene. Further, the mixture was stirred during 4 h under gentle heating. The solvent was distilled off. The residue was passed through a column with silica gel (eluent benzene). The yield is equal to 2.66 g (76.1 %) of colourless oil, n_D^{20} = 1.5630.

***N*-1-propargyloxyethoxyethyl-*N′*-pseudoephedrinothiourea (13).** The compound was synthesized in a similar manner as compound **12** from 1.85 g (0.01 M) of 1-propargyloxyethoxyethylisothiocyanate and 1.65 g (0.01 M) of *d*-pseudoephedrine. The yield is equal to 3.11 g (89.1 %) of light yellow oil, n_D^{20} = 1.5528.

***N*-benzyl-*N*'-vinyloxyethyl-β-*D*-glucopyranosylthiocarbamide (19).** To a solution of 1.34 g (0.005 mol) of glucosylbenzylamine **17** in 3 mL of alcohol was slowly added a solution of 0.005 M 2-vinyloxyethylisothiocyanatea in 5 mL of ethanol, under stirring at 20–22 °C. In 20–30 min after the adding the solution of 2-vinyloxyethylisothiocyanate a precipitate was formed. The precipitate was filtered, washed with absolute ethanol and recrystallized from absolute ethanol. The yield is equal to 0.99 g (49.8 %), m. p. 66–67 °C.

***N*-2-Vinyloxyethylthiosemicarbazide of salicylic acid (25).** To a solution of 1.52 g (0.01 M) of salicylic acid hydrazide in 25 mL of isopropyl alcohol at a room temperature was slowly added 1.29 g (0.01 M) of 2-vinyloxyethylisothiocyanate dissolved in 5 mL isopropyl alcohol, dropwise. The mixture was stirred at 40–45 °C during 2 h, and then it was cooled. A white crystalline precipitate formed was filtered, dried and recrystallized from absolute isopropanol. The yield of **25** was equal to 70 %, m. p. 163–165 °C.

4-(2-hydroxyethyl)-5-(2-hydroxyphenyl)-2*H*-1,2,4-triazole-3(4*H*)-thione (26). To an

aqueous alkali solution 0.56 g (0.01 M) of KOH in 30 mL of distilled water was added 2.81 g (0.01 M) of salicylic acid (2-vinyloxyethyl)thiosemicarbazide **25**. The reaction mixture was heated at 85 °C during 1 h, and then it was cooled and acidified with hydrochloric acid to obtain pH 3–4. The precipitate formed was filtered and recrystallized from 70 % aqueous ethanol solution. The yield of product **26** was equal to 69 %, m. p. 184–186 °C.

CONCLUSION

Thus, for the first time, the reaction of alkaloid cytisine, *l*-ephedrine, *d*-pseudoephedrine, as well as glucosylbenzylamine and xylosylbenzylamine aminoglycosides with vinyloxyethylisothiocyanate and with its acetal isothiocyanates was used for synthesizing to characterize novel 2-vinyl-, *N*-1-propargyl, and *N*-1-phenyloxyethoxyethyl-*N*′- aminothiourea basing on the mentioned alkaloids and aminoglycosides. By the example vinylethoxythiocarbamoyl *N*-derivatives as well as *l*-ephedrine and *d*-pseudoephedrine and cytisino-*N*-(1-propargyloxyethoxyethyl)thiourea it has been demonstrated that the mentioned thiourea species quite readily undergo hydrolyzing in the presence of weak acids. Basing on salicylic acid hydrazide, we synthesized and studied the acidic hydrolysis of corresponding vinyloxyethylthiosemicarbazide to convert into 1,2,4-triazole-3(4*H*)-thione. The composition and structure of thiourea derivatives synthesized were confirmed by means of elemental analysis, IR spectroscopy, ^{1}H and ^{13}C NMR spectrometry, and mass spectrometry and XRD structural analysis.

REFERENCES

1 Petrov K. A., Andreev L. N., *Usp. Khim.*, 38, 1 (1969) 41.
2 Mozolis V. V., Yokubytite S. P., *Usp. Khim.*, 42, 7 (1973) 1310.
3 Gazaliev A. M., Zhurinov M. Zh., Fazylov S. D., Novye Bioaktivnye Proizvodnye Alkaloidov, Gylym, Almaty, 1992.
4 Nurkenov O. A., Fazylov S. D., Kulakov I. V., Musina L. A., Alkaloid Anabazin i Yego Proizvodnye, Glasir, Karaganda, 2010.
5 Ibraev M. K., Turdybekov D. M., Takibaeva A. T., Nurkenov O. A., Turdybekov K. M.,Gazaliev A. M., Adekenov S. M., *Zh. Obshch. Khim.*, 76, 4 (2006) 672.
6 Gazaliev A. M., Nurkenov O. A., Turdybekov K. M., Fazylov S. D., Ibraev M. K., Turdybekov D. M. and Issabaeva M. B., *Mendeleev Commun.*, 16, 4(2006) 243.
7 Nurkenov O. A., Gazaliev A. M., Ibraev M. K., Turdybekov D. M., Sultanov A. S., Turdybekov K. M., Adekenov S. M., *Zh. Obshch. Khim.*, 76, 7 (2006) 1187.
8 Nurkenov O. A., Markova I. V., Shalbaeva A. B., Turdybekov K. M., Gazaliev A. M., *Zh. Obshch. Khim.*, 69, 4 H(1999) 679.
9 Nedolya N. A., Baranskiy V. A., Trofimov B. A., *Zh. Org. Khim.*, 31, 3 (1995) 321.
10 Nedolya N. A., Brandsma L., Trofimov B. A., *Zh. Org. Khim.*, 31, 3 (1995) 325.
11 Dmitrieva L. L., Nikitina L. L., Albanov A. I., Nedolya N. A., Nedolya N. A., Baranskiy V. A., Trofimov B. A., *Zh. Org. Khim.*, 41, 11 (2005) 1617.
12 Nedolya N. A., Gerasimova V. V., Pavsheva N. P., *Zh. Org. Khim.*, 25, 12 (1989) 2501.
13 Aynabaev A. A., Kulakov I. V., Nurkenov O. A., Gazaliev A. M., Vseros. Nauch. Konf. "Sovremennye Problemy Organicheskoy Khimii", Posvyashchennaya 100-letiyu so Dnya Rozhdeniya Akademika N. N. Vorozhtsova (Thesises), Novosibirsk, 2007, p. 129.
14 Kulakov I. V., Nurkenov O. A., Turdybekov D. M., Aynabaev A. A., Turdybekov K. M., Gazaliev A. M., *Khim. Prirod. Soyed.*, 1 (2009) 56.
15 Kulakov I. V., Sintez, Stroyenie, Khimicheskiye Prevrashcheniya i Biologicheskaya Aktivnost' Novykh Azot- i Serosoderzhashchikh Polifunktsionalnykh Proizvodnykh Nekotorykh Alkaloidov, Monosakharidov i Geterotsiklov (Author's Abstract of Doctoral Dissertation in Chemistry), Fitokhimiya, Karaganda, 2010.
16 Alimbaeva A. S., Nurkenov O. A., Zhakina A. Kh., Kulakov V. I., Turdybekov D. M., Turdybekov K. M., *Zh. Obshch. Khim.*, 79, 7 (2009) 1175.
17 Selezneva E. S., Belousova Z. P., Ivanchina A. I., Tengaev E. I., *Khim.-Farm. Zh.*, 40, 3 (2006) 27.
18 Ivanskiy V. I., Khimiya Geterotsiklicheskikh Soyedineniy, Vyssh. Shkola, Moscow, 1978, p. 559.
19 Berim I. G., Khimicheskaya Zashchita Rasteniy, Nauka, St. Petersburg, 1996, p. 115.
20 Golyshin N. M., *ZhVKhO im. D. I. Mendeleeva*, 29, 1 (1984) 74.
21 Van Gestel J., Heeres J., Janssen M., Van Reet G., *Pestic. Sci.*, 11, 1 (1980) 95.