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SYNTHESIS AND INTRAMOLECULAR HETEROCYCLIZATION OF *N*-ALLYLTHIOCARBAMIDE DERIVATIVES OF THE ALKALOIDS CYTISINE AND ANABASINE INTO 1,3-THIAZOLINE DERIVATIVES AND FEATURES OF THEIR MOLECULAR STRUCTURES

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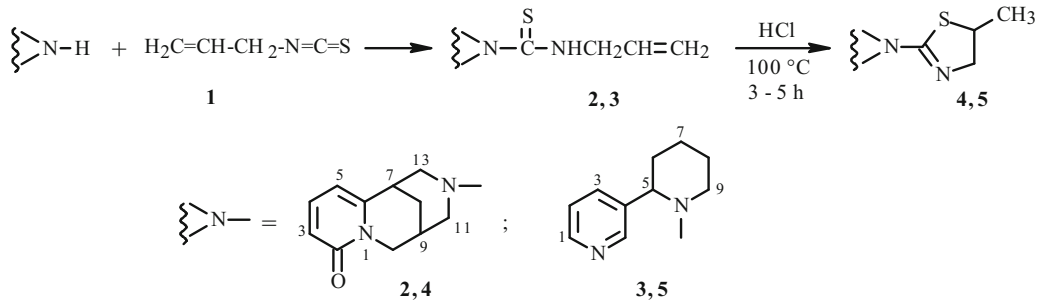
Allylthiourea derivatives were synthesized from the alkaloids cytisine and anabasine and allylisothiocyanate. 1,3-Thiazoline derivatives were synthesized from them via intramolecular heterocyclization using HCl and heating in a sealed ampul. The structures of the synthesized compounds were proved by IR and PMR spectroscopy, mass spectrometry, and x-ray structure analysis.

Keywords: alkaloids, cytisine, anabasine, allylisothiocyanate, intramolecular heterocyclization, 5-methyl-1,3-thiazoline, x-ray structure analysis.

Methods for preparing heterocyclic thiazoline derivatives from the corresponding allyl-containing thioureas via the action of various reagents, e.g., solutions of hydrogen halides and halogens, have been reported [1, 2].

In continuation of our research on the synthesis and study of the reactivity of thiourea derivatives of alkaloids [3–5], we synthesized *N*-allylthiocarbamide derivatives from the alkaloids cytisine and anabasine by reacting equimolar amounts of the alkaloids and allylisothiocyanate (**1**) in alcohol or benzene. Then we studied possible intramolecular heterocyclization of the resulting allylthiocarbamide derivaties **2** and **3** into the corresponding 1,3-thiazoline derivatives using HCl. The synthesized *N*-allylthiocarbamide derivatives of cytisine and anabasine **2** and **3** underwent intramolecular heterocyclization according to the following scheme upon heating on a boiling water bath in a sealed glass ampul in conc. HCl solution for 3–5 h:



The acidic reaction resulted in the formation in good yields of the five-membered S-containing heterocyclic compounds 2-*N*-cytisino-5-methyl-1,3-thiazoline (**4**) and 2-*N*-anabasino-5-methyl-1,3-thiazoline (**5**), which were after additional recrystallization white crystalline compounds that were soluble in many organic solvents except saturated hydrocarbons.

Compound **5** was prepared without preliminary purification and isolation of intermediate **3**. Compound **3** under the forcing conditions of the ampul cyclization did not show any visible signs of decomposition or polymerization of the starting anabasine framework that were observed during various acylation and alkylation reactions.

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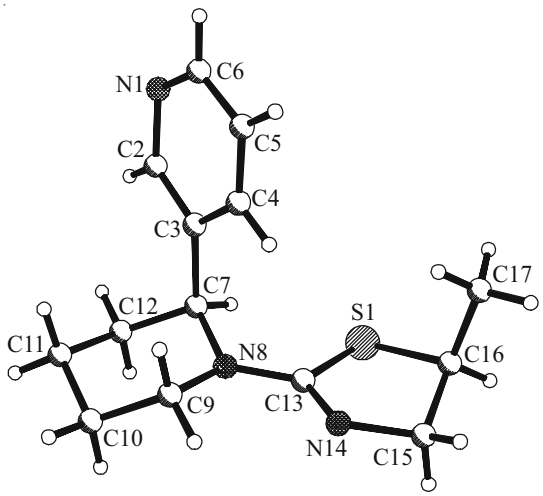
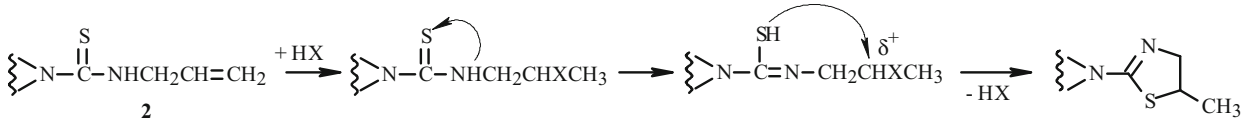


Fig. 1. Molecular structure of 2-*N*-anabasino-5-methyl-1,3-thiazoline (**5**).

The mechanism of this reaction in the first step included Markovnikov addition of hydrogen halide to the double bond of the thiourea allyl group. Then, nucleophilic attack of the S atom (in the thiourea thiol form) at the secondary C atom C–X with a partial positive charge and subsequent intramolecular cyclization gave the 1,3-thiazoline derivative.



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IR spectra of **2** and **4** had absorption bands for C=N at 1603 cm^{-1} and cytisine amide C=O at 1653.

Mass spectra of alkyl- and allyl-derivatives of cytisine [6] exhibited characteristic fragments with *m*/*z* and relative intensity I_{rel} (%) 203 (100) and 58 that were assigned to $N–CH_2^+$ of the cytisine framework and the alkyl radical as a result of the stability of the quinolizidine cytisine framework.

In contrast with alkyl-substituted cytisine derivatives, the mass spectrum of **4** contained a peak for the molecular ion at 289 $[M]^+$ with relative intensity 100%. This could indicate that **4** was thermally stable to the action of electron impact and that the N–C bond of the piperidine and thiazoline rings was rather strong.

PMR spectra of **4** and **5** showed that significant conjugation with the 1,3-thiazoline ring of protons in α-positions to the N atom of the piperidine ring cause them to appear at weaker field than those in the simple alkyl or alkylacyl derivatives of these alkaloids. Some proton resonances were split and doubled. This may indicate that rotational conformers were present. Thus, a resonance with an integrated intensity of 1H that appeared as a broad doublet at 5.22 ppm in the PMR spectrum of **5** was assigned to equatorial proton H-9, which did not appear in the weak-field part of the spectrum that is uncharacteristic for it in other anabasine derivatives studied by us earlier. The methine proton of the piperidine ring appeared as a triplet, each peak of which was also split into a doublet of about 3.3 Hz. This indicated that rotation of the pyridine and thiazoline rings relative to the piperidine ring affected it. The thiazoline methyl protons in the PMR spectrum of **4** with integrated intensity 3H were recorded as two strong doublets with SSCC J = 6.3 Hz and a distance between the doulets of about 24 Hz. This could be explained by the presence in the DMSO solution of two rotational isomers (*R* and *S*) around the chiral C atom (with peak intensity ratio 5:6) with the methyl axial and equatorial relative to the plane of the thiazoline ring.

An x-ray structure analysis (XSA) was carried out in order to establish the possible absolute configuration of synthesized 1,3-thiazoline derivatives **4** and **5** and to investigate further *N*-substituted derivatives of anabasine and cytisine.

We found earlier [4, 7] that bulky electron-accepting groups in crystals of *N*-substituted anabasine derivatives can change the orientation of the pyridine ring relative to the piperidine ring from equatorial to axial. Figure 1 shows a general view of **5**.

The bond lengths and angles in **5** were close to normal [8]. The piperidine ring adopted an ideal chair conformation (ΔC^7_s = 0.67 Å, like in anabasine *O*,*O*-diethylthiophosphate [9], *N*-anabasino(2-vinyloxyethylamino)methanethione [7], and *N*-(anabasino-1-carbonothioyl)furan-2-carboxamide [4]). The pyridine ring was planar within ±0.005 Å and oriented axially relative to the piperidine ring (torsion angle C3C7C8C9 = 74.4°), in contrast with the equatorial orientation in anabasine *O*,*O*-diethylthiophosphate [9]. This same orientation of the pyridine ring was observed in *N*-anabasino(2-vinyloxyethylamino)methanethione [7] and *N*-(anabasino-1-carbonothioyl)furan-2-carboxamide [4].

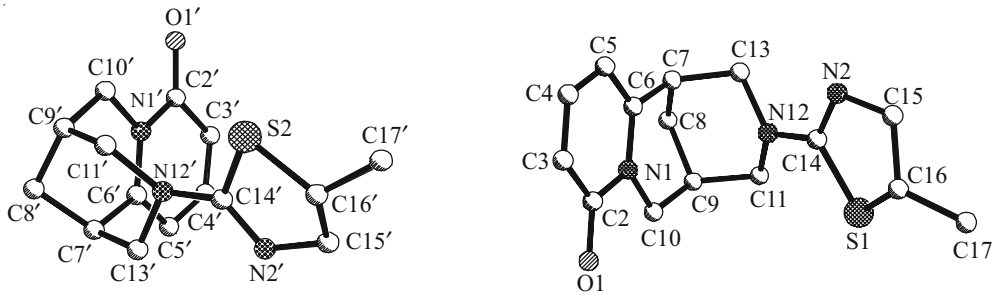

Fig. 2. Molecular structure of 2-*N*-cytisino-5-methyl-1,3-thiazoline (**4**).

This example again confirmed our previous hypothesis that such an orientation of the pyridine ring relative to the piperidine ring is due to non-equivalent repulsion between the bulky heterocyclic subsituent and the pyridine ring. The bulky 1,3-thiazoline substituent on N8 is oriented equatorially. The 1,3-thiazoline ring itself has a distorted *twist*-boat conformation ($\Delta C_2^{16,15} = 6.1$ Å). The ring is distorted because of the methyl in the 5-position on C16, which is situated in the crystal packing in the more favorable axial position relative to the plane of the thiazoline ring (torsion angle C13S1C16C17 = –94.4°) and pulls this atom to the α-side.

Figure 2 shows a general view of **4**, the molecular structure of which also turned out to be interesting.

The structure of **4** consisted of two asymmetric units, molecules **4a** and **4b**, that were situated in independent parts of the cell. The bond lengths and angles in the cytisine framework were close to normal [8]. The exceptions were bond angles around N12, which had trigonal planar coordination (sum of bond angles 354 and 350°, respectively). The coordination of N12 was pyramidal (sum of bond angles 335.7 and 334.0°) in previously studied *N*-methylcytisine [10] and *N*-cyanomethylcytisine [11], respectively. The difference in the coordination of N12 in the aforementioned molecules was due to a mesomeric effect. The dihydropyridine ring in **4a** and **4b** was planar within ±0.005 Å. Carbonyl atom O1 was situated practically in this plane (deviation of 0.06 Å from the plane). The tetrahydropyridine ring adopted a distorted boat conformation with bridging C7 deviating from the average plane of the other atoms by 0.76 Å. The piperidine ring had a distorted chair conformation. The 1,3-thiazoline ring in **4a** was planar within ±0.02 Å, in contrast with **4b**, where this ring had a flattened envelope conformation ($\Delta C_2^{1,2} = 4°$) with atom C16′ deviating by –0.32 Å from the plane of the other atoms. The conformation of this ring may have been due to interaction of electron clouds of the methyl, C16′, and the S atom. In contrast with **5**, the methyl was oriented equatorially and lay in the plane of the atoms of this ring (torsion angle N2C15C16C17 = 176.1° and –168.3° in **4a** and **4b**, respectively).

EXPERIMENTAL

IR spectra were taken in KBr disks on an Avatar-320 spectrometer. PMR spectra were recorded in DMSO-d_6 on a Bruker DRX 500 spectrometer at 500 MHz relative to TMS internal standard. Mass spectra were obtained in a Finnigan Mat.Incos 50 instrument with direct sample introduction at ionizing energy 70 eV. TLC was performed on Sorbfil plates using 2-PrOH:C_6H_6:NH_4OH (10:5:2) with development by iodine vapor. Single crystals of **4** and **5** for XSA were grown by slow evaporation from appropriate solvents at room temperature.

XSA of 4. Unit-cell constants and intensities of 7181 independent reflections were measured on a Bruker P4 automated diffractometer using Mo K_α-radiation, graphite monochromator, θ/2θ-scanning, and $2\theta \le 57°$. The crystals were orthorhombic, transparent (0.6 × 0.3 × 0.18 mm), $a = 8.299(3)$, $b = 14.613(4)$, $c = 23.8204(7)$ Å, $V = 2888.78(16)$ Å^3, $d_{calc} = 1.331$ g/cm^3, $Z = 8$ ($C_{15}H_{19}N_3OS$), space group $P2_12_12_1$. The structure was solved by direct methods and refined by anisotropic full-matrix least-squares methods for nonhydrogen atoms. Positions of H atoms were calculated geometrically using a rider model. A total of 5889 reflections with $I > 2\sigma(I)$ was used. The final agreement factors were R = 0.0595 and $wR_2 = 0.1631$. The structure was solved using the SHELXS-93 program and refined using the SHELXL-97 program [12]. Geometric parameters for **4** were deposited in the CCDC (CCDC 755771).

XSA of 5. Unit-cell constants and intensities of 3347 independent reflections were measured on a Bruker APEX-II CCD automated diffractometer using Mo K_α-radiation, graphite monochromator, θ/2θ-scanning, and $2\theta \le 56.6°$. The crystals were monoclinic, transparent ($0.032 \times 0.10 \times 0.60$ mm), $a = 6.331(3)$, $b = 7.960(4)$, $c = 13.548(7)$ Å, $\beta = 94.93(2)°$, $V = 680.32(6)$ Å^3, $d_{calc} = 1.276$ g/cm^3, $Z = 2$ ($C_{14}H_{19}N_3S$), space group $P2_1$. The structure was solved by direct methods and refined by anisotropicc full-matrix least-squares methods for nonhydrogen atoms. Positions of H atoms were calculated geometrically using a rider model. A total of 3275 reflections with $I > 2\sigma(I)$ was used. The final agreement factors were R = 0.0406 and $wR_2 = 0.1212$. The structure was solved using the SHELXS-93 program and refined using the SHELXL-97 program [12]. Geometric parameters for **5** were deposited in the CCDC (CCDC 740930).

Cytisino-*N*-allylthiocarbamide (2). A warm suspension of cytisine (1.9 g, 0.01 mol) in anhydrous benzene (20 mL) was stirred vigorously, treated dropwise with a solution of allylisothiocyanate (1.1 g, 0.011 mol) in benzene (5 mL), stirred at 35–40°C for another ~2 h, and cooled. The resulting white precipitate was filtered off and washed with benzene to afford **2** (2.77 g, 96%), mp 229–230°C (2-PrOH:DMF, 10:1), $C_{15}H_{19}N_3OS$. IR spectrum (ν, cm^{-1}): 1533 [NH–C(S)–], 1644 ($C=O_{amide}$).

Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 289 (11.1) $[M]^+$, 189 (13), 160 (32), 147 (22.8), 146 (49.7), 134 (19.3), 117 (19), 68 (22.8), 60 (16.4), 56 (19.3), 44 (40), 41 (100), 39 (63.3).

PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.88, 1.95 (2H, dd, $J_{8,7} = 12.4$, $J_{8,9} = 13.0$, H-8), 3.09 (1H, br.d, J = 13.0, H-9), 3.17 (2H, br.d, J = 11.4, H-11), 3.29 (1H, br.d, J = 11.9, H-7), 3.66 (1H, dd, $J_{10a,9} = 6.2$, H-10a), 3.94, 4.13 (2H, m, C<u>H</u>$_2$–CH=), 3.99 (1H, d, $J_{10e,10a} = 15.3$, H-10e), 4.76, 4.87 (2H, both br.d, J = 11.6, 15.9, H-13a, H-13e), 4.93 (2H, m, –CH=C<u>H</u>$_2$), 5.69 (1H, m, –C<u>H</u>=CH$_2$), 6.12 (1H, d, $J_{5,4} = 6.9$, H-5), 6.19 (1H, d, $J_{3,4} = 9.0$, H-3), 7.30 (1H, dd, H-4), 7.70 (1H, br.t, J = 5.4, N–H).

2-*N*-Cytisino-5-methyl-1,3-thiazoline (4). Cytisino-*N*-allylthiocarbamide (**2**, 1.45 g, 0.005 mol) in conc. HCl (10 mL) in a sealed ampul was heated on a water bath for 3 h and cooled. The ampul was opened. The mixture was neutralized with aqueous NaOH solution (40%) until slightly basic. The separated oil was extracted several times with benzene and dried over anhydrous Na_2SO_4. Solvent was distilled to afford white crystalline **4** (1.17 g, 81%), mp 166–167°C (hexane:benzene), $C_{15}H_{19}N_3OS$. IR spectrum (ν, cm^{-1}): 1603 (C=N), 1653 ($C=O_{amide}$).

Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 289 (100) $[M]^+$, 274 (27), 160 (30), 146 (39), 41 (58).

PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.10, 1.15 (3H, dd, J = 6.3, C<u>H</u>$_3$–CH), 1.90 (2H, m, H-8), 2.43 (1H, br.s, H-9), 3.11 (1H, br.s, H-7), 3.20 (2H, m, H-11), 3.42 (1H, dd, J = 6.2, =N–C<u>H</u>a), 3.68 (2H, m, H-13), 3.75 (1H, dd, $J_{ba} = 7.6$, =N–C<u>H</u>b), 3.78 (1H, m, S–C<u>H</u>), 3.90 (1H, dd, $J_{10a,9} = 6.3$, H-10a), 3.95 (1H, d, $J_{10e,10a} = 15.1$, H-10e), 6.16 (1H, d, $J_{5,4} = 7.6$, H-5), 6.22 (1H, d, $J_{3,4} = 9.4$, H-3), 7.33 (1H, dd, H-4).

2-*N*-Anabasino-5-methyl-1,3-thiazoline (5). A solution of anabasine (1.62 g, 0.01 mol) in anhydrous benzene (5 mL) was stirred vigorously, treated dropwise with a solution of allylisothiocyanate (1.1 g, 0.011 mol) in benzene (5 mL), stirred at 35°C for another ~2 h, diluted with hexane (50 mL), and cooled to 0°C. The solvent was decanted from the oil formed on the bottom of the flask. The oil was washed again with hot hexane and again cooled and decanted to afford **3** (2.40 g, 92%) as a light-yellow viscous oil that was used further to prepare **5**. Compound **3** (2.40 g, 9.2 mmol) was dissolved in conc. HCl (15 mL), heated in a sealed ampul on a water bath for 5 h, and cooled. The ampul was opened carefully. The mixture was neutralized with aqueous NaOH solution (40%) until slightly basic. The separated light-brown oil was extracted several times with benzene and dried over anhydrous Na_2SO_4. Solvent was distilled until the solid was almost dry. The solid was treated with hexane and left to crystallize upon cooling. The resulting crystals were filtered off and washed with hexane to afford light-gray crystalline **5** (1.30 g, 50%). Recrystallization and decolorization with activated carbon in hexane:benzene (3:1) afforded almost white crystals, mp 100–101°C, that were suitable for an XSA. Elemental analyses of **5** agreed with those calculated. $C_{15}H_{19}N_3OS$. IR spectrum (KBr, ν, cm^{-1}): 1593 (C=N), 1390 (C–N).

Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 261 (30) $[M]^+$, 260 (100), 232 (17), 200 (16), 186 (16), 161 (44), 118 (27), 117 (25), 105 (22), 104 (19), 92 (22), 78 (17), 41 (62), 39 (28).

PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.25 (3H, d, J = 6.6, CHC<u>H</u>$_3$), 1.22–2.30 (6H, m, H-6, H-7, H-8), 3.00 (1H, t, $J_{5,6} = 12.8$, H-5), 3.59 (1H, dd, J = 4.2, =N–C<u>H</u>a), 3.79 (1H, br.d, H-9a), 3.90 (1H, dd, $J_{ba} = 7.1$, =N–C<u>H</u>b), 3.95 (1H, m, S–C<u>H</u>), 5.22 (1H, br.d, H-9e), 7.39 (1H, dd, $J_{2,3} = 4.7$, H-2), 7.61 (1H, d, $J_{3,2} = 7.9$, H-3), 8.44 (1H, d, H-1), 8.46 (1H, s, H-4).

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