SYNTHESIS AND CRYSTAL STRUCTURE OF CYTISINO-*N*-(2-HYDROXYETHYL)-THIOCARBAMIDE

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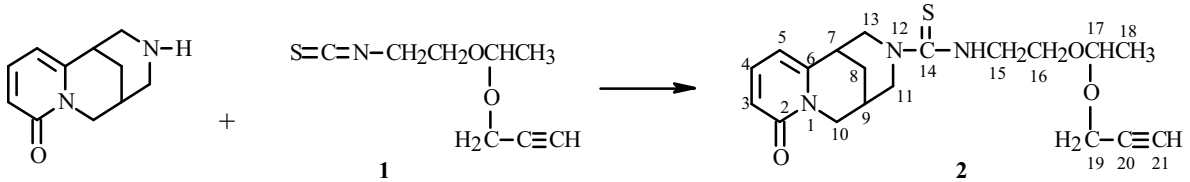
A thiourea derivative of the alkaloid cytisine was synthesized by reacting it with 1-propargyloxy-ethoxyethylisothiocyanate. It was shown that the synthesized acetal thiourea derivative underwent hydrolysis in acidic medium to cytisino-N-(2-hydroxyethyl)-thiocarbamide, the molecular structure of which was confirmed by an x-ray structure analysis.

Key words: alkaloid cytisine, acetal thiourea derivative, isothiocyanates, PMR spectroscopy, x-ray structure analysis.

Thioureas are an important class of S-containing organic compounds that are widely used both in organic synthesis and in practice in industry, agriculture, and medicine. Most thiourea derivatives possess valuable pharmacological properties and are used as antituberculosis, antimicrobial, antiulcer, and other therapeutically active compounds [1, 2].

The reactions of various isothiocyanates with cytisine, anabasine, and ephedrine alkaloids have been previously studied [3-5]. 2-Vinyloxyethylisothiocyanate has attracted special interest as a starting material because it is a highly reactive bifunctional synthon with unique synthetic potential for simple vinyl ethers and isothiocyanates. The corresponding isothiocyanate acetal **1** was synthesized based on 2-vinyloxyethylisothiocyanate by the known method [6] using electrophilic addition of propargyl alcohol to the isocyanate vinyl bond. 1-Propargyloxyethoxyethylisothiocyanate (**1**), in turn, provides broad access to more complicated thiourea acetals that are undoubtedly interesting for creating new biologically active compounds.



1 **2**

Therefore, we synthesized the thiourea derivative of physiologically active cytisine and **1** in benzene or alcohol solution by direct addition of the alkaloid to **1**.

The addition of cytisine, like an ordinary amine, to **1**, a heterocumulene, occurred by the well-known mechanism.

Synthesized **2** was a white crystalline compound that was moderately soluble in organic solvents.

The formation of thiourea derivative **2** was proved by mass spectrometry and PMR and ^{13}C NMR spectroscopy, which are described in the Experimental section. The PMR spectrum of **2**, in contrast with cytisine itself and its *N*-alkyl derivatives, showed a significant weak-field shift of the piperidine protons that was surely related to the introduction of the thiocarbonyl fragment. Mass spectral analysis of **2** found peaks with *m*/*z* values and relative intensities I_{rel} (%) for the molecular ion at 375 (7) $[M]^+$ and fragments from the cytisine skeleton and thiourea and acetal moieties with $>N-^+$ 189 (51), $>N-C(S)NH(CH_2)_2^+$ 276 (55), $>N-C(S)^+$ 233 (40), $C_5H_8NOS^+$ 130 (56), and $C_5H_8NO_2S^+$ 146 (67), and the propyne fragment $CH_2C\equiv CH^+$ 39 (100).

Preliminary bioscreening of **2** for hepatoprotective activity found that it had therapeutic and preventive activity.

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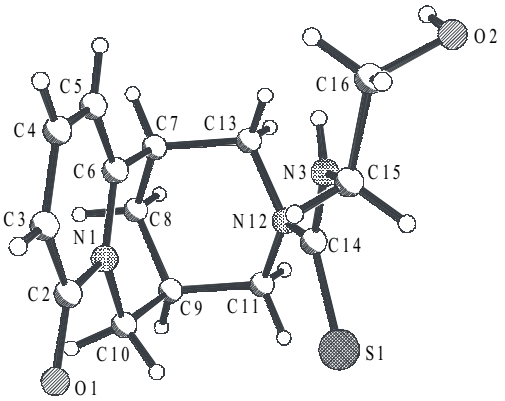
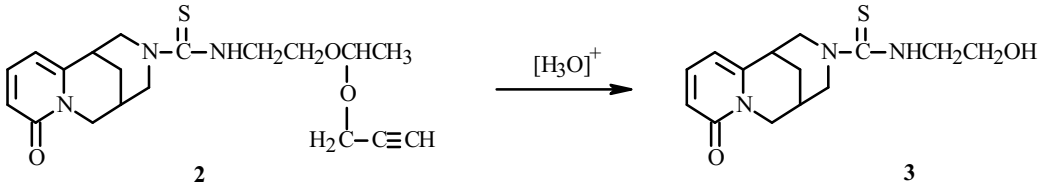


Fig. 1. Molecular structure of cytisino-*N*-(2-hydroxyethyl)-thiocarbamide (**3**).

The target product **2** underwent partial hydrolysis at the acetal bond if the synthesis was carried out in aqueous ethanol with subsequent crsytallization from ethanol (90%). Fractional crystallization from benzene and ethanol isolated the hydrolysis product of **2**, cytisino-*N*-(2-hydroxyethyl)-thiocarbamide (**3**) in about 10% yield.

Because acetals are known to be rather easily hydrolyzed in the presence of acids, we confirmed the aforementioned hypothesis by mild hydrolysis of **2** into **3** by boiling an alcohol solution of **2** in the presence of several drops of acetic acid.



2 **3**

This isolated in good yield cytisino-*N*-(2-hydroxyethyl)-thiocarbamide (**3**), the structure of which was proved by mass spectrometry, PMR spectroscopy, and x-ray structure analysis. Figure 1 shows the molecular structure of **3**.

The bond lengths and angles in the cytisine skeleton of **3** are normal and close to the corresponding values in *N*-methylcytisine [7], *N*-cyanmethylcytisine [8], and *O*,*O*-dimethyl-*N*-cytisinylamidophosphate [9]. The exceptions were the bond angles around N12. Thus, the coordination of N12 is pyramidal in *N*-methylcytisine and *N*-cyanmethylcytisine (sum of bond angles 335.7° and 334.0°) whereas in **3** and *O*,*O*-dimethyl-*N*-cytisinylamidophosphate the coordination is trigonal planar (sum of bond angles 355° and 354.8°, respectively). The difference in the coordination of the N atom in *N*-methylcytisine and *N*-cyanmethylcytisine, on one hand, and in **3** and *O*,*O*-dimethyl-*N*-cytsinylamidophosphate, on the other, is due to the mesomeric effect between the unshared electron pair of the N atom and the double bond C14=S1 and O=P in the last. The dihydropyridine ring is planar within ±0.009 Å. The carbonyl O1 atom was almost in the plane of the remaining atoms with a deviation of 0.06 Å. The tetrahydropyridine ring N1C6C7C8C9C10 adopted the distorted boat conformation ($\Delta C_s^8 = 9.04$ Å) with bridging atom C8 deviating from the average plane of the remaining atoms by 0.73 Å(I). The piperidine ring had an almost ideal chair conformation ($\Delta C_2^{7,13} = 0.97$ Å). The bulky substituent on N12 was in the axial orientation relative to the piperidine ring (torsion angle C7C13N12C14 = 100°). The hydroxyl was oriented axially relative to the average plane of C14N3C16C17. This position of the OH group was due to the presence of a strong intermolecular H-bond O2–HO2 (x,y,z)...O1(1+x,y,z) (H2O...O1 = 1.926 Å, O2–HO2...O1 = 163.9°) that stretches it. Infinite chains along the *a* axis bonded by another intermolecular H-bond N3–HN3(x,y,z)...O1(1+x,y,z) (N3–HN3...O1 = 2.202 Å, N3–HN3...O1 = 159.1°).

EXPERIMENTAL

PMR spectra in DMSO-d_6 were recorded on a Bruker DRX500 spectrometer at 500 MHz operating frequency with TMS internal standard; ^{13}C NMR spectra in $CDCl_3$, at 125 MHz operating frequency; mass spectra, in a Finnigan Mat.Incos 50 with direct sample introduction at ionization energy 70 eV. Melting points were determined on a Boetius instrument. TLC was performed on Sorbfil plates with detection by iodine vapor.

X-ray Structure Analysis. Cell constants and intensities of 1798 reflections were measured on an automated four-circle Bruker P4 diffractometer (λ MoKα-radiation, graphite monochromator). The crystals were monoclinic, a = 7.3546(7), b = 13.0173(9), c = 7.9229(5) Å, V = 696.15(9) Å^3, Z = 2 ($C_{14}H_{18}N_2O_2$), d_{calc} = 1.328 cm^3, space group $P2_1$.

A total of 1675 independent reflections with $I > 2\sigma$ was used in the calculations. The structure was solved by direct methods and refined by anisotropic full-matrix least-squares methods for nonhydrogen atoms. H atoms were fixed geometrically by the rider model except for the hydroxyl H that was found and refined anisotropically. The final agreement factors were R = 0.032 and R_w = 0.089. Atomic coordinates, bond lengths, and torsion and bond angles were deposited in the Cambridge Crystallographic Data Centre (CCDC 710729). All calculations were performed using the SHELXL-97 programs.

Cytisino-*N*-(1-propargyloxyethoxyethyl)-thiocarbamide (2). 1-Propargyloxyethoxyethylisothiocyanate (1.85 g, 0.01 mol) was treated with cytisine (1.9 g, 0.01 mol) dissolved in anhydrous benzene (10 mL), stirred for 4 h at room temperature, cooled, and filtered to afford a white crystalline compound (3.41 g, 91%), mp 120-121°C (benzene). $C_{19}H_{25}N_3O_3S$. Mass spectrum (EI, 70 eV, m/z, I_{rel}, %): 375 (7) $[M]^+$, 189 (51), 276 (55), 233 (40), 130 (56), 146 (67), 39 (100).

PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.18 (3H, d, $J_{18,17}$ = 7.0, H-18), 1.90 (2H, m, H-8), 3.08 (1H, br.d, H-9), 3.16 (2H, m, H-11), 3.32 (1H, m, H-7), 3.40 (4H, m, H-15, H-16), 3.45 (2H, m, H-13), 3.65 (1H, m, H-10a), 3.97 (1H, d, $J_{10e,10a}$ = 15.0, H-10e), 4.13 (1H, q, $J_{17,18}$ = 7.1, H-17), 4.73 (2H, m, H-19), 4.86 (1H, t, J = 10.3, H-21), 6.12 (1H, d, $J_{5,4}$ = 7.0, H-5), 6.20 (1H, d, $J_{3,4}$ = 8.8, H-3), 7.31 (1H, dd, $J_{4,5}$ = 6.9, H-4), 7.61 (1H, br.s, N–H).

^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): 163.29, (C-2), 117.53 (C-3), 138.83 (C-4), 105.52 (C-5), 148.33 (C-6), 34.85 (C-7), 26.00 (C-8), 27.87 (C-9), 53.16 d (C-10), 54.67 (C-11), 48.82 (C-13), 183.76 (C-14), 46.04 (C-15), 74.46 (C-16), 99.40 (C-17), 19.65 (C-18), 63.97 (C-19), 79.54 (C-20), 77.06 (C-21).

Cytisino-*N*-(2-hydroxyethyl)-thiocarbamide (3). A solution of **2** (0.75 g, 2 mmol) in ethanol (5 mL, 85%) was treated with acetic acid (two drops) and refluxed for 2 h. The solvent was evaporated. The solid was crystallized from hexane to afford a white crystalline compound (0.52 g, 88%), mp 194-195°C (ethanol). $C_{14}H_{19}N_3O_2S$. Mass spectrum (EI, 70 eV, m/z, I_{rel}, %): 293 (34) $[M]^+$, 190 (37), 160 (38), 146 (100), 103 (64), 44 (53).

PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.91 (2H, m, H-8), 3.08 (1H, br.d, H-9), 3.15 (2H, m, H-11), 3.30 (1H, m, H-7), 3.35 (2H, m, H-15), 3.40 (2H, m, H-13), 3.64 (1H, m, H-10a), 3.99 (1H, d, $J_{10e,10a}$ = 15.4, H-10e), 4.53 (1H, t, J = 5.5, O<u>H</u>), 4.81 (2H, dd, $J_{16,15a}$ = 13.2, $J_{16,15b}$ = 11.8, H-16), 6.13 (1H, d, $J_{5,4}$ = 6.9, H-5), 6.20 (1H, d, $J_{3,4}$ = 9.0, H-3), 7.30 (1H, dd, $J_{4,5}$ = 6.9, H-4), 7.49 (1H, br.t, J = 10.3, N–H).

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