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SYNTHESIS AND CRYSTAL STRUCTURE OF N-ETHYL-N-CYTISINOCARBOTHIOAMIDE

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Based on (–)-cytisine alkaloid and ethyl isothiocyanate, N-ethyl-N-cytisinocarbothioamide is synthesized and its structure is proved by ^{1}H NMR spectroscopy and single crystal X-ray diffraction. The mesomeric effect is shown in the carbothioamide group formed. It is found that π-conjugation between nitrogen atoms and the thiocarbonyl group is weakened due to the steric hindrance between hydrogen atoms of the piperidine ring and the thioamide group.

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INTRODUCTION

One of topical issues of modern chemical science is the search for methods allowing the rational use of natural plant raw materials and the creation of new biologically active compounds based on them. In this aspect, of special interest are plant alkaloids which take a “privileged” position among naturally occurring compounds due to their peculiar structure and high practical value. Alkaloids attract attention primarily by their pharmacological activity; many of them turned out to be valuable drugs, which stimulated their comprehensive study, the synthesis of new derivatives, as well as the search and design of more complex structures and the analysis of the “structure-activity” relationship [1, 2].

Thiourea derivatives deserve a special attention among new biologically active derivatives of alkaloids. Many of them have not yet been fully understood in terms of their pharmacological activity and began to be intensively investigated. According to publications, many thiourea derivatives of naturally occurring compounds possess valuable pharmacological properties and can be used as antituberculous, antineoplastic, antiphlogistic, antimicrobial, and other therapeutically active substances [3-5].

EXPERIMENTAL

^{1}H NMR spectra were recorded on a JNN-ECA Jeol 400 spectrometer (399.78 MHz) using the DMSO-d_6 solvent. Chemical shifts were measured relative to the TMS internal standard. The melting points were determined on a Boetius

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apparatus. The reaction course and the purity of the obtained compounds were controlled by thin layer chromatography (TLC) on Silufol UV-254 plates in the aqueous 2-propanol–benzene–25% ammonia solution system (10:5:2). The plates were exposed to iodine vapor.

Synthesis of N-ethyl-N-cytisinocarbothioamide (1). Cytisine (1.9 g, 0.01 mol) was dissolved in ethanol; then, an ethyl isothiocyanate solution (0.95 g, 0.011 mol) in 5 mL of ethanol was added dropwise with vigorous stirring. The mixture was stirred for 10 h at 50-60 °C. The completion of the reaction was monitored by TLC. The solution was cooled; a white scaly precipitate was filtered off and washed with a small amount of cold ethanol. After recrystallization from ethanol 2.35 g (85%) of white substance **1** with m.p. 235-236 °C was obtained. The elemental analysis data for compound **1** corresponded to the calculated data for ($C_{14}H_{19}N_3OS$). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J, Hz): 0.89 (3H, t, $J = 7.2$, C17-H$_3$), 1.82-1.90 (2H, m, C16-H$_2$), 3.01-3.12 (2H, m, H-8), 3.25 (1H, quint, $J = 6.8$, H-9), 3.36-3.59 (5H, m, H-7, H-11, H-13), 4.71, 4.86 (2H, dd, $J = 12.9$, $J = 12.8$, CH$_2$-10), 6.08 (1H, dd, $J = 7$, $J = 1.4$, H-5), 6.15 (1H, dd, $J = 9.1$, $J = 1.4$, H-3), 7.25 (1H, dd, $J = 9.2$, $J = 6.9$, H-4), 7.37 (1H, s, NH).

Single crystal X-ray diffraction experiment. The unit cell parameters and the intensities of 8345 reflections (2965 independent, $R_{\text{int}} = 0.027$) were measured on a Bruker KAPPA APEX2 CCD diffractometer (MoK_α, graphite monochromator, φ,θ-scanning, $2.537 \le \theta \le 27.102°$) at 298 K.

Crystals of **1** are monoclinic, space group $P2_1$, $a = 8.0376(2)$ Å, $b = 9.3416(2)$ Å, $c = 9.4586(2)$ Å, $\beta = 92.604(1)°$, $V = 709.46(3)$ Å^3, $Z = 2$ ($C_{14}H_{19}N_3OS$), $M = 277.38$ g/mol, $d_{\text{calc}} = 1.298$ g/cm^3, $\mu = 0.224$ mm^{-1}. The initial set of measured intensities was processed and absorption correction was applied using SAINT [6] and SADABS [7] programs from the APEX2 software (multiscan, $T_{\min} = 0.7422$, $T_{\max} = 0.7790$).

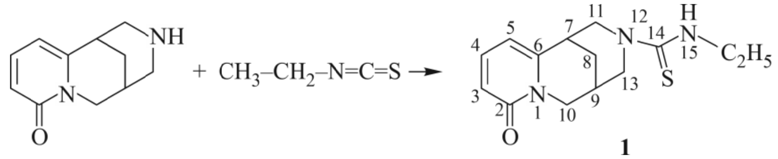
The structure was determined by a direct method. The positions of non-hydrogen atoms were refined in the anisotropic approximation by full-matrix LSM. The hydrogen atom of the amino group was located from difference maps; its position was refined in the isotropic approximation. The other hydrogen atoms were placed in geometrically calculated positions which were refined in the isotropic approximation with fixed positional and thermal parameters (riding model). 2864 independent reflections with $I \ge 2\sigma(I)$ were used in the calculations; the number of refined parameters was 177. The final divergence factors are $R_1 = 0.0298$, $wR_2 = 0.0314$ (for the reflections with $I \ge 2\sigma(I)$); $R_1 = 0.0779$, $wR_2 = 0.0798$ (for all reflections); $GOOF = 1.006$. The residual density peaks are $\Delta\rho = 0.171$ e/Å^3 and -0.157 e/Å^3.

The structure was determined and refined using SHELXS-97 [8] and SHELXL-2018/3 [9] software. The XRD data in the form of a CIF file have been deposited with the Cambridge Crystallographic Data Center (CCDC 1538196).

RESULTS AND DISCUSSION

It is known that the main method for synthesizing thioureas is the interaction of isothiocyanates with amines. Previously [3-5], we studied the interaction reactions of different isothiocyanates (allyl-, phenyl-, (vinyloxy)ethyl isothiocyanates, etc.) with cytisine, anabasine, and ephedrine alkaloids. In continuation of this research and to expand an arsenal of new biologically active substances with the thiourea moiety we performed the addition of cytisine alkaloid to ethyl isothiocyanate in an alcohol medium (Fig. 1).

The analysis of the ^{1}H NMR spectrum of compound **1** showed proton signals typical of the cytisine moiety. The H3–H5 protons at sp^2-hybridized C3–C5 carbon atoms appear in the downfield (6.08-7.25 ppm). The protons at sp^3 C7–C10,



1

Fig. 1. Crystal packing of the molecules of N-ethyl-N-anabasinocarbothioamide (**1**).

C11, and C13 carbon atoms resonate in a wide range of 3.01-4.86 ppm. Methyl (C17–H_3) and methylene (C16–H_2) protons of the ethylen group appear as a triplet at 0.89 ppm and a multiplet at 1.82-1.90 ppm respectively. The thioamide N15–H proton is a narrow singlet in the downfield spectral region at 7.37 ppm. The ratio of integral intensities corresponds to the structure of **1**.

To determine the spatial structure, we performed the single crystal X-ray diffraction analysis of N-ethyl-N-cytisinocarbothioamide (**1**) whose general view is depicted in Fig. 2. The configuration of chiral C7 and C9 centers is correlated with that known in the (–)-cytisine molecule [10]. The Flack parameter is 0.02(2) [11].

It is found that the bond lengths and bond angles in the cytisine core of the structure of **1** are normal [12], except the N12 bond angles. The dihydropyridine ring is planar with an accuracy of ±0.02 Å; the carbonyl O1 atom is almost in the plane of the atoms of this ring, the deviation is 0.11 Å. The tetrahydropyridine ring N1C6C7C8C9C10 takes a distorted 8α-*sofa* conformation ($\Delta C_S^8 = 8.3°$ [13]), with the bridging C8 atom being out of the mean plane of the other atoms of the ring by 0.73 Å (±0.04 Å). The piperidine ring is in a distorted *chair* conformation ($\Delta C_S^8 = 2.6°$, $\Delta C_2^{7,8} = 0.9°$).

It should be noted that the configuration of the nitrogen atom in the pyridine ring of the (–)-cytisine molecule is pyramidal, while it is planar trigonal in **1**. The pyramidal configuration of the nitrogen atom is observed in cytisine N-derivatives, where the addition of some groups does not result in conjugation of the nitrogen lone pair with their electrons. For example, in N-methylcytisine [10] and N-acetonylcytisine [14] molecules where there is no corresponding conjugation, the electronic configuration of the N12 atom is pyramidal (the sums of bond angles are 335.7° and 334.3° respectively).

When cytisine derivatives contain the carbonyl group conjugated with the nitrogen lone pair, the atomic configuration changes and becomes planar trigonal, such as in 3-bromo- (**2**) and 3-iodo-N-acetylcytisine (**3**) molecules [15]. This is explained by the mesomeric effect due to conjugation between the nitrogen lone pair and the double C=O bond. This effect also leads to some elongation of the C=O bond and a contraction of the N–C bond in the amide group relative to normal $C(sp^3)_2$–C=O of 1.210 Å and $N(sp^3$, pyramidal)–$C(sp^2)$ of 1.416 Å) [12]. Here, the $C(sp^3)$–N–C=O torsion angles are close to zero, which characterizes a high degree of conjugation. The respective geometric parameters of the molecules are given in Table 1.

The mesomeric effect is also observed when the carbonyl group is substituted by the thiocarbonyl group. Thus, in morpholine N-derivatives 2-(4-bromophenyl)-1-(morpholine-4-yl)ethanethione (**4**) [16] and 2-(4-methylphenyl)-1-

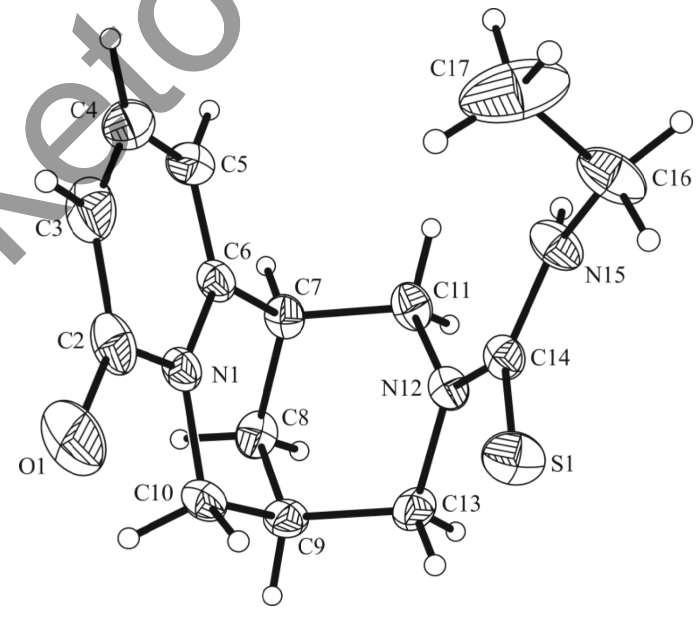


Fig. 2. Synthesis scheme of N-ethyl-N-cytisinocarbothioamide (**1**) (termal vibrational ellipsoids at a 30% probability level).

TABLE 1. Selected Geometric Parameters of Compounds **1-11**

Compound	Sum of bond angles ∑ω, deg		Bond length *d*, Å			Torsion angle τ, deg		C–H···H–N2 contact, Å; H–C···N2–H pseudo-torsion angle, deg.
	∑ω (N1)	∑ω (N2)	*d* (N1–C(sp^2))	*d* (N2–C(sp^2))	*d*(C=O), *d*(C=S)	τ(C–N1–C=S)	τ(C–N2–C=S	
–$(CH_2)_2$N1–C(=O)–C(sp^3)–								
2 [15]	360.0(3)	-	1.356(4)	-	1.228(4)	3.3(3)	-	-
3 [15]	359.9(7)	-	1.359(5)	-	1.209(5)	1.9(7)	-	-
–$(CH_2)_2$N1–C(=S)–C(sp^3)–								
4 [16]	359.7(8)	-	1.338(6)	-	1.659(6)	–3.3(8)	-	-
5[#1] [17]	359.7(12)	-	1.340(11)	-	1.696(9)	2.2(11)	-	-
	359.8(12)	-	1.330(11)	-	1.662(9)	–2.7(11)	-	-
–$(CH_2)_2$N1–C(=S)–N2H–C(sp^3)–								
1	359.8(3)	360.0(4)	1.360(3)	1.335(3)	1.693(2)	–13.0(3)	–10.8(4)	1.90; –41.1
6 [18]	358.8(2)	359.8(2)	1.363(2)	1.352(2)	1.700(1)	23.7(2)	18.6(2)	1.90; 49.7
7 [19]	357.6(5)	360.0(5)	1.354(4)	1.346(4)	1.699(3)	24.0(4)	8.2(4)	1.88; 47.7
8 [20]	356.9(3)	360.0(3)	1.354(3)	1.339(3)	1.695(2)	9.6(3)	–8.8(3)	1.80; 6.3
9 [22]	359.5(2)	358.7(2)	1.339(2)	1.346(2)	1.712(1)	–14.1(3)	–7.4(3)	1.98; –42.9
10[#1] [23]	360.0(7)	360.0(9)	1.317(6)	1.346(6)	1.704(5)	0.3(7)	–0.3(7)	2.19; –51.2
	360.0(8)	360.0(9)	1.330(6)	1.358(6)	1.688(5)	–1.0(6)	–1.6(7)	2.17; –54.5
11 [24]	360.0(2)	359.9(2)	1.348(1)	1.348(1)	1.703(1)	1.5(1)	–0.5(1)	2.16; –53.1 2.20; 60.7

[#1] Two crystallographically independent molecules.

(morpholine-4-yl)ethanethione (**5**) [17] the nitrogen atom has a planar trigonal configuration; an elongation of the C=S bond and a contraction of the N–C bond in the thioamide group (standard C(sp^3)$_2$–C=S bond is 1.559 Å) are observed [12]. There is also a high degree of conjugation of the nitrogen lone pair and the C=S bond (Table 1).

The addition of ethyl isothiocyanate to cytisine gives compound **1** containing the carbothioamide group, where the second N15 nitrogen atom with a planar trigonal configuration is also involved in conjugation with the C=S bond (Table 1). This configuration of N1 and N2 nitrogen atoms of the carbothioamide group is also observed in three cytisine derivatives: N-adamantylcytisine-12-thiocarbamide (**6**) [18], N-cytisinyl-N′-(2,3,4,6-tetrakis(O-acetyl)-β-D-glucopyranosil)thiocarbamide monohydrate (**7**) [19], cytisine-N-(2-hydroxyethyl)thiocarbamide (**8**) [20]. However, the C(sp^3)–N1–C=S torsion angle greatly deviates from zero in the molecules of **1**, **6-8**, compared to the respective angle in the molecules of **2-5**. The C(sp^3)–N2–C=S torsion angle also significantly deviates from zero in the molecules of **1**, **6-8**, which decreases the degree of conjugation of the N1 and N2 lone pairs with the C=S bond (Table 1).

The analysis of the molecular geometry of **1** revealed that it can be much facilitated by the short C11–H···H–N15 contact of 1.90 Å, which is significantly less than the sum of Van der Waals radii of hydrogen atoms (2.32 Å) [21]. This contact would be even shorter if the C11–N12–C14=S1 and C16–N15–C14=S1 torsion angles were smaller. Generally, the H–C13···N15–H pseudo-torsion angle is –41.1°. Such a contraction of the C–H···H–N2 contact with a large H–C···N2–H pseudo-torsion angle is observed in compounds **6**, **7**. In the molecule of **8** due to the formation of the intermolecular N2–H···O hydrogen bond (N···O distances of 3.021 Å, H···O of 2.02 Å, the N–H···O angle of 159°) the C–N2–C=S torsion angle takes a negative value relative to the C–N1–C=S angle, which results in an even greater contraction of the C–H…H–N2 contact to 1.80 Å (Table 1). The substitution of the 6-membered piperidine ring by the more labile 7-membered hexamethyleneimine ring, as in N-(((2-(4-chlorophenyl)ethyl)amino)thiocarbonyl)-7,8-dihydroxy-2,3,4,5-tetrahydro

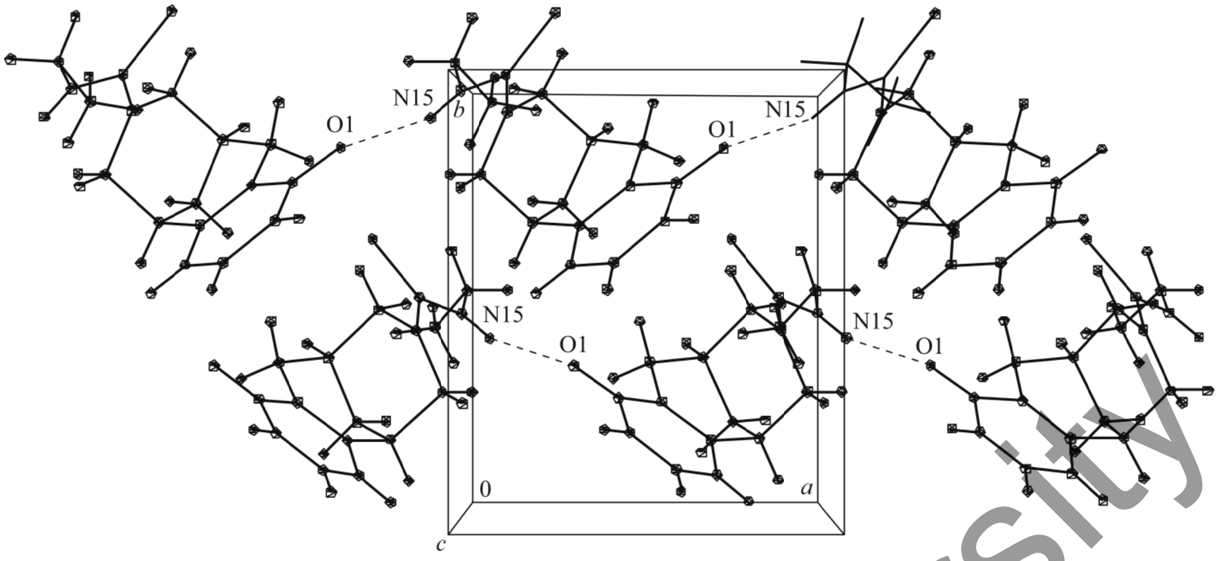


Fig. 3. Structure of N-ethyl-N-cytisinocarbothioamide (**1**) (thermal ellipsoids are shown at the 30% probability level).

benzacepine (**9**) [22], results in only a small increase in the C–H···H–N2 contact to 1.98 Å. Conversely, when the piperidine ring is substituted by a more rigid 5-membered pyrrolidine ring, as in N-methylrirrolidine-1-carbothioamide (**10**) [23], the C–H···H–N2 distance increases almost to the sum of hydrogen Van der Waals radii, leading to an increase in the degree of conjugation of N1 and N2 lone pairs with the C=S bond (Table 1). It should be noted that in the sterically unhindered 1,1,3-trimethylureas (**11**) molecule [24], with almost complete conjugation of π electrons of the carbothioamide group, the contacts of the hydrogen atom of the secondary amine with the nearest H atoms of the methyl group have similar values (Table 1).

In the crystal, the molecules of **1** form chains along the [*a*, 0, 0] direction due to weak N15–H···O1 hydrogen bonds (*x*+1, *y*, *z*) (distances N–H of 0.87(2), N···O of 2.812(2) Å, H···O of 2.00(2) Å, the N–H···O angle of 155(2)°) (Fig. 3).

Thus, our study showed that the addition reaction of the (–)-cytisine alkaloid to ethyl isothiocyanate in an alcohol medium produced N-ethyl-N-cytisinocarbothioamide in which the mesomeric effect between the nitrogen atom of the piperidine ring and the thioamide group was observed. It was found that the π-conjugation between the tertiary nitrogen atom and the thiocarbonyl group and between the secondary nitrogen atom and the thiocarbonyl group was weakened due to the steric hindrance between hydrogen atoms of the piperidine ring and the thioamide group.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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