CRYSTALSOLVATES OF *N*-(3-ETHYLTHIO-1,2,4-THIADIAZOL-5-YL-AMINOCARBONYLMETHYL)CYTISINE

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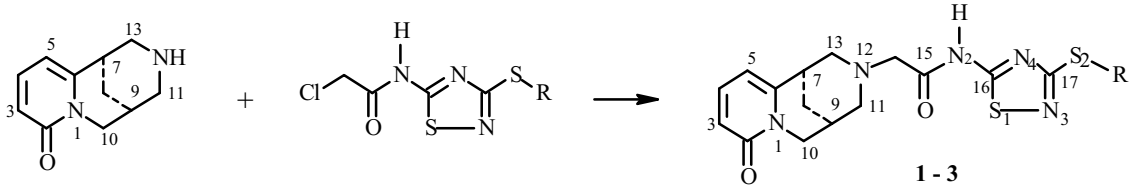
The crystal structures of N-*(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine with waters of hydration, water and methanol, and acetone were studied by x-ray diffraction. Three conformers formed by rotation of the 3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl moiety relative to the cytisine core were detected in the studied crystal structures. Different conformations of* N-*(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine and intermolecular H-bonds may have favored formation of different crystal solvates depending on the crystallization conditions.*

Key words: alkaloids, cytisine derivatives, solvate morphology, x-ray diffraction analysis.

Chemical transformation of the alkaloid cytisine [1-4] and its pharmacological properties and structure—activity relationships [2, 3] have recently been of great interest. This is due to the broad spectrum of their biological activity and the unique behavior of cytisine in chemical conversions. Cytisine contains several active centers that can react with receptors. Therefore, the introduction of additional heterocyclic pharmacophores can enhance known activity or produce new pharmacological properties.

In continuation of our research on the chemical modification of cytisine, we synthesized its 1,2,4-thiadiazole derivatives [5] by alkylation of cytisine using 3-alkylthio-5-chloroacetylamino-1,2,4-thiadiazoles on the scheme:



1 - 3

R = $(CH_2)_n$-CH_3, where n = 0 - 5

n = 1 · H_2O (**1**)

· 0.5 H_2O · CH_3OH (**2**)

· 0.5 $(CH_3)_2CO$ (**3**)

We observed polymorphism and different solvates during a study of the crystal structure of *N*-(3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine (n = 0). Solvent molecules were included as solvates in the crystals [6]. It seemed interesting to explain the formation of polymorphs and different solvates in crystal structures of *N*-(3-alkylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisines with bulkier substituents on the S atom, e.g., ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, and *n*-hexyl (n = 1-5).

Therefore, we attempted to prepare single crystals suitable for x-ray diffraction analysis (XDA) from various common solvents using the aforementioned cytisine derivatives at various temperatures, e.g., in a refrigerator (0-4°C), thermostatted (45°C), and at room (20-25°C) temperature. In contrast with *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine (n = 1), we could not grow single crystals suitable for XDA of the other 1,2,4-thiadiazolylcytisines containing relatively bulkier substituents on the S atom (C_3-C_6, n = 2-5, respectively).

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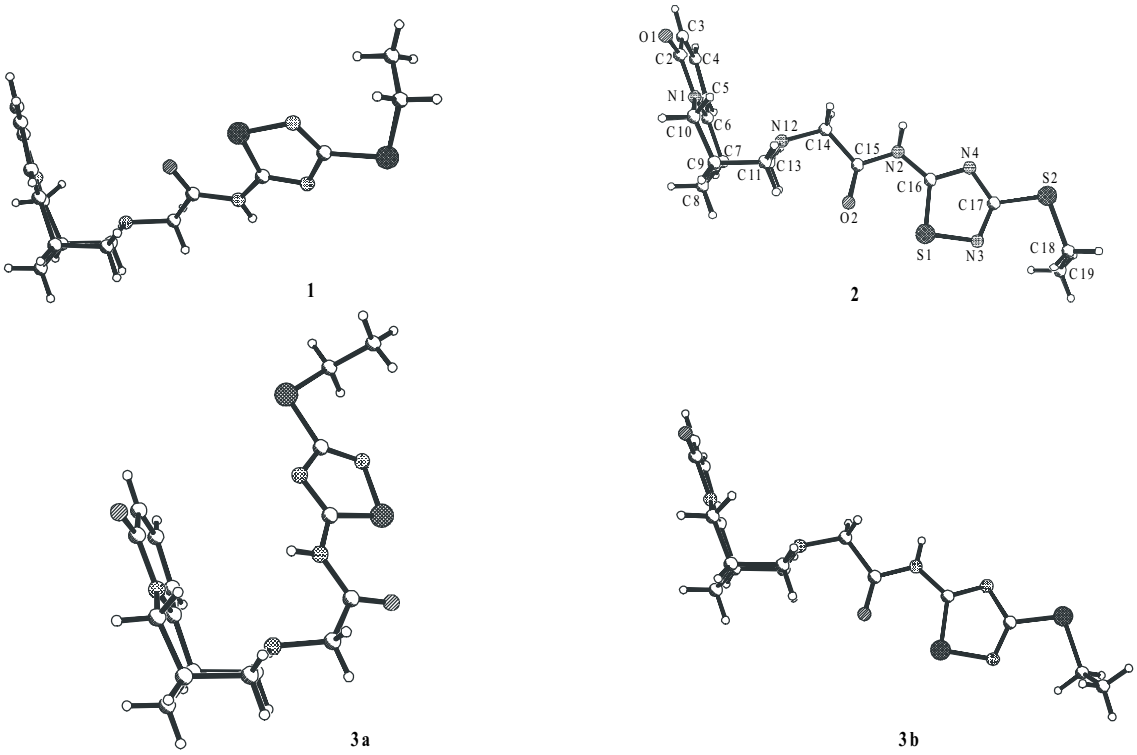


Fig. 1. Molecular structures of **1**-**3**.

We observed in the preliminary stages of the XDA that single crystals of *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine (n = 1) grown in various solvents [aqueous ethanol (**1**), aqueous methanol (**2**), absolute acetone (**3**)] had different unit-cell constants and space groups. This meant that the single crystals were different solvates (or polymorphs) and *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine, like the methyl derivative (n = 0), behaved like a host for solvent molecules. In order to explain the reasons for these effects and the nature of the host—guest intermolecular interactions, we performed XDA of *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine crystals grown under the aforementioned conditions.

Judging from the XDA, crystals of **1**, **2**, and **3** contained water molecules, methanol + 0.5 water molecules, and acetone, respectively, i.e., solvates were included. Two molecules of *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine (n = 1) in different conformations and one acetone molecule made up the asymmetric unit in crystals of **3**. Crystals grown from aqueous ethanol and acetone grew as hydrates (**1**), like that observed in *N*-(3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine (n = 0) [6].

Figure 1 shows the structures of the *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisines in crystals (**1**-**3**) in approximately the same projection (perpendicular to the plane of C7, C9, C11, and C13). The conformation of the relatively rigid cytisine core of these structures did not differ and was practically the same as that found for cytisine itself [7-9] and its various N12-derivatives [3, 6, 10, 11].

The bulky 3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl fragment (atoms N12–...–C18) in all four independent molecules was practically planar within ±0.103 (**1**), ±0.030 (**2**), ±0.138 (**3a**), and ±0.039 (**3b**) Å. The positions of the carbonyl and S–CH_2CH_3 groups in this fragment (*syn*-, anti-) relative to the five-membered ring in **1**, **2**, **3a**, and **3b** were almost identical. The carbonyl and S1 of the thiadiazolyl ring were mutually *cis*, which favored formation of an intramolecular interaction S1...O2 [2.606(3) Å (**1**), 2.620(3) (**2**), 2.681(5) (**3a**), 2.628(3) (**3b**)]. Invertomers (viewed as *Z*- and *E*-isomers) that could arise because of hindered rotation around the N2–C15 bond were not found in these structures.

TABLE 1. Torsion Angles Around –N12–C14–, –C14–C15–, and –C17–S2– Bonds Characterizing Conformations in Structures of **1-3** {Conformers **a-d** Found in Crystal Solvates and Polymorphs of *N*-(3-Methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine (n = 0) [6]}

Structure	C11-N12-C14-C15	N12-C14-C15-N2	N3-C17-S2-C18
a*	−142.0	3.5	177.4
b*	−166.2	−171.1	2.3
c	65.0	176.2	−0.4
d	−161.7	44.8	−4.5
1	−171.7	−162.7	18.4
2	64.7	−179.4	−2.5
3a	−161.3	37.6	−11.7
3b	67.0	172.8	1.9

*Average values are given.

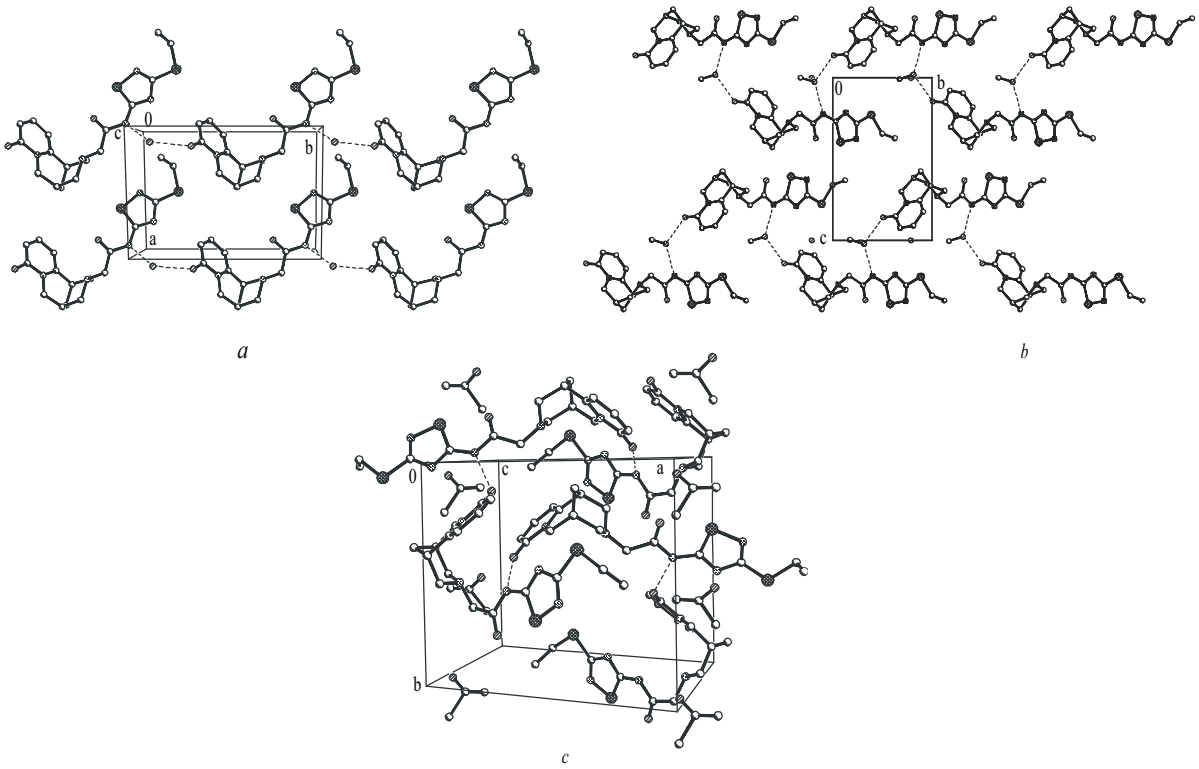
The conformation in the crystals varied because of rotation around the N12–C14 and C14–C15 bonds of the almost planar 3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl fragment. Figure 1 and Table 1 show that this fragment (N12–...–C18 portion) in the structures of **2** and **3b** is placed practically the same relative to the cytisine core (not considering the orientation of the terminal methyl) whereas the other conformers differ from each other. Therefore, three conformers similar to conformers occurring in crystal solvates and polymorphs of *N*-(3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine were observed in the four independent molecules of *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine.

Four conformations (**a-d**) of the host molecule were observed previously in crystal solvates and polymorphs of *N*-(3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine [6]. The numerical values in Table 1 show that the molecules in **1** and **3a** adopted conformations **b** and **d**, respectively; in **2** and **3b**, conformation **c**, i.e., the same conformers that were characteristic for the methylthiadiazolyl cytisine derivative (n = 0) were observed in the ethylthiadiazolyl cytisine derivative (n = 1) (Table 1).

Thus, the molecular structures of *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine in the structures of **1-3** revealed that three conformers differing in the placement of the thiadiazolyl fragment relative to the cytisine core were observed in the four independent molecules.

Figure 2a shows the molecular packing in crystal hydrate **1**. Intermolecular H-bonds involving water molecules through >N2–H2...O1w and O1w–H2w...O1=C2< schemes were observed in the crystal. Molecules of *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine formed an infinite chain along the *b* axis through waters of crystallization. The parameters of the N2–H2...O1w H-bond were N2...O1w, 2.797(4) Å and H2...O1w, 1.96 Å; angle N2–H2...O1w, 165.3°. For the next H-bond (O1w–H2w...O1), these parameters were 2.761(4) and 1.85 Å and 169.2°. The molecular packing of **1** [in the hydrate of *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine] was isostructural with that observed in the hydrate of *N*-(3-methylthio-1,2,4-thiadiazol-5-ylaminocarbonylmethyl)cytisine [6]. This was consistent with the similarity of the unit-cell constants and the same space group. A small difference was noted only in the *a* axis [8.344(3) and 8.003(5) Å, respectively] and the monoclinic β angle [103.31(3)° and 99.52(5)°, respectively]. The differences in the other values were insignificant.

Figure 2b shows the molecular packing in the crystal of **2**. Analysis of the crystal structure of **2** found intermolecular H-bonds involving the methanol according to the scheme >N2–H...Om–H and Om–H...O1=C2<. The parameters of the H-bonds were N2...O1m, 2.721(5) and H2...O1m, 1.90 Å; angle N2–H2...O1m, 163.5°; O1m...O1, 2.656(5) and H1m...O1, 1.78 Å; angle O1m–H1m...O1, 168.6°. An infinite chain along the *b* axis was formed by these H-bonds. Furthermore, a weak intermolecular S1...S1 interaction [S1...S1(1-x, y, 1-z), 3.573(2) Å] was observed. The waters of crystallization were located in special positions and occupied voids at Van-der-Waals distances and were not involved in forming intermolecular H-bonds.



a *b* *c*

Fig. 2. Packing diagram of **1** (a), **2** (b), and **3** (c).

The acetone of crystallization in the structure of **3** was located in voids of the host molecule packing (Fig. 2c). It was not involved in intermolecular interactions although the host molecules were located at Van-der-Waals distances from the acetone and intermolecular H-bonds were found in the structures of **1** and **2** for the solvate molecules. The acetone molecule had anomalously large thermal parameters because of the lack of such interactions. Its geometry was determined with large uncertainties.

The crystal of **3** did contain intermolecular H-bonds N–H...O=C between conformationally different host molecules (**3a** and **3b**). Successively placed molecules of **3a** and **3b** formed an infinite ribbon along the *b* axis. The parameters of these H-bonds were N2...O1′, 2.910(6), H2...O1′, 2.04 Å; angle N2–H2...O1′, 145.2°; N2′...O1, 2.690(5), H2′...O1, 1.67 Å; angle N2′–H2′...O1, 161.7°.

Thus, *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine, like *N*-(3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine, forms various solvates and is a potential host molecule (clathrate generator). The different conformations of *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine and the intermolecular H-bonds may favor formation of different crystal solvates (possibly polymorphs) depending on the crystallization conditions (medium effect).

EXPERIMENTAL

The synthesis and spectral characteristics of *N*-(3-alkylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisines have been published [5]. It was difficult to grow single crystals of the different solvates of *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine that were suitable for XDA. Single crystals of other 1,2,4-thiadiazoles with bulkier alkyl substituents (C_3-C_6 with n = 2-5, respectively) on the S atom could not be grown (white powders formed on the bottom of the containers). Single crystals for the XDA were obtained by slow evaporation of the appropriate solvents at room temperature.

X-ray Diffraction Analysis. The unit-cell constants of crystals of **1**-**3** were determined and refined on a Stoe Stadi-4 diffractometer (T = 300 K, graphite monochromator). Table 2 lists the principal parameters of the x-ray structure analysis and the calculations. A three-dimensional data set of reflections was obtained on the same diffractometer by ω/2θ-scanning using Cu Kα-radiation for crystals of **1** and **3**; Mo Kα-radiation, for **2**. Absorption corrections were applied using psi-scans for **1** and **3**.

TABLE 2. Principal Crystallographic Parameters and X-ray Diffraction Characteristics for Structures of **1-3**

Structure	**1**	**2**	**3**
Molecular formula	$C_{17}H_{21}N_5O_2S_2 \cdot H_2O$	$C_{17}H_{21}N_5O_2S_2 \cdot 0.5\ H_2O \cdot$	$2(C_{17}H_{21}N_5O_2S_2)\cdot(CH_3)_2CO$
MW	409.52	CH_3OH	841.09
System	Monoclinic	432.56	Monoclinic
Space group	$P2_1$	Monoclinic	$P2_1$
Z	2	C2	2
a, Å	8.344 (3)	4	14.262 (5)
b, Å	11.867 (5)	20.725 (4)	11.119 (6)
c, Å	9.996 (4)	8.050 (2)	14.430 (7)
β	103.31 (3)	14.654 (3)	111.62 (3)
V, Å^3	963.2 (7)	117.06 (3)	2127.2 (18)
ρ, g/cm^3	1.412	2177.2 (7)	1.313
Crystal size, mm	0.80×0.58×0.31	1.320	0.80×0.75×0.50
2θ scanning range	3.0≤θ≤60.0°	0.85×0.80×0.75	3.0≤θ≤60.0°
μ_{exp}, mm^{-1}	2.75	1.5≤θ≤27.5°	2.49
Number of reflections	1507	0.28	3342
Number of reflections I>2σ (I)	1485	2688	3173
R_1 (I>2σ (I) and total)	0.029 (0.030)	2431	0.046 (0.049)
wR_2	0.080 (0.080)	0.053 (0.060)	0.121 (0.125)
S	1.04	0.146 (0.154)	1.08
Electron-density difference peaks	0.17 and -0.23 e Å^{-3}	1.11	0.25 and -0.26 e Å^{-3}
		0.60 and -0.35 e Å^{-3}	

The structures of **1-3** were solved by direct methods using the SHELXS-97 programs. Structures were refined using the SHELXL-97 program. All nonhydrogen atoms were refined by full-matrix anisotropic least-squares methods (over F^2). The positions of H atoms were located geometrically and refined with fixed isotropic thermal parameters $U_{iso} = nU_{eq}$, where n = 1.5 for methyls and 1.2 for others and U_{eq} was the equivalent isotropic thermal parameter of the corresponding C atoms. H atoms of amino groups, waters, and hydroxyls were found in difference electron-density syntheses and were refined using the rigid-body model (AFIX 3). Bond lengths of the acetone in **3** were reduced to normal values [12] using DFIX.

The data from the XDA were deposited as CIF-files in the Cambridge Crystallographic Database (CCDC 674781, 674782, 674783 for **1-3**, respectively).

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