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ORIGINAL ARTICLE

# 1,2,4-Thiadiazol derivatives of cytisine alkaloid: solvate formation and phase transitions

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**Abstract** 1,2,4-Thiadiazol derivatives of cytisine alkaloid—*N*-(3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl) (**1**), *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl) (**2**), *N*-(3-hexylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl) (**3**) cytisine have been crystallized from different solvents and by X-ray and TG–DSC method were studied. By X-ray analysis the structures of the crystal solvate of **2** with dioxane have been determined. By topology represented solvate belongs to tabulate type. In the crystal structure two conformers of the host molecules were determined. By TG–DSC method has been shown, that methyl-, ethyl-, and hexyl cytisine derivatives can exist in two phase forms. But, unlike methyl- and ethyl-derivatives, hexyl-derivative of cytisine not form inclusion compounds.

**Keywords** Alkaloids · Cytisine derivatives · X-ray single-crystal diffraction · Thermogravimetric analysis

## Introduction

Cytisine alkaloid and its derivatives attract considerable attention of researchers due to a broad spectrum of physiological activities [1, 2] and peculiarity of chemical transformations [3, 4]. As the continuation of studies on chemical transformation, cytisine derivatives containing 1,2,4-thiadiazole fragment have been synthesized according to the Scheme 1 [4]:

Previous X-ray investigation of *N*-(3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine (**1**) and *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl) cytisine (**2**) crystals, obtained in different solvents have showed their unique ability to form solvates [5–7]. For compound **1** ($n = 0$) the solvates with water, methanol, benzene, chloroform, pyridine, 1,4-dioxane were obtained [6], for compound **2** ($n = 1$) the solvates with water, water/methanol, acetone were obtained [7]. Also three polymorph modifications of cytisine derivative **1** have been obtained [6]. Total amount structures of the compound **1** and **2** solved by X-ray method is 12 (9 solvates and 3 polymorphs).

However, all our attempts to get the monocrystals of 1,2,4-thiadiazol cytisine derivatives, containing more bulky substitutes at sulphur atom (C3–C6, $n = 2$–5) were unsuccessful and in all cases it was the powder-like mass. In this connection, it was decided to use TG–DSC method to study solvate formation and phase transition of above-mentioned objects.

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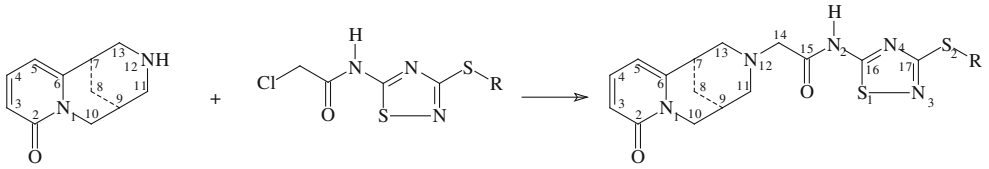
## Experimental

### Synthesis

Synthesis and spectral characteristics of *N*-(3-alkylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisines are described in [4].



R = $(CH_2)_n$-$CH_3$, where n=0 – 5

**Scheme 1** The synthesis of N-(3-alkylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisines

### Recrystallization

Monocrystals for X-ray analysis are obtained by slow evaporation of **2** solution in 1,4-dioxane at room temperatures.

### Molecular modelling

Conformation calculations on the molecular mechanics were made with the "MOPAC2009" program package [8]. An energetic surface is drawn with the program "Surfer 9 Demo" [9].

### Thermal analysis

The TG–DSC measurements were carried out with a Netsch Simultaneous Analyzer STA 409 PG equipped with a TG–DSC sample carrier supporting a type K (Low RG Silver) thermocouple and aluminium crucibles. All investigations were done in nitrogen atmosphere with nitrogen flow rate of 60 mL $min^{-1}$. The temperature range was 20–330 °C at a heating rate of 5 K $min^{-1}$. The sample mass was 6 mg. The measuring system was calibrated with standard compounds: potassium nitrate, indium, bismuth, tin, zinc and cesium chloride.

### X-ray experiment

Cell dimensions were established from the intensity data measurements on CCD Xcalibur Ruby (Oxford Diffraction) diffractometer using graphite-monochromated Cu Kα radiation. The strategy for the data collection was evaluated using CrysAlisPro [10] software. The structure was solved by direct methods using the SHELXS [11] program of the SHELXTL package and refined by least-squares with SHELXL [12, 13]. In the structure, the positions of all non-hydrogen host atoms were obtained by direct methods and the non-hydrogen guest atoms were located in difference electron density maps. All non-hydrogen atoms were refined with anisotropic temperature factors. Hydrogen atoms were placed with geometric constraints and refined with isotropic temperature factors. Crystallographic data for **2** dioxane solvate are given in Table 1.

**Table 1** Crystal data, experimental and refinement parameters

| | |
|---|---|
| Structure | **2**/dioxane |
| Molecular formula | $2(C_{17}H_{21}N_5O_2S_2)\cdot 1.5C_4H_8O_2$ |
| $M_r$ | 913.12 |
| Crystal symmetry | Monoclinic |
| Space group | *C*2 |
| Z | 4 |
| *a* (Å) | 25.053(5) |
| *b* (Å) | 11.579(2) |
| *c* (Å) | 15.674(3) |
| *β* (°) | 93.65(3) |
| V ($Å^3$) | 4537.7(16) |
| *ρ* ($g/cm^3$) | 1.322 |
| Temperature (K) | 100 |
| Crystal dimension (mm) | 0.50 × 0.35 × 0.15 |
| Range scanned, 2*θ* (°) | 7.06–141.29 |
| $\mu_{exp}$ ($mm^{-1}$) | 2.41 |
| No. reflection collected | 17138 |
| No. reflection with $I > 2\sigma(I)$ | 8216 |
| $R_1$ ($I > 2\sigma(I)$ and total) | 0.0386 (0.0414) |
| $wR_2$ | 0.1044 (0.1065) |
| S | 1.029 |
| Largest diff. peak and hole (e $Å^{-3}$) | 0.445; −0.290 |

## Discussion of results

### Crystal structure

Solvate **2** with dioxane crystallizes in space group *C*2 (Z = 4) with two host molecules of *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine with different conformation and 1.5 guest molecules dioxane in the independent unit. One of guest molecules occupies general and another one occupies special position (on twofold axis). Despite the fact, that the experiment have been carry out at low temperature (100 K), atoms of methylene groups of dioxane molecule, occupying general position are disordered by two positions (0.54:0.46, respectively).

The conformation of two asymmetric molecules of (*N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl) cytisine (**2a**, **2b**) is shown on Fig. 1 in identical projection.

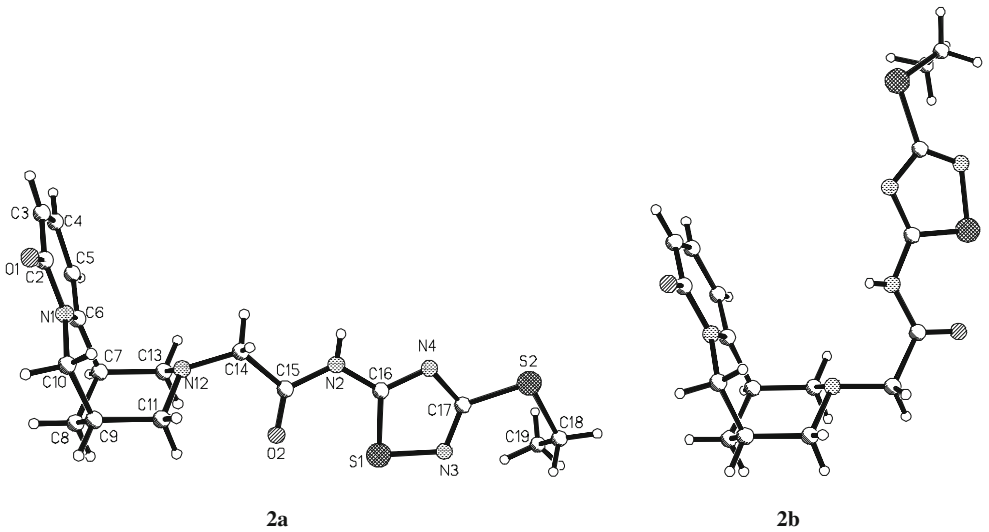



**Fig. 1** The conformation and numbering of atoms in two asymmetric molecules **2** in the crystal

**Table 2** The torsion angles(°) between N12–C14– and –C14–C15– bonds—in the molecules **2a**, **2b** and in other known crystal solvates and polymorphs of 1,2,4-thiadiazolyl derivatives of cytisine (conformers **a**–**d**)[a] [5–7]

| Conformers | C11–N12–C14–C15 | N12–C14–C15–N2 |
|---|---|---|
| **a** | −142.0 | 3.5 |
| **b** | −166.2 | −171.1 |
| **c** | 65.0 | 176.2 |
| **d** | −161.7 | 44.8 |
| **2a** | 72.1 | 165.2 |
| **2b** | −168.8 | 40.0 |

[a] Average values given

As shown on Fig. 1, the conformation of the rigid cytisine moieties in these molecules not differ one from another and agree with early founded conformation of cytisine [14–16] and its N12-derivatives [3, 17, 18].

The bulky 3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl-fragment (atoms N12–···–C18) in both host molecules of the asymmetric unit are almost planar with accuracy of ±0.047 Å (**2a**), ±0.159 (**2b**) Å (without taking account end methyl group). In this flat fragment *sin*-, *anti*-arrangement of carbonyl and S-$CH_2CH_3$ groups relatively to five-membered rings in the molecules **2a** and **2b** is same. *Sin*-orientation of the carbonyl group and atom S1 of thiadiazolic ring determine the intermolecular short contact S1···O2 (2.708(2) Å (**2a**), 2.558(2) Å (**2b**)). Differences between molecules **2a** and **2b** due to intra-molecular rotations around –N12–C14– and –C14–C15 bonds. The values of torsion angles of bonds—characterizing conformation mobility of molecules **2a** and **2b**, and also their values in others conformers (**a**–**d**), realized in known

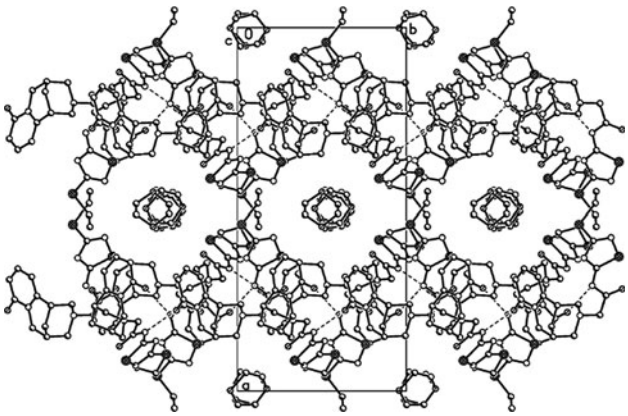


**Fig. 2** Crystal packing of the **2**/dioxane solvate. Hydrogen atoms are omitted for clarity

crystal solvates and polymorphs of 1,2,4-thiadiazolyl derivatives of cytisine, are shown in Table 2.

As it is shown in Table 2, the conformation of the two asymmetric molecules of *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine **2a** and **2b** practically do not differ from conformers **c** and **d**, realized in others known crystal solvates and polymorphs of *N*-(3-methyl-[5,6] and *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl) cytisines [7].

The packing of **2**/dioxane solvate is shown of the Fig. 2. In the crystal structure the host molecules **2a** and **2b** are united via N2(**2a**)–H···O1(**2b**) and N2(**2b**)–H···O1(**2a**) intermolecular H-bonds (Table 3) forming the endless one dimensional chains in [010] direction. As result of packing of these chains, in the crystal structure the system of channels running in [001] direction is formed. Inside of these channels dioxane molecules located without forming specific host–guest interactions (true clathrates).

**Table 3** H-bonds in the **2**/dioxane solvate

| Atoms involved | D–H (Å) | H···A (Å) | D···A (Å) | D–H∠A (°) | Symmetry codes for acceptors |
|---|---|---|---|---|---|
| N2(**2a**)–H···O1(**2b**) | 0.83(3) | 1.85(3) | 2.675(3) | 175(3) | |
| N2(**2b**)–H···O1(**2a**) | 0.72(3) | 2.16(3) | 2.789(3) | 147(3) | 1/2 − x, 1/2 + y, 1 − z |

The crystal packing is mainly stabilized by van der Waals forces. For this reason, the disordering of the guest molecules is observed even at low temperatures (100 K). It is necessary to notice, that in all previously investigated crystal solvates of *N*-(3-methyl- and *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisines solvent molecules are located in the closed cryptate type cavities [5, 6, 19], their sizes vary from 15 to 529 $Å^3$ depending on the volume of a solvent molecule.

## Molecular modelling

Discovery four conformers (**a**–**d**) in all studied crystals of *N*-(3-methyl-, ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisines suggested an idea to estimate a conformation mobility of the planar 3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl fragment by a method of molecular mechanic [20].

For this reason the rotation of above mentioned fragment (in isolated medium) around cytisine moiety has been simulated by changing the values of torsion angles around N12–C14 and C14–C15 bonds by every 10° up to 360°. Special conditions affecting conformational change of cytisine moiety and ethyl group have not been applied. The results of calculation are given in Fig. 3 as three-dimensional diagram with various hollows, wells and prohibited areas. This data can be applied also to the molecule **1** because the replacement of ethyl group of **2** by methyl group should not cause considerable change of potential surface.

As can be seen from potential surface (Fig. 3) of tension energy of *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine, there are observed a wide potential hole (in range −180° to 50° and −60° to 110° of C11–N12–C14–C15 and N12–C14–C15–N2 torsion angles, accordingly) and minimum values as the channel (in range of 55–105° of C11–N12–C14–C15 torsion

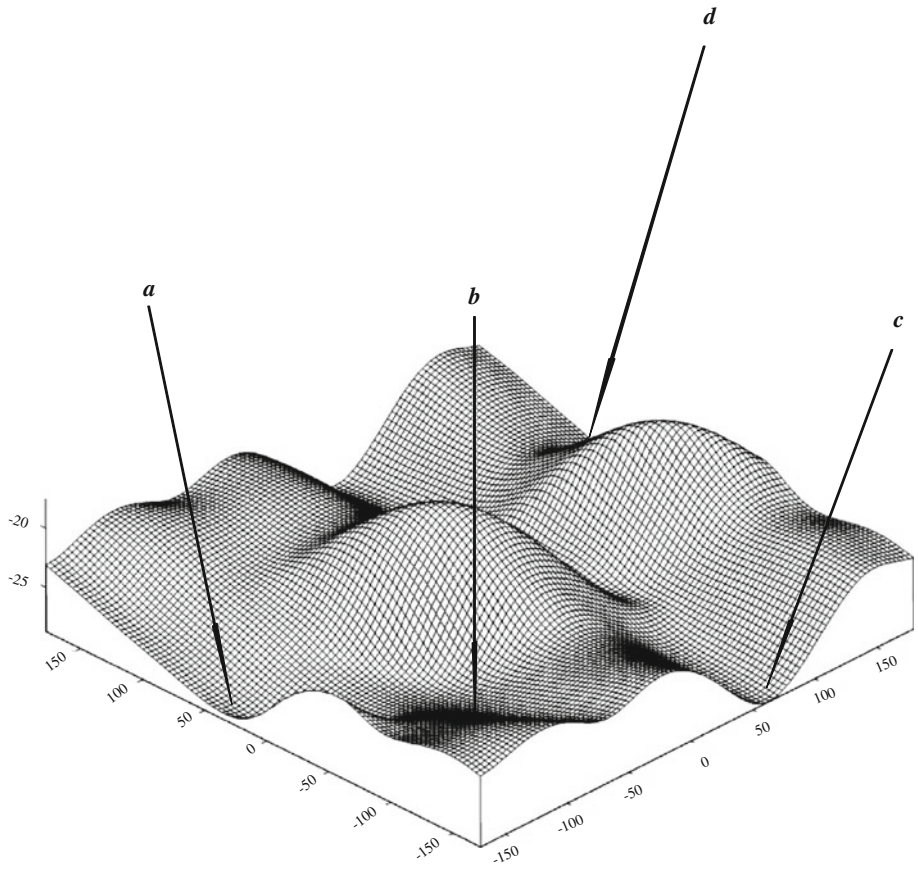



**Fig. 3** Diagram of potential surface of 3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl fragment rotation around cytisine moiety in the molecule **2** (conformations **a**–**d** from X-ray data)

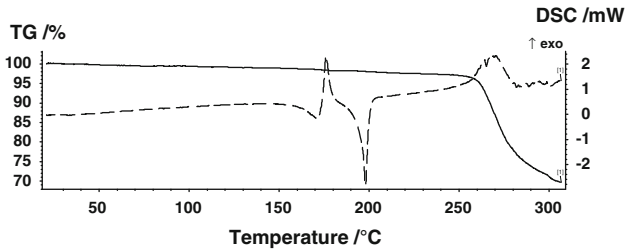



**Fig. 4** TG–DSC curve for product of crystallization **1** from DMFA

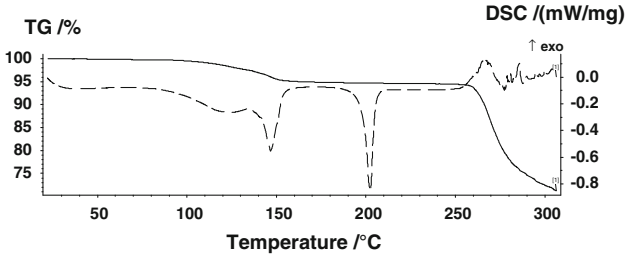



**Fig. 5** TG–DSC curve for solvate **1** with acetonitrile

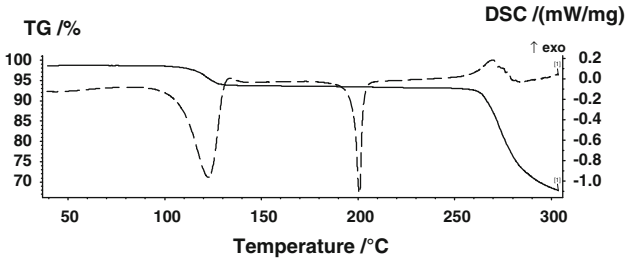



**Fig. 6** TG–DSC curve for solvate **1** with toluene

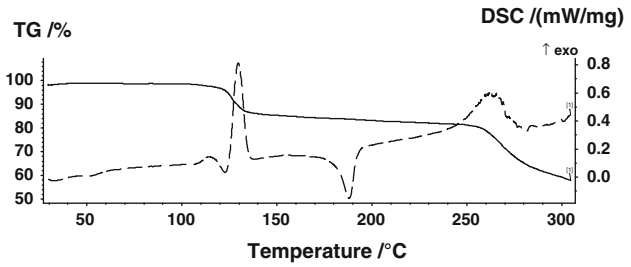



**Fig. 7** TG–DSC curve for solvate **1** with *o*-xylene

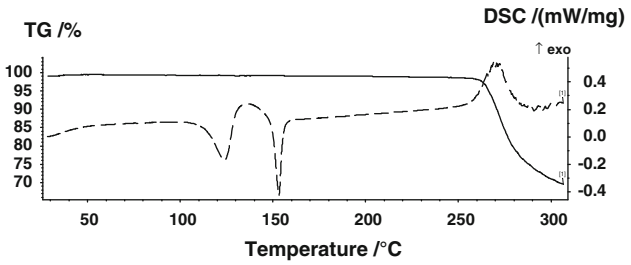



**Fig. 8** TG–DSC curve for product of crystallization **2** from acetonitrile

angles). Torsion angles corresponding to minimum areas of surface are in close agreement with **a**, **c** and **d** conformations observed in the crystals. It is remarkable, that in range of 55–105° of C11–N12–C14–C15 torsion angles, N12–C14–C15–N2 torsion angle can accept any values, i.e. takes place free rotation of thiadiazol fragment around C4-C15 bond. Experimentally found conformation of **a** (−142.0° and 3.5°) and **d** (−161.7° and 44.8°) are located in the field of a wide potential hole, and conformation of **c** (65.0° and 176.2°) is located in the field of energetic channel minimum.

Closeness of 2 theoretical energetic minimum values ($\Delta E_{tension} \approx 2$ kcal/mol) and flatness of general potential surface (except for some prohibited zones) give evidence of conformational lability of 1,2,4-thiadiazol-5-yl-aminocarbonylmethyl fragment around cytisine moiety in a wide range of torsion angles. Apparently, packing factor, including the principle of the tightest packing with favorable intermolecular forces, is responsible for **b** conformation in the crystal.

## TG–DSC investigations

Powder-like products of crystallization of compound **1**, **2** and **3**, obtained from various solvents were studied by TG–DSC analysis to determine including ability, solvate stoichiometry of cytisine derivatives and their possible phase transitions caused by heating. Results of investigations are shown in Figs. 4, 5, 6, 7, 8, 9, and 10.

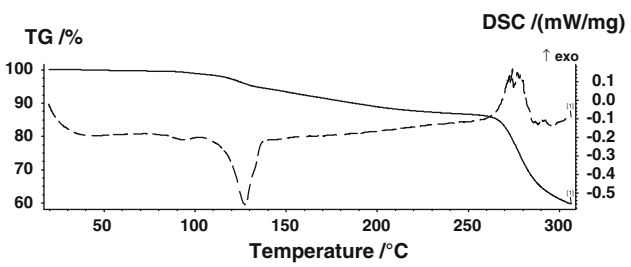



**Fig. 9** TG–DSC curves for solvate **2** with dioxane

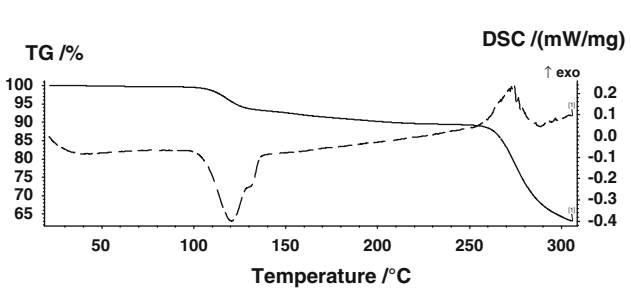



**Fig. 10** TG–DSC curves for solvate **2** with toluene

*TG–DSC analysis of N-(3-methylthio-1,2,4-thiadiazol-5-yl-amino-carbonylmethyl)cytisine (**1**) solvates*

The **1** crystallized from DMFA, acetonitrile, *o*-xylene and toluene. The products of crystallization were studied by TG–DSC method. The results have shown, that with all solvents, except for DMFA methylcytisine forms solvates. The Fig. 4 shows TG–DSC curves of **1** crystallized from DMFA. In the temperature interval 20–260 °C the sample mass is constant, but on DSC diagram endothermic (171 °C), exothermic (176 °C) and endothermic (198 °C) peaks were observed. The first peak corresponds to the melting of the polymorphic form I, second exothermic peak corresponds to crystallization of the form II, which melts at 198 °C. Thus, with DMFA compound **1** does not form solvate.

Solvate of **1** with acetonitrile is stable up to 110 °C (Fig. 5). In the temperature range of 110–160 °C mass loss of 5% is observed, which corresponds to the host:guest ratio of 2:1. As mass loss takes place, the endothermic peak (147 °C) is observed. The next endothermic peak (202 °C) corresponds to the melting point of **1**. The absence of the re-crystallization exothermic peak just after the endothermic peak related to the release of a guest molecule means that molecule **1** in the complex with acetonitrile is in the form II.

Also the molecule **1** in the complex with toluene is in the form II (Fig. 6). The release of guest components occurs in one stage in the interval of 110–135 °C and mass loss is 6,3% that corresponds to the 3:1 host–guest stoichiometry of the solvate. The further heating of the sample leads to the melting of the form II at 201 °C.

Solvate of **1** with *o*-xylene is stable up to 110 °C (Fig. 7). The further heating leads to the loss of guest components ($\Delta m = 13\%$), that corresponds to the 2:1 host–guest stoichiometry of the solvate. In this solvate molecule **1** exists in the form I, because just after the endothermic peak ($T_{max} = 123$ °C) the exothermic peak (130 °C) is observed. Thus, while losing a guest molecule, the initial form I of molecules **1** transform to the form II. Further heating leads to melting at 188 °C.

*TG–DSC investigation of N-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine (**2**) solvates*

For TG–DSC investigation the samples of **2** crystallized from acetonitrile, dioxane and toluene have been used. As it is shown in the Fig. 8 from acetonitrile **2** crystallizes forming a polymorphic modification I, which melts at 125 °C (endothermic peak); afterwards a new polymorphic form II crystallizes (exothermic peak 138 °C) which melts at 152 °C (endothermic peak).

From dioxane and toluene compound **2** (Fig. 9) crystallizes as solvates, which is in agreement with TG–DSC data. Solvate with dioxane is stable up to 115 °C, and at higher temperature the mass loss in conjunction with endothermic process is observed. Mass loss of 5.35% corresponds to the initial 4: 3 host–guest stoichiometry in the solvate of **2**. Apparently, in the solvate with dioxane, **2** exists in the form I and while dioxane molecule is released from the solvate, melting of **2** occurs. The formation of the form II is not observed.

The similar pattern is observed for the complex of **2** with toluene (Fig. 10). The mass loss observed in the interval of 110–140 °C is 6.56%, which corresponds to the initial 4:3 host–guest ratio in the solvate formed by **2** with toluene. Here also compound **2** is in the form I and its transition to the form II is not observed.

*TG–DSC investigations of N-(3-hexylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine (**3**)*

TG–DSC study has shown (Fig. 11), that crystallization of the compound **3** from acetone (curve 1), acetonitrile (curve

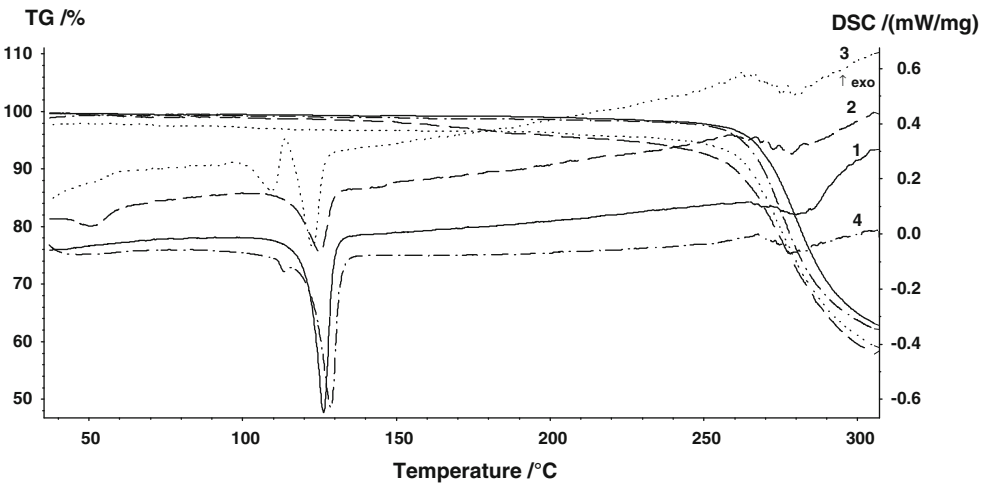



**Fig. 11** TG–DSC curves of the products of crystallization **3** from: acetone (*1*), acetonitrile (*2*), ethyl acetate (*3*), and toluene (*4*)

2), ethyl acetate (curve 3), and toluene (curve 4) does not lead to the formation of solvates. However, from DSC curves it can be seen, that **3** also has two polymorphic modifications. From all studied solvents (except ethyl acetate) **3** crystallizes in the form of II, which melts at T = 123–125 °C. The compound **3** crystallizes from ethyl acetate forming a polymorphic modification I, which melts at 109 °C; then it re-crystallizes to the form II (exothermic peak at 114 °C), and at 123 °C melting of the form II can be observed.

## Conclusion

By X-ray analysis method it has been shown, that the molecule of *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine forms channel type clathrate with dioxane guest molecules located in the cavities of clathrate channels. By TG–DSC method it has been shown, that methyl-, ethyl-, and hexyl cytisine derivatives can exist in two phase forms. But, unlike methyl- and ethyl-derivatives of cytisine, its hexyl derivative was found unable to form inclusion compounds under conditions studied.

## Supplementary material

Materials of X-ray analysis as CIF file are deposited in the Cambridge Crystallographic Data Centre (CCDC references number 775281). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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