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ORIGINAL ARTICLE

A new polymorphic form and crystal solvates of N-(3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine

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Abstract By the single-crystal X-ray diffraction the structures of a new polymorphic form and crystal solvates of N-(3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl) cytisine ($C_{16}H_{19}N_5O_2S_2$) with dioxane and pyridine have been determined. The crystal structures of solvates are isostructural to previously investigated benzene solvated crystal. Crystal solvates are formed at 2:1 ratio of "host" and solvents. Conformations of the host molecules found in the asymmetric unit of crystal solvates are different like it was observed in benzene solvated crystal. A new polymorphic form is obtained from ethyl acetate.

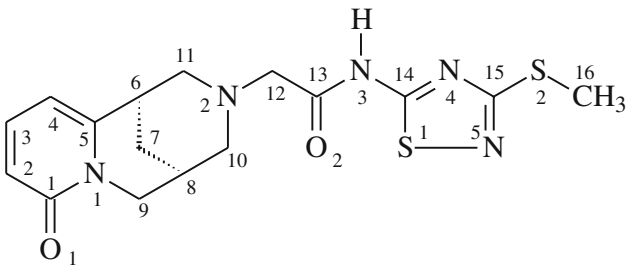
Keywords Cytisine alkaloid · Cytisine derivatives · Host–guest complexes · Polymorphic crystals · Single-crystal X-ray diffraction

Introduction

Our previous crystal structural investigations showed that N-(3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl) cytisine (**1**) is favorable to form solvent included crystals. As well as it was found that **1** forms polymorphic crystals. Structures of water, methanol, chloroform and benzene included crystals and two polymorphic forms produced from acetone and ethanol solution were determined and discussed in last work [1]. Because of flexibility the molecule **1** was occurred at four conformation state in crystals. In particular, 2:1 benzene solvated crystal represented itself as channel type crystal. Therefore, crystallization of the compound **1** from variety solvents was our interest. This paper presents the characterization of crystals of **1** obtained from ethyl acetate, dioxane and pyridine.

Crystallization of **1** from ethyl acetate produced a new polymorphic form of compound which differs from earlier obtained polymorphs by shape and cell parameters. The preliminary determinations of cell parameters of crystals obtained from dioxane and pyridine (molecules which are geometrically close to benzene molecule) solutions of **1** showed that unit cell parameters of crystals do not differ essentially from cell parameters of benzene solvated crystal and this suggested to us about forming of solvent included crystals in those cases.

Schematic formula of compound **1** with numbering schema is shown below (each element is numbered separately). I is notable that cytisine used for synthesis of **1** was enantiomeric and consequently compound **1** also. This makes the molecule interesting in future crystallographic researches.



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Experimental

Recrystallization

The crystals of the new polymorphic form (**I**) were obtained from absolute ethyl acetate by slow evaporation at room temperature. By the same way dioxane and pyridine solvated crystals (**II** and **III**) were obtained from the relevant solutions of title compound in dioxane (preliminarily absolutized) and pyridine.

X-ray experiment

Intensity data of crystals **I–III** were measured by a Stoe Stadi-4 diffractometer at room temperature. Preliminary lattice parameters and orientation matrices were obtained from 10 to 15 reflections, found at $10 < 2\theta < 20$ range and were re-refined using 26–32 reflections at $25 < 2\theta < 32$ range. All data were collected using graphite-monochromated Mo Kα ($\lambda = 0.71073$ Å) radiation with the $\omega/2\theta$-scan method. Absorption correction for crystals of **I** and **II** is made by the psi-scan method. All structures were solved by direct methods and refined using SHELXTL software [2]. Non-hydrogen atoms were refined with anisotropic displacement parameters, and all hydrogen atoms except for amide hydrogen atoms were placed in idealized positions and refined with a riding model, where hydrogen U values at 1.2 times the equivalent isotropic U of the atoms to which they are attached (1.5 for the methyl groups). Amide hydrogen atoms were found by differential-Fourier analysis near N3. Crystal data, data collection parameters and refinement results are listed in Table 1.

Discussion of results

Asymmetric unit of the new polymorph **I** consists of one molecule of **1**. Conformation of the molecule is different from conformations found in earlier obtained polymorphs [1]. This conformation is stabilized by intermolecular H-bonds. Carbonyl and amino groups of the molecule take part in formation intermolecular H-bonding: carbonyl oxygen of O1 H-bonded to amine hydrogen of the molecule translated by 2_1 (O1···N3 2.75 Å, > N3–H···O1 1.78 Å, angle 149.2°) resulting H-bonded chain along *b*. View of molecule and crystal packing is shown in Fig. 1. So in the packing of molecules play role intermolecular H-bonding, that packing mode is totally different from polymorphs obtained in the past. Comparison of crystal densities shows that density (1.36) of the polymorph **I** is significantly smaller than densities (1.43) of earlier investigated polymorphs [1].

X-ray structural analysis shows that crystals **II** and **III** contain the crystallizing molecules of dioxane and pyridine

Table 1 Main crystallographic parameters and characteristics of X-ray experiment for crystals **I–III**

	I	II	III	[1]
Molecular formula	$C_{16}H_{19}N_5O_2S_2$	$2(C_{16}H_{19}N_5O_2S_2) \cdot C_4H_8O_2$	$2(C_{16}H_{19}N_5O_2S_2) \cdot C_5H_5N$	$2C_{16}H_{19}N_5O_2S_2 \cdot C_6H_6$
Formula wt.	377.48	843.07	834.06	833.11
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1$	$P2_1$	$P\ 2_1$
Z	2	2	2	2
a (Å)	9.548(12)	11.978(10)	11.060(6)	11.130(7)
b (Å)	7.982(11)	11.389(9)	11.427(7)	11.448(9)
c (Å)	12.364(16)	16.025(7)	16.581(7)	16.747(9)
β	102.25(10)	105.59(5)	105.61(3)	105.30(5)
V (Å^3)	921(2)	2105.7(3)	2018.3(19)	2058(2)
Dx (g/cm^3)	1.361	1.330	1.372	1.344
Crystal size (mm)	0.50 × 0.25 × 0.10	0.50 × 0.25 × 0.10	0.50 × 0.25 × 0.25	1.00 × 0.50 × 0.30
Crystal color	Colorless	Colorless	Colorless	Colorless
2θ range	$1.50 \le \theta \le 26°$	$1.77 \le \theta \le 26°$	$1.91 \le \theta \le 26°$	$1.50 \le \theta \le 26°$
μ_{exp} (mm^{-1})	0.31	0.28	0.29	0.28
Reflection independent	1944	4365	4195	4259
Refln obs.($I > 2\sigma(I)$)	985	2155	2536	3478
R_1 ($F^2 > 2\sigma(F^2)$)	0.092	0.097	0.078	0.045
wR_2 (F^2)	0.172	0.141	0.126	0.137
S	1.19	1.23	1.22	1.16
Residual electron density (e Å^{-3})	0.24 and −0.24	0.26 and −0.22	0.23 and −0.23	0.18 and −0.21

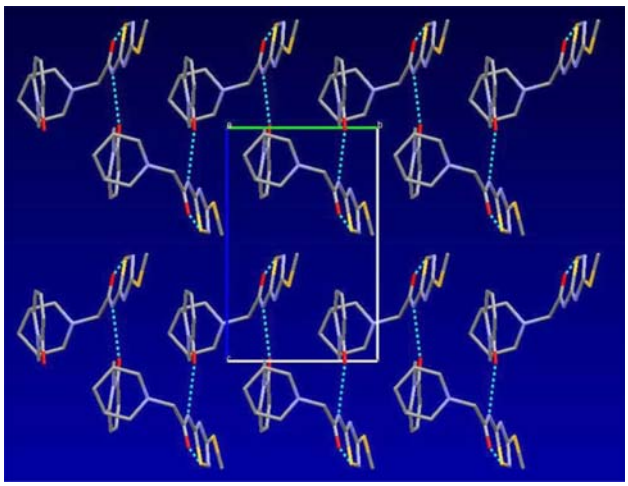

Fig. 1 Crystal structure of polymorph **I**

accordingly, i.e., there occurs an inclusion phenomenon. Asymmetric unit of crystals **II** and **III** consists of two molecules of **1** with different conformations (conformers **A**, **B**) and one solvent molecule, dioxane and pyridine, respectively, as guest. The same isostructural 2:1 crystal solvate was observed with benzene [1]. Packing of molecules in isostructural crystal solvates of **II** and **III** are shown on Fig. 2.

Packing analysis of crystals **II** and **III** shows the presence of intermolecular interactions between conformationally distinct molecules of **1** with N–H and O=C groups due to which it is formed the infinite H-bonded chain along *b* axis consisting of alternating sequences of **A** and **B** conformers, similar to chain observed in benzene solvated crystal. Parameters of these interactions in **II** as the following: distances of N3A···O1B 2.72 Å and H3A···O1B 1.71 Å, angle is equal to 165.5°, and also distances O1A···N3B 2.85 Å and O1A···H3B 2.20 Å, angle O1A is equal to 141.6°. Parameters of these interactions in **III** the following: distances N3A···O1B 2.71 Å and H3A···O1B 1.93 Å, angle is equal to 171.3°, and also distances O1A···N3B 2.83 Å and O1A···H3B 2.10 Å, angle is equal to 142.6°.

Figure 3 shows molecular structures of **1** found in the polymorph **I** and in crystal solvates of **II** and **III** (conformers **A** and **B)** in identical projection on a plane approximately perpendicular to plane of four C6, C8, C10, C11 atoms.

A relatively rigid cytisine core in structures **I–III** is conformationally identical and practically do not differ from found for the cytisine itself [3–5] and for its various derivatives by atom N2 [1, 3, 6, 7]. A bulky 3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl fragment (atoms N2···C16) at all independently found molecules of **1** is practically planar with precision ±0.248 Å (**I**), ±0.096 Å (**IIA**), ±0.137 Å (**IIB**) and ±0.106 Å (**IIIA**), ±0.139 Å (**IIIB**). In this fragment, the location of carbonyl and S–CH_3 groups regarding to five-membered ring (syn-, anti-) are identical in all structures of **I–III**, though in earlier obtained

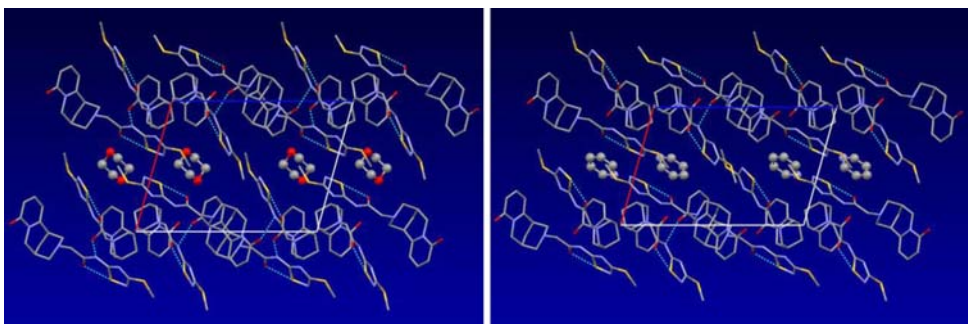

Fig. 2 Crystal packing in dioxane (II) and pyridine (III) solvated crystals

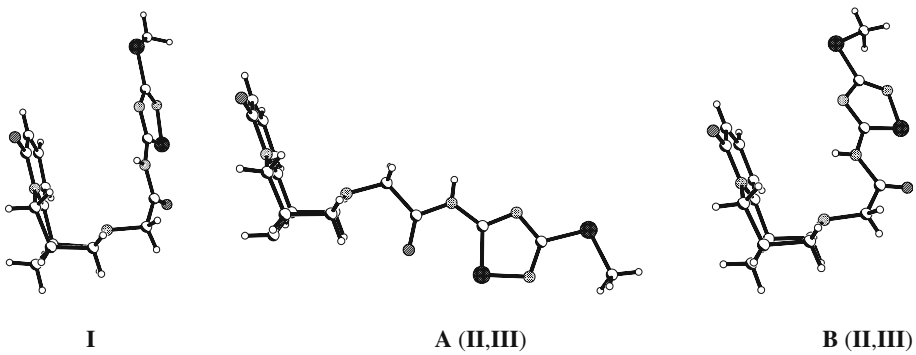

Fig. 3 Molecular structure of N-(3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine found in a polymorph **I** and in crystal solvates of **II** and **III** (conformers **A** and **B)**

Table 2 Torsion angles at N2–C12, C12–C13 and C15–S2 bonds characterizing a conformation of the molecule **1** in crystals of **I–III**

Crystal forms	Conformers	C10–N2–C12–C13	N2–C12–C13–N3	N5–C15–S2–C16
I	–	−159.2	66.9	0.7
II	**A**	69.4	168.0	−3.3
III		64.6	177.3	−1.2
[1]		64.9	176.2	−0.4
II	**B**	−162.9	34.1	0.6
III		−161.3	43.6	−4.9
[1]		−161.7	44.8	−4.5

polymorphs the S–CH_3 group was rotated approximately on 180° relatively to thiadiazolyl ring. In this fragment, a carbonyl group and atom S1 of thiadiazolyl ring is relatively *syn*-oriented and hence in crystal structures of **I–III** takes place an intramolecular interaction O2···S1, where the distance for molecules **IIA** and **IIB** are 2.71 Å and 2.62 Å and for molecules **IIIA** and **IIIB** are 2.69 Å and 2.63 Å, accordingly. In polymorph **I** this value is equal to 2.64 Å.

The conformational difference in molecules of **1** is realized due to rotation of planar 3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl fragment relatively to cytisinic core (around-N2–C12-and-C12–C13-bonds). The conformers **A** and **B** realizing in structure **II** and **III**, practically do not differ from observed in benzene solvated crystal [1]. Torsion angles responsible for conformation can be seen in Table 2. In structure **I** visual view of the molecule **1** is close to conformer **B** observed in **II** and **III**, but a flat fragment here is rotated more (66.9°) around the C12–C13 bond.

Thus, the analysis of molecular structures of **1** in crystals of **I–III** shows that five independent molecules found in asymmetric units are realized as three conformeric states, which differ by an arrangement of thiadiazolyl fragment relatively to cytisine core.

Conclusions

The title compound forms isostructural 2:1 crystal solvates with six-membered ring guest compounds such as benzene, dioxane and pyridine. Third polymorph of **1** is formed from ethyl acetate that two polymorphs were obtained from acetone. The shape of the molecule **1** can vary easy that this favors to form various crystal solvates and polymorphs depending on a condition of crystallization (effect of medium).

Supplementary material

CCDC 706490 (for I), 706491 (for II) and 706492 (for III) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://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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