J Incl Phenom Macrocycl Chem (2008) 61:71–76
DOI 10.1007/s10847-007-9394-0

ORIGINAL ARTICLE

Crystal solvates and polymorphs of *N*-(3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine

B. Tashkhodjave · K. K. Turgunov · A. G. Tojiboev · U. S. Makhmudov · T. F. Ibragimov · V. A. Saprykina · Kh. M. Shakhidoyatov

Received: 13 July 2007 / Accepted: 30 November 2007 / Published online: 3 January 2008

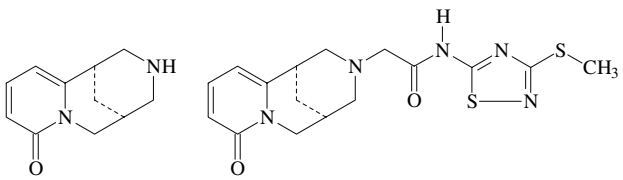
Abstract A polymorphs, crystallohydrate and crystallosolvates of *N*-(3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine, $C_{16}H_{19}N_5O_2S_2$, with chloroform, methanol, benzene have been obtained and crystal structures have been determined by the method of single crystal X-ray diffraction. In the investigated crystals *N*-(3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine have taken four types of conformation due to intramolecular rotations around N–C and C–C bonds. So free rotations in the molecule assisted in formation a different crystallosolvates and polymorphs depending on nature of solvents. The thermal decomposition of the hydrate and methanol solvated crystals was studied by means of a TG-DSC.

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

Introduction

Cytisine alkaloid (**1**) and its derivatives attract considerable attention of researchers due to a broad spectrum of physiological activities [1, 2] and peculiarity in chemical transformations [3, 4]. There are several reaction centers in the molecule of **1**, which can interact with receptors, so introduction of additional heterocyclic pharmacophor groups to molecule is interesting in the plane of study biological activities of product substances. In this connection a series of cytisine derivatives containing a 1,2,4-thiadiazole fragment have been synthesized [5].

Previous crystal structural investigation of *N*-(3-ethylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine among synthesized substances have showed that compound behaves as host molecule in crystal formation with different solvents [6]. Based on this knowledge we have studied crystal structures of another derivative—a *N*-(3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl)cytisine (**2**).



1 **2**

Crystals were obtained by dissolving the titled compound of **2** in solvents of acetone, chloroform, methanol and benzene. Crystallization in acetone resulted in formation two polymorphic crystals, **I** and **II,** accordingly. Crystalization of the **2** from ethanol also yielded form **II**. Whereas crystallization in chloroform, methanol and benzene have led to formation solvent containing crystals, **III**, **V** and **VI** accordingly. Hydrate form crystal, **IV**, have been obtained by crystallization of **2** in non-absolute methanol. Experiments show that **IV** will form with other solvents also if they contain water.

B. Tashkhodjave · K. K. Turgunov (✉) · A. G. Tojiboev · U. S. Makhmudov · T. F. Ibragimov · V. A. Saprykina · Kh. M. Shakhidoyatov
Institute of the Chemistry of Plant Substances, Academy of Sciences of Republic of Uzbekistan, Kh.Abdullaev str., 77, Tashknent 100170, Uzbekistan
e-mail: kk_turgunov@rambler.ru

Experimental part

Synthesis and spectral characteristics of (**2**) are described in [5].

X-ray experiment

Intensity data of crystals **I–VI** were measured with a Stoe Stadi-4 diffractometer. Preliminary lattice parameters and orientation matrices were obtained from 10 ~ 15 reflections found at $10 < 2\theta < 20$ 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 at room temperature with the $\omega/2\theta$-scan method. All structures were solved by direct methods and refined using SHELXTL [7]. Non-hydrogen atoms were refined with anisotropic displacement parameters, and hydrogen atoms were placed in idealized positions. Crystal data, data collection parameters and refinement results are listed in Table 1.

Thermal analysis

The thermal decomposition of the crystals forms of **IV** and **V** was studied by means of a simultaneous TG-DSC system (NETZSCH STA 409 PC) using open aluminium crucible.

Discussion of results

Asymmetric unit of **I** and **II** consist of one molecule of **2**, where no great difference is observed in conformation of molecules. Packing analysis shows that 2_1 related molecules mutually close stand by their planar residue part (C14 atom lies on 2_1 axis). Intermolecular short contacts are observed in both of **I** and **II** between aromatic carbonyl oxygen O1 and sulfur S1 of thiadiazolic ring and consequently is formed molecular assembles. The O1···S1 distances are 3.21 Å in **I** and 3.32 Å in **II**. Reversed direction of this assembles relative to the neighboring ones lead to arise $P2_12_12_1$ symmetry in **II** (Fig. 1).

Asymmetric unit of chloroform solvated crystal **III** consist of one molecule of **2** and one molecule of chloroform. Packing analysis shows that O1···S1 contacted molecular associations of host molecules are formed as observed in the polymorph crystals of **I** and **II** (O1···S1 distances are 3.33 Å. From similarity of associations and their arrangements it is formed comparable cell length in two direction: in *a* and *b* (Table 1). Chloroform molecules are located in zig–zag fashion layers (Fig. 2). Between host and chloroform molecules is observed no interactions, reason may be that active N–H group is blocked by conformational state of molecule **2**.

Crystallization of **2** in methanol, containing water molecules as impurity, at room temperature produced hydrate form crystals of **IV**. The same hydrate form crystal has been received with non-absolute solvents of ethanol and acetone, also. Solvate form crystal of **V** has been obtained only when compound **2** is crystallized in absolute methanol.

Asymmetric unit of **IV** consist of one molecule **2** and one molecule of water. Water molecule hydrogen bonded to the amine hydrogen of the molecule (N3···Ow 2.78 Å, H···Ow 2.02 Å, and N3–H···Ow 146.9°). This water molecule also is bonded to aromatic carbonyl oxygen of next molecule translated by *b* axes (O1···Ow 2.72 Å, O1···H(w) 1.87Å and O1···H–Ow 161.9°), so in such manner it is formed 1D chains along *b* axis.

Analogous structure is formed in crystal **V**. Methanol molecules occupy water places in crystal, forming 1D H-bond chains along *b*. Hydrogen-bonding geometry are as follows: N3···O(m) 2.72 Å, N3–H···O(m) 1.97 Å, N3–H···O(m) 167.4°. For O(m)–H···O1 are 2.69 Å, 1.96 Å and 167.1° accordingly. So water and methanol molecules play as guests in **IV** and **V**. H-bond chains in **IV** and **V** are shown in Fig. 3.

Simultaneous differential scanning calorimetric (DSC) and thermogravimetric (TG) investigations of the thermal decomposition of crystals **IV** and **V** have been performed (Fig. 4). DSC-TG analysis of these crystals shows that release of the guest molecules during a linear temperature scan occurs in the temperature intervals 105–133 °C. The observed mass loss correspond to the results of the X-ray structure analysis for **IV**. However determined host–guest ratio does not exactly correspond to the X-ray data for **V**. Reason may be partly desolvatation of sample until experiment or presence of another form crystals in the sample. Small exotherm at 133 °C in the DSC curve of **IV** shows intermediate phase forming which melts giving small endotherm at 145 °C. This intermediate is yet unexplained. Farther heating of samples from IV and V leads to melt of host compound at 200 °C.

Another host–guest type crystal form, **VI**, has been obtained by crystallization of **2** in benzene. Asymmetric unit of crystal **VI** consist of two host molecules and one benzene molecule as guest. Independent host molecules mutually hydrogen bonded by N3–H and O1′ = C1′ groups accordingly, where N3···O1′ distance is 2.83Å. This independent pair hydrogen bonded to neighbouring pairs translated by twofold screw of 2_1. The N3′···O1 distance is 2.73Å. In result are formed one-dimensional hydrogen bonded chains along *b*. Benzene molecules are located in the interchain cavities. Besides S1′···S2′ (i) intermolecular short contacts are observed between methiltio- and

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

	I	**II**	**III**	**IV**	**V**	**VI**
Molecular formula	$C_{16}H_{19}N_5O_2S_2$	$C_{16}H_{19}N_5O_2S_2$	$C_{16}H_{19}N_5O_2S_2 \cdot CHCl_3$	$C_{16}H_{19}N_5O_2S_2 \cdot H_2O$	$C_{16}H_{19}N_5O_2S_2 \cdot CH_3OH$	$2(C_{16}H_{19}N_5O_2S_2) \cdot C_6H_6$
Formula wt.	377.48	377.48	496.85	395.50	409.52	833.11
Crystal system	Monoclinic	Orthorhombic	Orthorhombic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_1$	$P2_1$	$P2_1$
Z	2	4	4	2	2	2
a, Å	9.479(6)	7.311(1)	7.25(2)	8.003(5)	8.211(2)	11.130(7)
b, Å	7.24(1)	9.545(2)	9.51(1)	11.847(7)	11.994(7)	11.448(9)
c, Å	13.265(9)	25.050(5)	32.28(5)	9.867(5)	10.272(6)	16.747(9)
β	106.96(5)			99.52(5)	92.64(4)	105.30(5)
V, Å^3	871.2(15)	1748.1(6)	2227.5(8)	921.9(9)	1010.6(8)	2058(2)
Dx, g/cm^3	1.439	1.434	1.482	1.425	1.345	1.344
Crystal size (mm)	1.00 × 0.50 × 0.30	0.75 × 0.60 × 0.25	0.80 × 0.30 × 0.15	1.00 × 0.75 × 0.75	1.00 × 0.75 × 0.72	1.00 × 0.50 × 0.30
Crystal color	Colorless	Colorless	Colorless	Colorless	Colorless	Colorless
2θ range	$1.50 \leq \theta \leq 25^o$	$1.50 \leq \theta \leq 25.00^o$	$2.23 \leq \theta \leq 25^o$	$2.0 \leq \theta \leq 25^o$	$1.50 \leq \theta \leq 27.5^o$	$1.50 \leq \theta \leq 26.00^o$
μ_{exp} (mm^{-1})	0.33	0.33	0.62	0.32	0.29	0.28
Reflection independent	1538	1804	2220	1672	2438	4259
Refln obs. ($I > 2\sigma$ (I))	1242	1389	1297	1568	2212	3478
R_1 ($F^2 > 2\sigma$ (F^2))	0.064	0.052	0.098	0.030	0.032	0.045
wR_2 (F^2)	0.179	0.112	0.281	0.069	0.082	0.104
S	1.06	1.20	1.10	1.14	1.12	1.16
Residual electron density (eÅ^{-3})	0.26 and −0.32	0.22 and −0.25	0.35 and −0.34	0.17 and −0.15	0.16 and −0.17	0.18 and −0.21

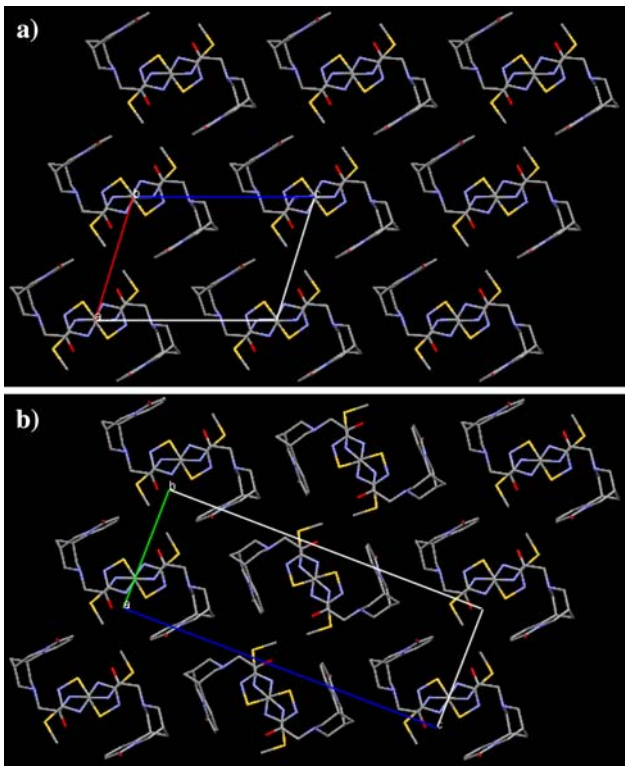


Fig. 1 Crystal packing in polymorph **I**(**a**) and **II**(**b**) showing similar molecular arrangement and giving close cell parameters (see Table 1). (H atoms are omitted for clarity here and further packing figures)

thiadiazolyl sulfurs of the same type molecules of **2** where S1′···S2′ ($i = 1 - x, -0.5 + y, 1 - z$) distance is 3.65 Å (Fig. 5).

Analysis of geometries show that conformation of molecule **2** is different in investigated crystals of **I–VI**. These conformations are caused mainly on account of rotation two rigid parts of the molecule, a cytisine fragment and 1,2,4-thiadiazol-5-yl-aminocarbonylic residue, around N2–C12 and C12–C13 bonds. If small differences do not be accounted host molecule are observed generally in four conformation state. The conformation view of molecules in

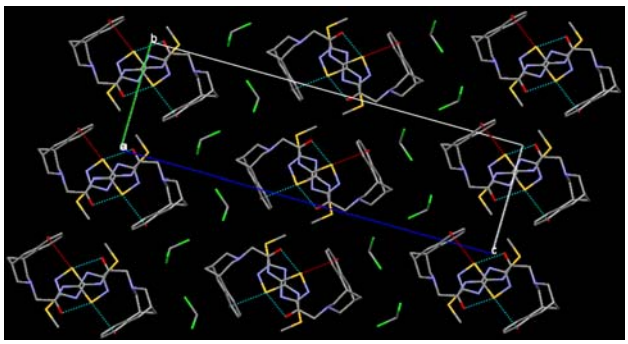


Fig. 2 Crystal packing in chloroform solvate, (**III**). In order to show comparability in crystal packing of **I–III**, cell is oriented as figured in Fig. 1

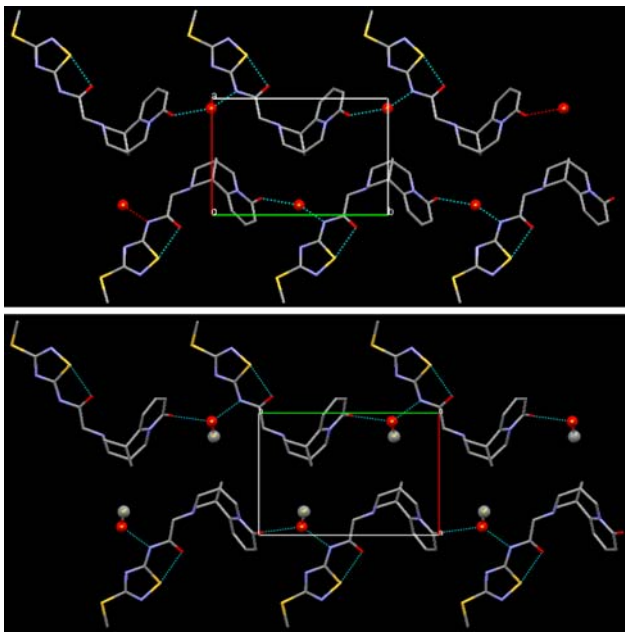


Fig. 3 Packing of molecules in crystals **IV** and **V**

the identical projection of cytisine fragment is given in Fig. 6. In crystals **I–III** conformation of molecules **2** are close each to other and they may be presented as shown in Fig. 6a. This conformation is stabilized by intramolecular H-bond formed between NH-group of molecule and

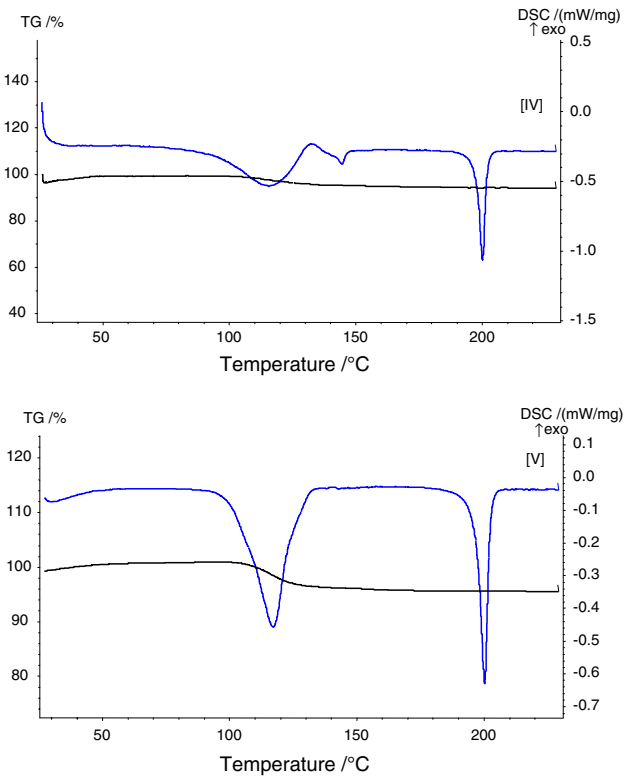


Fig. 4 Thermal degradation of crystal forms of **IV** and **V**

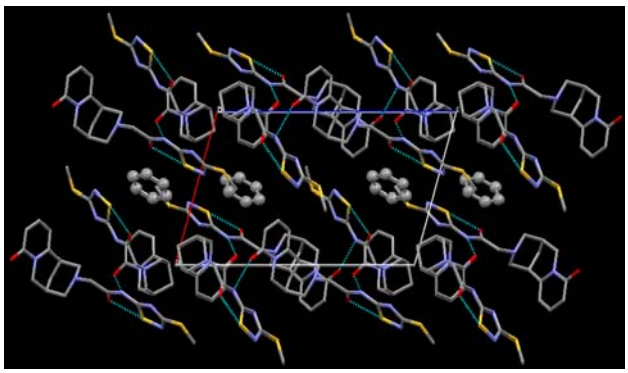


Fig. 5 Crystal structure of 2:1 benzene solvated form, **VI**

unshared electron pair of N2. Parameters of H-bond are as follow: distances are N2···N3 2.68, N2···H 2.25 Å and N2···H–N3 angle is 111.1° for structure **I**. For **II** these values are 2.69, 2.26 and 111.0 consequently.

In crystals **IV** and **V** molecule of **2** is in expanded form and the conformations may be presented as in Fig. 6b. While in crystal **VI** conformations of molecules, allocated in asymmetric unit, are mutually different where one of them is in compact form and second is more expanded form (6c–d). Exact values of torsion angles, indicating a conformation of the molecule, are given in Table 2.

Geometry of cytisine fragment in all case is the same and it does not differ from found structures for cytisine [8–10] and for their N-derivatives [3, 11, 12]. The 3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl-fragment in all seven molecules found in asymmetric units of **I–VI** are almost planar with accuracy ±0.022 (**I**), ±0.024 (**II**), ±0.013 (**III**), ±0.016 (**IV**), ±0.058 (**V**), ±0.054 (**VIa**) and ±0.095 Å (**VIb**) respectively. However orientation of S–CH_3 group relative to thiadiazolyl ring are mutually anti-sided in cases of **I–III** and **IV–VI** accordingly. In addition in crystals of **I–VI** carbonyl group and thiadiazolic S1 of 3-methylthio-1,2,4-thiadiazol-5-yl-aminocarbonylmethyl residue are mutually *syn*-located.

Conclusions

Crystal structural investigations show that molecule **2** can be in different conformations due to intramolecular

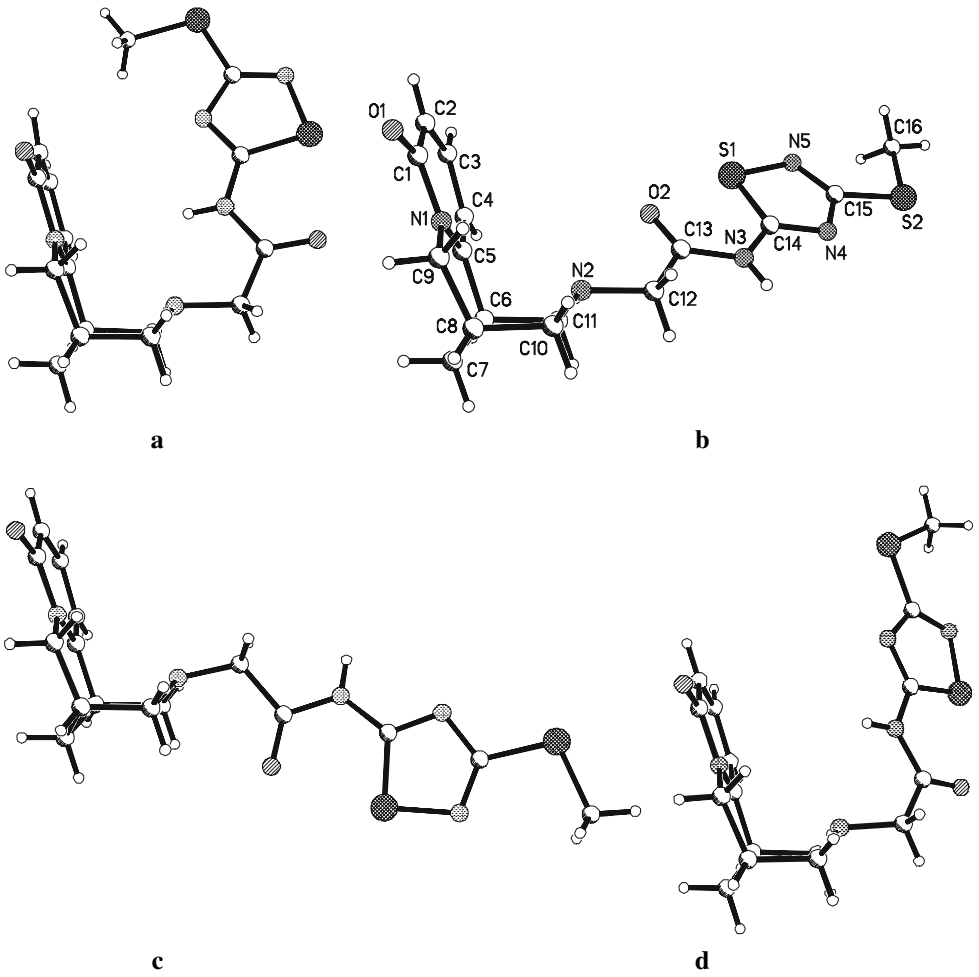


Fig. 6 Observed geometry of molecule **2** in crystals **I–VI**: (**a**) conformation observed in crystal forms of **I–III**; (**b**) conformation observed in crystal forms of **IV** and **V**; (**c**) and (**d**) conformations observed in crystal form of **VI**

Table 2 Torsion angles at N2–C12, C12–C13 and C15–S2 bonds in crystals of **I–VI**

Crystal	C10–N2–C12–C13	N2–C12–C13–N3	N5–C15–S2–C16
I	−139.61	3.33	177.57
II	−144.80	6.66	176.57
III	−141.50	0.72	178.08
IV	−171.49	−167.65	3.72
V	−160.97	−174.61	0.81
VIa	64.96	176.21	−0.41
VIb	−161.70	44.84	−4.50

rotations induced by molecular environments. And such conformation changeability of molecule and various intermolecular contacts makes them as hosts for organic solvents. Structures of **I–III** give evidence that when active N–H group of **2** blocked by doing intramolecular interactions, π–π force is dominative in the packing of host molecules. Participation of N–H group in intermolecular H-bonding is responsible for **2** to be in extended conformation state. Observations in structure **VI** allow to conclude that being in two conformation state of **2** is favored in forming H-bonded assembles of host molecules and consequently forming 2:1 host:guest solvate. Whereas with good hydrogen bond agents, such as water, **2** will form 1:1 inclusion compounds where the host molecules links by guest molecules producing supramolecule, as is observed in **IV** and **V**.

Supplementary material

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC—652420 for I, 652421 for II, 652422 for III, 652423 for IV, 652424 for V and 652425 for VI). Copies of the data can be obtained free of charge on application to the CCDC, 12 union Road, Cambridge CB2 1EZ, UK [Fax: (internet.) +44-(0)-1223/336033; E-mail: deposit@ccdc.cam.ac.uk] and are available from the authors.

Acknowledgements This work was financed by Research Foundation of Academy of Sciences of Uzbekistan, Grant No. 118-06.

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