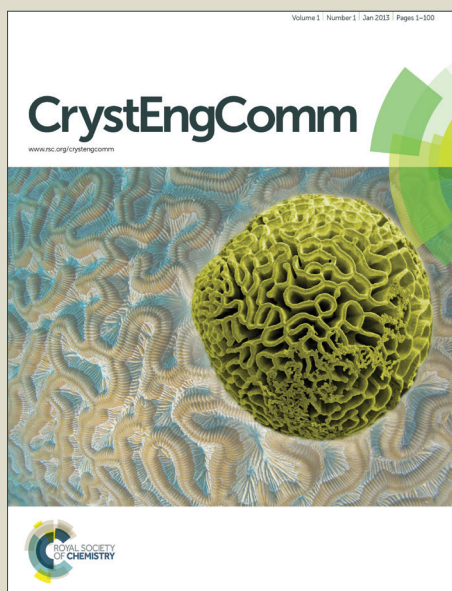


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PAPER

Z'=2 crystallization of the three isomeric piridinoylhydrazone derivatives of isosteviol: Inclusion of an "extra" molecule in a unitcell as a "cost" of transferring a robust mirror-symmetrical H-bonding motif from an racemic environment into a homochiral one

⁵ Olga A. Lodochnikova,^a Alexey B. Dobrynin,^a Olga V. Andreeva,^a Irina Yu. Strobykina,^a Vladimir E. Kataev,^a Igor A. Litvinov^a

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Crystallization of three diterpenoid isosteviol derivatives with a structural fragment of isoniazid
¹⁰ (isonicotinic acid hydrazide) and its isomers – hydrazides of nicotinic and picolinic acids (structures **5**, **6**
 and **7** respectively) was studied by single-crystal and powder XRD. These homochiral compounds
 crystallize in "Sohnke" space group $P2_1$ with two independent molecules. In crystals **5** and **6**, infinite H-
 bonded chain of alternating molecules A and B formed by N-H...O=C interaction is observed, while only
 pairwise same interactions between molecules A and B are realized in crystal **7**. In the H-bonded
¹⁵ associates of both types, the local (non-crystallographic) mirror-symmetry of nitrogen containing
 substituents in molecules A and B is observed. Such type of crystal packing – H-bonded chains or dimers
 formed by the N-H...O=C interaction through the glide plane – is the most typical packing in achiral
 compounds with a structural fragment of isoniazid and its isomers, as the CCDC analysis showed. Thus,
 structures **5-7** represent an interesting example of transferring a robust supramolecular mirror-symmetry
²⁰ motive from racemic environment into the homochiral one, but inclusion of an "extra" molecule in a
 unitcell is the crystallographic "cost" of such transfer.

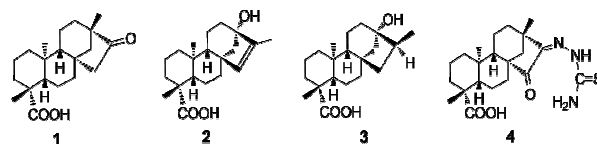
Introduction

In recent years, the phenomenon of compounds crystallization
 with more than one independent molecule is extensively studied<sup>1-
²⁵ 7</sup>. Among chiral compounds, this phenomenon occurs more
 commonly than among racemic ones. This fact is obviously
 caused by a limited set of symmetry elements in chiral space
 groups and, accordingly, with a hindrance to the realization of
 one or another homochiral associate in a crystal.
³⁰ Thus, in⁵, a certain crystal-chemical "problem" posed by the
 homochiral dimer is studied. This associate can be placed in a
 crystal without involving an "additional" molecule in the unit cell
 in only one way – by locating it on the 2-fold rotation axis. In
 some cases, this option is actually realized. However, a
³⁵ contradiction between the chirality of a compound and its
 tendency to preserve its dimer motif often leads to the formation
 of pseudocentrosymmetric $Z'=2$ crystal structure. Compounds
 containing carboxyl, amide and some other groups form
 structures of such type more often than another ones.⁵
⁴⁰ As stated previously^{8,9}, this is the way of how natural
 diterpenoid isosteviol **1** (16-oxo-beyeran-*ent*-19-oic acid) is
 crystallized – in its crystals, a homochiral dimer formed by the
 interaction between the carboxyl groups is realized not on the 2-
 fold axis, but in a pseudo-centrosymmetric manner. Structural

⁴⁵ isomers of isosteviol – 15-ene-steviol **2** (13-hydroxy-*ent*-kaur-15-
 ene-19-oic acid) and 16(*S*)-dihydrosteviol **3** (13-hydroxy-*ent*-
 kauran-19-oic acid) are also crystallized with two independent
 molecules. In these cases the formation of the $Z'=2$ structures is
 caused by a complicated system of hydrogen bonds¹⁰.

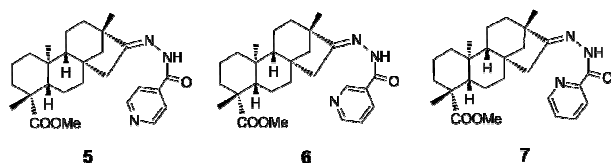
⁵⁰ At the same time, in a crystal of isosteviol 15-oxo-16-
 thiosemicarbazone **4**, we detected a sophisticated supramolecular
 associate – a homochiral tetramer formed by O-H...O and N-H...S
 interactions¹¹. The singularity of the tetramer is that it is situated
 at the intersection of three 2-fold axes (space group $I222$), thus
⁵⁵ avoiding the inclusion of "extra" molecule(s) in the unit cell.

The structural formulas of compounds **1-4** shown at Scheme 1.



Scheme 1 Isosteviol and its derivatives, our previously works⁹⁻¹¹.

In this paper, we present the $Z'=2$ crystal structures of hybrid
⁶⁰ compounds of isosteviols with isoniazid (isonicotinic acid
 hydrazide) and its isomers – hydrazides of nicotinic and picolinic
 acids (structures **5**, **6** and **7** respectively), and analyze the reasons
 for including an "extra" molecule into unit cell (Scheme 2).



Scheme 2 Isosteviol derivatives, presented in this work.

The structures presented in this publication differ from those studied previously. These compounds are constructed as "chiral skeleton – achiral substituent". The functional groups capable of hydrogen bonding are contained in the substituent. The main task was to find out what type of symmetry would be inherent to H-bonded associates.

We described the synthesis of compounds **5** – **7** before¹². It was also noted in our papers that covalent binding of the isosteviol and isoniazid did not lead to a synergism of the anti-tubercular activity demonstrated by them; but the subject of this present publication is the crystal-structural aspect of such

binding.

15 RESULTS AND DISCUSSION

Single crystal X-ray investigations

Compounds **5-7** are crystallized in space group $P2_1$ with very similar cell parameters (Table 1), i.e. the crystals of these compounds are isostructural. We carried out X-ray diffraction experiments at two different temperatures: 296 K and 150 K. Upon transition from room to low temperature we did not observe any significant changes of crystal structures therefore further we will discuss the geometrical parameters calculated from low-temperature experiments (we use the cif-files of room-temperature experiments for generation of powder patterns (see below)).

Table 1 Crystal data and parameters of X-ray diffraction experiment of compounds **5-7** at 150K.

Compound reference	5	6	7
Chemical formula		$C_{27}H_{37}N_3O_3$	
Formula Mass		451.60	
Crystal system		Monoclinic	
$a/\text{\AA}$	8.015(2)	7.966(3)	8.161(3)
$b/\text{\AA}$	19.658(5)	19.688(6)	19.967(6)
$c/\text{\AA}$	15.418(4)	15.559(5)	14.987(5)
$\beta/^\circ$	93.118(4)	92.608(5)	95.599(6)
Unit cell volume/ $\text{\AA}^3$	2426(1)	2438(1)	2430(1)
Space group		$P2_1$	
No. of formula units per unit cell, Z		4	
No. of reflections measured	22301	22443	36785
No. of independent reflections	11612	11580	11706
R_{int}	0.0748	0.1385	0.0464
Final R_I values ($I > 2\sigma(I)$)	0.0696	0.0773	0.0424
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.1238	0.1141	0.0924
Final R_I values (all data)	0.1287	0.2761	0.0518
Final $wR(F^2)$ values (all data)	0.1522	0.1777	0.0976
Flack parameter	0.6(13)	2(2)	-0.1(7)
CCDC numbers	973309	973308	973306

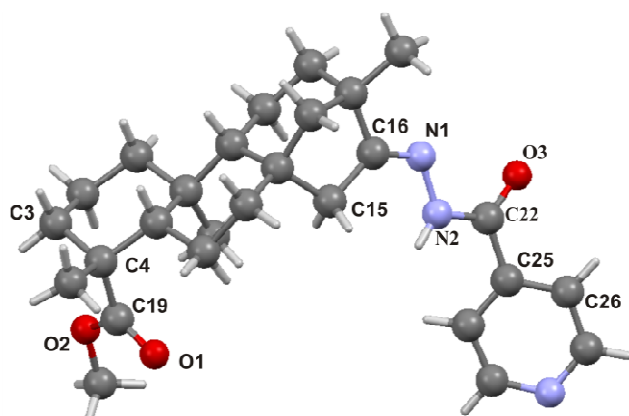


Fig 1 The geometry of molecule A in the crystal **5**.

Compounds **5-7** are crystallized with two independent molecules. The hard tetracyclic hydrocarbon skeleton of independent molecules has nearly the same geometry, but the differences in conformations are observed at the opposite ends of the molecules, namely, molecules A and B differ in the conformation of C^4/C^{16} substituents.

Thus, the ester group has a different position relative to the tetracyclic skeleton: In molecule A, the $C^3C^4C^{19}O^2$ fragment has eclipsed conformation, while in molecule B, the eclipsed conformation is observed in the $C^3C^4C^{19}O^1$ fragment.

The most interesting differences are observed in the pyridinoylhydrazone fragments of molecules A and B in all three crystals **5-7**. Let us consider these differences in more details.

Molecules A in crystals 5, 6 have practically the same geometry (Fig. 1). Pyridinoylhydrazonic fragment has a *trans*-conformation (the corresponding torsion angles along the chain have the values of about 180°), with the exception of the last chain link. Thus, O³C²²C²⁵C²⁶ torsion angle has a value close to 30° (Table 2). It is clear that the deviation from the *trans*-conformation of the last link was determined by the repulsion of the hydrogen atom at *ortho*-position of the pyridine ring and the

hydrogen atom in the hydrazidehydrazone moiety. The conformation of molecule's A pyridinoylhydrazonic fragment in crystal 7 differs from that in crystals 5, 6 by a smaller angle between the pyridine plane and the plane of a carbonyl group with substituents adjacent thereto (O³C²²C²⁵C²⁶ torsion angle is 17.3(2)°). Obviously, this is determined by the realization of an intramolecular hydrogen bond that is the only possible in *ortho*-isomer 7 (Fig. 2).

Table 2 Selected geometrical parameters of independent molecules A and B of the crystals 5-7.

	Molecule A			Molecule B		
	5	6	7	5	6	7
Bond distance						
N ¹ -C ¹⁶	1.281(4)	1.274(9)	1.274(2)	1.265(5)	1.273(10)	1.267(2)
N ¹ -N ²	1.392(4)	1.394(8)	1.385(2)	1.413(4)	1.410(9)	1.391(2)
N ² -C ²²	1.344(4)	1.35(1)	1.342(2)	1.346(4)	1.352(10)	1.348(2)
O ³ -C ²²	1.233(4)	1.234(9)	1.216(2)	1.231(4)	1.220(9)	1.216(2)
Bond angles, deg.						
N ² -N ¹ -C ¹⁶	116.1(3)	115.1(6)	113.6(1)	114.8(3)	113.5(6)	114.1(1)
N ¹ -N ² -C ²²	116.8(3)	115.8(6)	120.6(1)	116.4(3)	116.5(6)	118.8(1)
O ³ -C ²² -N ²	123.3(3)	123.8(6)	125.3(2)	122.6(3)	123.1(7)	124.8(1)
O ³ -C ²² -C ²⁵	120.0(3)	119.4(6)	121.7(1)	119.8(3)	121.1(7)	121.1(1)
N ² -C ²² -C ²⁵	116.7(3)	116.8(6)	113.0(1)	117.6(3)	115.8(7)	114.1(1)
Torsion angles, deg.						
N ² N ¹ C ¹⁶ C ¹⁵	-2.3(5)	-1(1)	2.3(2)	9.6(5)	10(1)	6.8(2)
C ¹⁶ N ¹ N ² C ²²	-179.9(3)	-178.7(6)	-176.7(1)	-152.6(3)	-153.1(7)	-167.8(1)
N ¹ N ² C ²² O ³	-4.3(5)	-5.2(10)	0.1(3)	20.8(5)	19(1)	12.4(2)
N ¹ N ² C ²² C ²⁵	175.5(3)	176.2(6)	-179.7(1)	-159.7(3)	-161.8(6)	-167.7(1)
N ² C ²² C ²⁵ C ²⁶	-146.6(3)	-147.6(7)	-162.9(2)	145.1(3)	143.7(7)	162.2(1)
O ³ C ²² C ²⁵ C ²⁶	33.3(5)	34(1)	17.3(2)	-35.4(4)	-37(1)	-18.0(2)

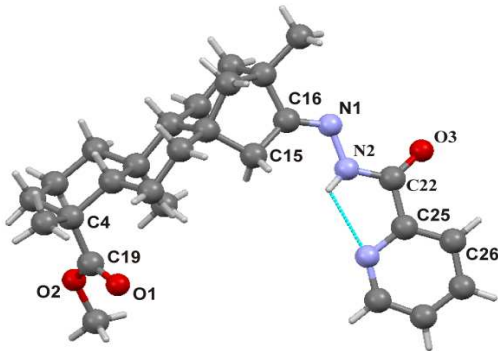


Fig. 2 Weak intramolecular N-H...N interaction in the crystal 7 (here molecule A is presented).

As for molecules B, formally, the conformation of pyridinoylhydrazonic fragment can also be defined as a *transoid* one, but in such cases, the substantial deviations of torsion angles from 180° are observed (Table 2).

Thus, conformational changes of a nitrogen-containing fragment in molecules B in crystals 5, 6, being estimated through the deviation of the corresponding torsion angles from 180°, are approximately identical (the deviation in magnitude is about 30° for the torsion angle of C¹⁶N¹N²C²², a deviation about 20° for an angle N¹N²C²²C²⁵) while the corresponding conformational changes of a nitrogen-containing fragment of a molecule B in the crystal 7 is significantly less (the deviations from *trans*-conformation is about 10°), probably, because of the existence of intramolecular interaction N-H...N(Py).

What did give rise to such deviation from *transoid* conformation of the nitrogen-containing molecular fragments in

molecules B? Such conformational changes of pyridinoylhydrazonic fragment in molecules B led to the formation of the approximate mirror similarity of this fragment in molecules A (Fig. 3).

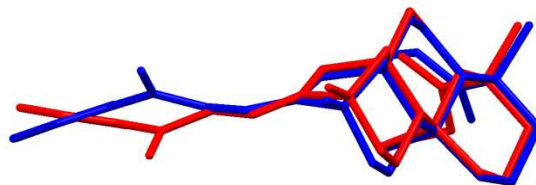


Fig. 3 Overlay of molecule A and B in crystal 5. Hydrogen atoms are omitted for clarity

Probably, such conformational changes should provide realization of the hydrogen bonds of N-H...O=C type between molecules A and B, and the mirror-symmetry of pyridinoylhydrazonic moieties is the necessary condition to accomplish this realization.

In crystals 5, 6 such conformational changes are sufficient to form infinite hydrogen-bonded chains (Fig. 4, Table 3), while only pairwise interactions between molecules A and B are realized in the crystal of *ortho*-isomer 7 owing to essentially lesser conformational changes (Fig. 5).

In the last case only N^{2B}-H^{2B}...O^{3A} interaction occurs while the distance N^{2A}...O^{3B} equals 4.016(2) Å, and that testify to the absence of the second interaction. The local mirror-symmetry of nitrogen containing substituents in molecules A and B are observed in hydrogen-bonded associates of both types (Fig. 6).

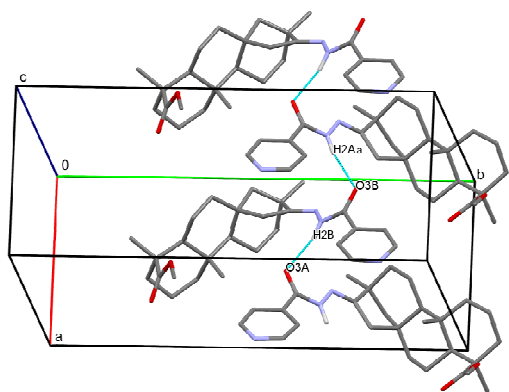


Fig.4 Infinite H-bonded chain of alternating molecules A and B in crystal 5. Only hydrogen atoms involved in H-bonding are shown. Symmetry code: a $[-1+x,y,z]$.

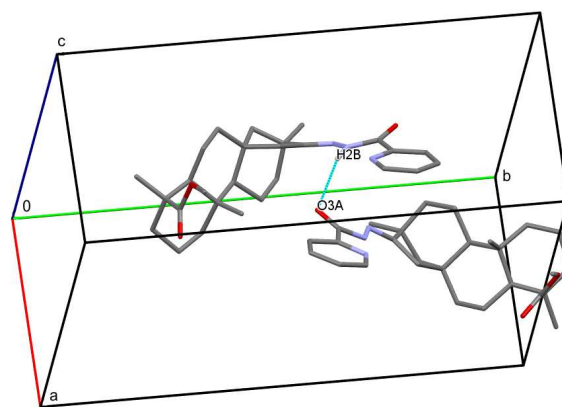


Fig.5 H-bonded dimer of molecules A and B in crystal 7. Only hydrogen atoms involved in H-bonding are shown.

Table 3 Hydrogen bonds in crystals 5–7 by X-Ray data.

Crystal	Interaction	Symmetry operation	Distance D–H, Å	Distance H...A, Å	Distance D...A, Å	$\angle$ D–H...A, °
5	N ^{2A} –H ^{2A} ...O ^{3B}	1+x,y,z	0.89(3)	2.20(3)	3.071(4)	166(3)
	N ^{2B} –H ^{2B} ...O ^{3A}	-	0.95(4)	2.02(4)	2.945(4)	165(3)
6	N ^{2A} –H ^{2A} ...O ^{3B}	-	0.92(5)	2.18(5)	3.097(7)	175(5)
	N ^{2B} –H ^{2B} ...O ^{3A}	-1+x,y,z	0.96(6)	2.07(6)	2.977(7)	156(6)
7	N ^{2B} –H ^{2B} ...O ^{3A}	-	0.85(2)	2.47(2)	3.271(2)	159(2)
	N ^{2A} –H ^{2A} ...N ^{3A}	-	0.88(2)	2.24(2)	2.660(2)	110(2)
	N ^{2B} –H ^{2B} ...N ^{3B}	-	0.85(2)	2.31(2)	2.686(2)	107(2)

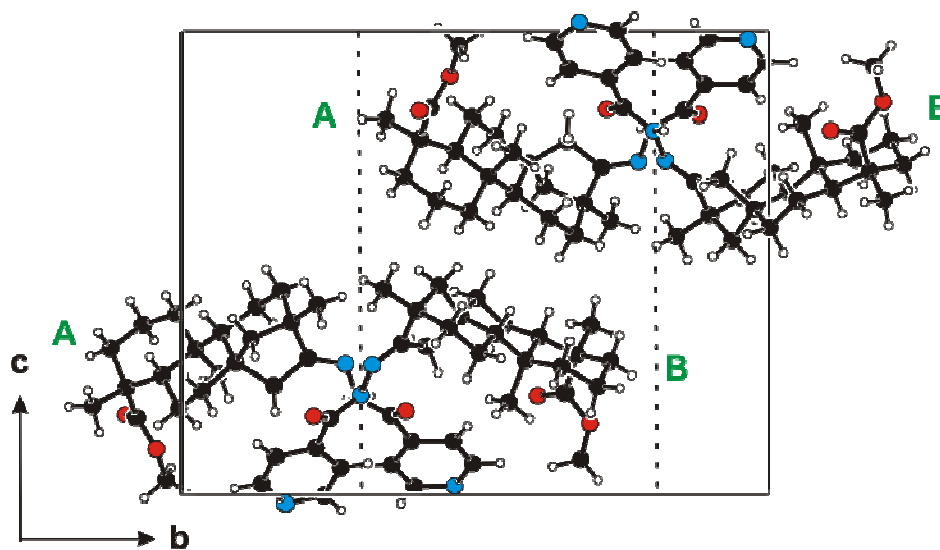


Fig.6 The projection of the structure 5 down *a* axis. The configurations of the diterpenoid fragments are the same, but the conformation of pyridinoylhydrazone moiety is *pseudo-left* in molecule A and *pseudo-right* in molecule B. The two independent molecules are related by a local, *pseudo-a*-glide operation (shown by a dotted line) which is perpendicular to *b*, but the diterpenoid fragment cannot be related by a glide.

Such conformational changes in molecules B are accompanied by some elongation of N¹–N² bonds in comparison with the same bonds of the corresponding molecules A in the crystals 5 and 6. Obviously, this occurs owing to some decrease of the conjugation of lone pair of N² atoms with π system of the C¹⁶=N² bond in molecules B. In the crystal 7 the corresponding fragment is more

flat (torsion angle close to 180 degrees), so the N¹–N² bond length in the independent molecules is almost the same. Also for *para*- and *meta*-isomers the N²N¹C¹⁶ bond angle is slightly greater in molecules A than in molecules B, and in the latter case the steric repulsion of atoms N² and C¹⁵ is partially compensated by twisting of the N¹=C¹⁶ bond of 10°. In molecules A such twisting

is absent, and steric repulsion of atoms N² and C¹⁵ leads to some increase in the bond angle discussed.

It should be noted that the inevitable implementation of the same motives of structure-forming intermolecular interactions in isostructural crystals is conventionally considered to be an immutable truth. In our case, the system of hydrogen bonds in crystal **7** differs from that in crystals **5** and **6**. We were unable to find any similar examples of different systems of intermolecular interactions in isostructural crystals, probably, because previously such cases were not paid any special attention to, and this fact requires a special study.

In addition to classical hydrogen bonds, secondary interactions stabilize the chain in crystals **5** and **6**, and also the dimer in a crystal **7** (Fig. 7, Table 4). So, C^{15B}-H^{15D}...O^{3A} interactions are observed in all three structures.

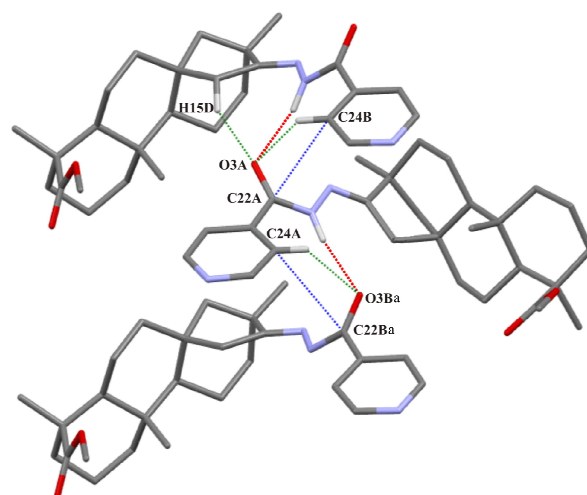


Fig.7 The N-H...O (shown in red dotted), C-H...O (shown in green dotted) and $\pi\cdots\pi$ (shown in blue dotted) interactions in crystal **5**. Only hydrogen atoms involved in N-H...O and C-H...O interactions are shown. Symmetry code: a [1+x,y,z].

Table 4 C-H...O interactions in crystals **5-7**.

Interaction	Symmetry operation	Crystal	Distance D-H, Å	Distance H...A, Å	Distance D...A, Å	Angle $\angle$ D-H...A, °
C ^{15B} -H ^{15D} ...O ^{3A}	-	5	0.99	2.41	3.258(4)	143
	-1+x,y,z	6	0.99	2.42	3.289(7)	146
	-	7	0.99	2.59	3.508(2)	155
C ^{24A} -H ^{24A} ...O ^{3B}	1+x,y,z	5	0.95	2.44	3.125(4)	129
	-	6	0.95	2.51	3.209(8)	131
C ^{24B} -H ^{24B} ...O ^{3A}	-	5	0.95	2.56	3.273(4)	132
	-1+x,y,z	6	0.95	2.52	3.17(7)	126

Also, the C²⁴-H²⁴...O³ interaction was observed in the structures **5** and **6**. As well, short contacts C²²...C²⁴ were observed in these two structures, that can apparently be interpreted as weak $\pi\cdots\pi$ interaction of the carbonyl group and the pyridine ring (distances C^{22A}...C^{24B} 3.305(5)Å, C^{22B}...C^{24A} 3.318(5)Å in crystal **5**, C^{22A}...C^{24B} 3.23(1)Å, C^{22B}...C^{24A} 3.35(1)Å in crystal **6**) belonging to neighboring molecules. It is important to note that the molecules A and B are involved in the interaction of stereochemically different (diastereotopic) sides of the carbonyl group (*Re* in molecule A and *Si* in the molecule B), which agrees with a mirror-symmetrical conformation of the pyridinoylhydrazone fragments. In structure **7**, the key position for the $\pi\cdots\pi$ -interaction in the pyridine ring is occupied by N³ atom and it also forms the short contacts with C²² atom of the carbonyl group of the neighboring molecule having distance C^{22A}...N^{3B} 3.199(3) Å. This interaction is observed only in the pair of molecules A and B that form a dimer. There is no similar interaction C^{22B}...N^{3A} (the respective distance equals to 3.560(3) Å).

CSD search

In order to test how rare is such supramolecular organization of

isoniazide's derivatives and its structural isomers, we have performed a CSD-searches¹⁴.

We searched structures, containing a fragment of isoniazid and its structural isomers (*ortho*- and *meta*-). Most of the detected structures contained a fragment of isoniazid (*para*-isomer), and several examples of structures contained isomeric moiety.

Surprisingly, the search resulted in the absence of chiral structures of this type (stated above). All selected compounds are achiral and, therefore, in most cases, crystallize in centrosymmetric space groups. To compare with our data, we selected only those crystal structures, in which interactions N-H...O=C were found, to find out what is the symmetry of H-bonded chains or dimers.

We selected 17 structures (Table 5) with isoniazid fragment. Chains of interacting molecules are formed by the glide plane in 11 founded structures (in these cases, this element of symmetry is crystallographic, unlike structures **5-7**). H-bonded chains are formed by alternating, crystallographically independent molecules A and B in four cases (in these cases, *pseudo*-glide symmetry between them is observed). Only in one case, the H-bonded chain is formed by a translation along an axis 4₁, and in one case – by a translation along one of crystallographic axes.

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Table 5. The structural analogs of compounds 5-7 from the CSD and symmetry operation by means of which N-H...O=C interactions in them are realized.

	Glide plane		Symmetry operation		Axes 4 ₁
	crystallographic	non-crystallographic	Translation		
Structures with an isoniazid fragment	11 ^a	4 ^b	1 ^c		1 ^d
Structures with a fragment of <i>meta</i> -isomer of an isoniazid	1 ^e	1 ^f	1 ^g		-
Structures with a fragment of <i>ortho</i> -isomer of an isoniazid	2 ^h	1 ⁱ	-		-

^a) BOGSEW, CIZQUX, HILLOE, LAWDAP, NIQNUX, OGEKOB, QERLIJ, RAVRUB, RERYUJ, ROFCIZ, YIQFUA^b) HESRUT, HOFQID, SAZBIF, YIQFOA^c) QERJED^d) LOHVUA^e) YIRFAH^f) EDEQIO^g) CIPVAZ^h) KIXGEE, SINBOHⁱ) SAZBEB

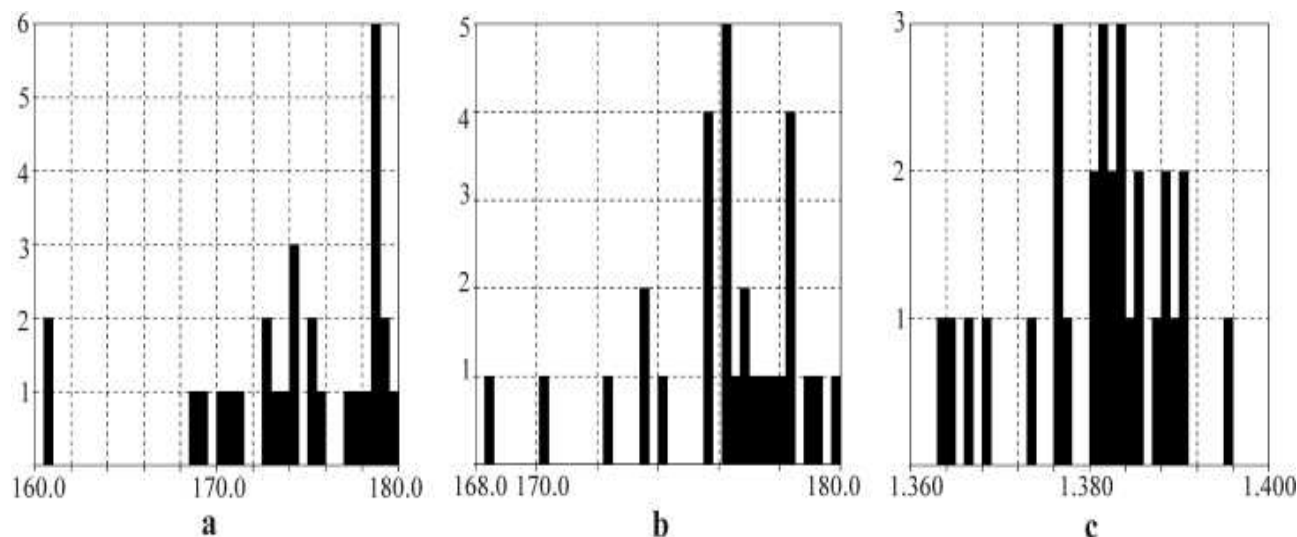
Among three selected structures containing the fragment of isoniazid's *meta*-isomer, we detected one structure with a crystallographic glide plane, one structure with a *pseudo*-glide plane, and one structure with an infinite chain of H-bonded molecules, formed by translation.

Among three selected structures containing the fragment of isoniazid's *ortho*-isomer, we detected two structures with infinite H-bonded chains formed by the crystallographic glide plane, and one structure with a *pseudo*-glide symmetry between independent molecules A and B.

We analyzed the values of the torsion angles C=N-N-C(O), N-

N-C(O)-C(Ar), and the lengths of N¹-N² bonds within the selected structures. The corresponding histograms are given in figure 8.

Indeed, it should be noted that in a centrosymmetric crystals the -C=N-N-C(O) torsion angles is in a range 161°-180°, the =N-N-C(O)-C_{ar} torsion angles is in a range 168°-180° and the N-N bond length does not exceed the value of 1.39 Å. In accordance with this, the three above-mentioned parameters of molecules B in crystals 5 and 6 have values that go beyond the random deviations. This fact is caused a specific reason - the formation of the local glide plane, rather than by a "local frustration".

**Fig.8** Histograms of the torsion angles -C=N-N-C(O) (a), =N-N-C(O)-C_{ar} (b), and the bond lengths N¹-N² (c) in crystals with pyridinoylhydrazonic fragment from CSD

Thus, the analysis showed that the most typical crystal packing exist in achiral compounds with a structural fragment of isoniazid and its isomers. Such type of crystal packing is formed by N-H...O=C hydrogen bond through the glide plane. Accordingly,

mirror-symmetric molecules alternate in such hydrogen-bonded chains (or dimer). In our structures 5-7 presence of the chiral diterpenoid skeleton does not prevent a pyridinoylhydrazonic fragment to form the interaction in the usual manner, namely,

through the glide plane. However, since the chiral crystal **5-7** does not contain a mirror-symmetrical molecule, the local mirror symmetry of nitrogen-containing substituents is achieved by conformational changes in the latter. As a result, structures **5-7** represent the interesting example of transfer a robust supramolecular motive from racemic environment in the homochiral one. Crystallographic “cost” for such a transfer is the inclusion of an “extra” molecule in the unitcell.

Powder Diffraction Data

The compounds **5-7** were examined by powder X-Ray crystallography to estimate the purity of the samples and check of

possible presence of polymorphs. The overlay of the experimental powder diffraction patterns with the calculated ones (Fig. 9) shows good correlation of the crystal structures with the bulk material. This fact indicates the absence of any other crystal form in all three samples.

The intensive scattering in the beginning of the first diffraction curve is caused by the long time of expositions (see «Materials and methods») of the small quantities of the sample **5**. The experiments was performed on the glass plate and background scattering was not subtracted from the experimental one.

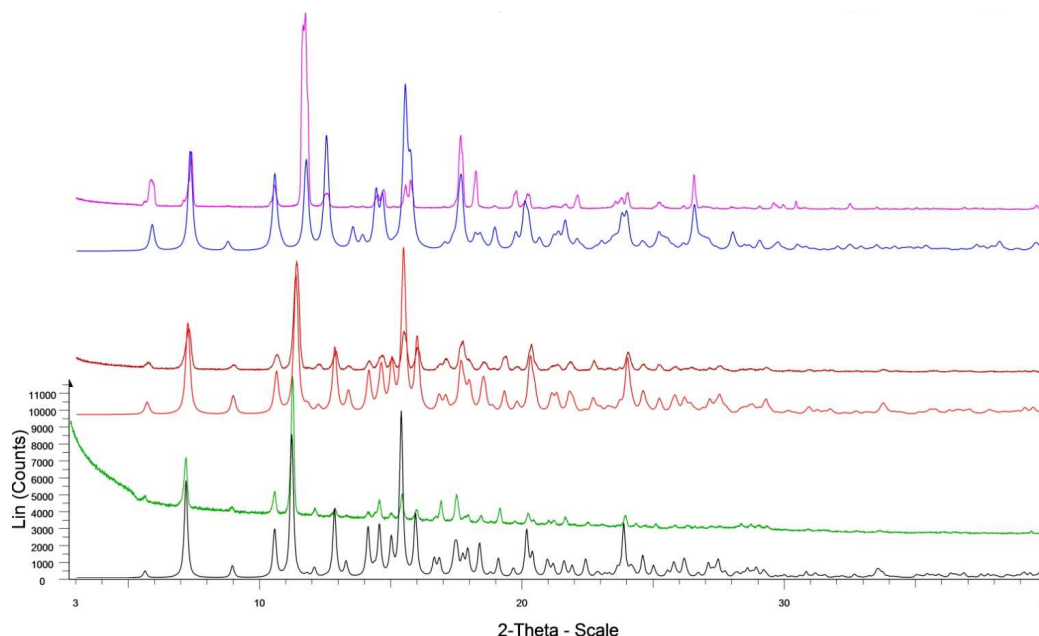


Fig.9 Powder X-Ray diffraction patterns of **5-7**, bottom-up: theoretical and experimental for **5**, **6**, **7**

IR Study

The above mentioned analysis of crystal packing has shown an interesting pattern of hydrogen bonds in the crystals of **5-7**. Namely: two nonequivalent intermolecular hydrogen bonds were observed in the crystals **5**, **6** as well as two nonequivalent intramolecular N-H...N interaction and one intermolecular H-bond which is weaker than similar bonds in the **5**, **6** have been detected in the crystal **7**. Intrigued by the question of how these characteristics of the crystal structure are manifested in the IR spectra, we have continued a study of all three samples.

The regions of NH stretching vibrations as well as the carbonyl absorptions are of great interest to us (i.e., the spectrum above 3000 cm^{-1} and the region 1500-1750 cm^{-1}). According to the literature data, the region of 1500-1750 cm^{-1} is rather difficult for IR spectra analysis of compounds with pyridinoylhydrazone fragments.¹⁵⁻²⁰ This is caused by the presence in this area of spectra both the absorption bands for C=N and C=O groups, as well as the signals referring to the pyridine moiety. It is not always possible to identify unambiguously each of these signals. In addition, the absorption band $\nu(\text{C=O})$ of the ester group is also expected in this part of the spectra.

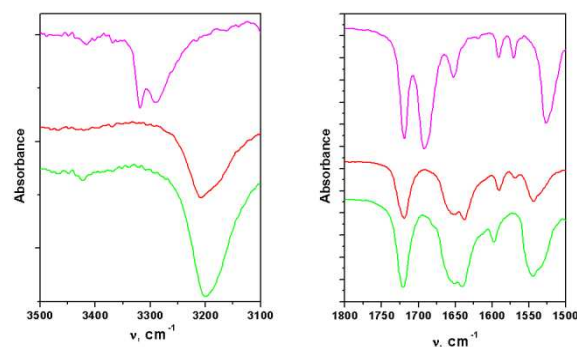


Fig.10 IR spectral data (ν , cm^{-1}) in the N-H (left) and C=O (right) stretching regions of compounds **5-7**, bottom-up: green **5**, red **6**, pink **7**.

IR spectra of the crystals **5** and **6** are quite similar to each other (Fig. 10), which is explained by the similarity of their structures as well as by the presence in both crystals the infinite chains formed by the hydrogen bonds N-H...O=C.

In previous publication,¹² based on the literature data about $\nu(\text{C}=\text{N})$ vibrations in benzylimine of isosteviols (1660 cm^{-1}),²¹ we have supposed, that a high intensity band appearing as a doublet ($1640, 1656\text{ cm}^{-1}$) for *para*- and ($1638, 1653\text{ cm}^{-1}$) for *meta*-isomers is the result of the overlapping of the “amide I”

($\nu(\text{C}=\text{O})$) and $\nu(\text{C}=\text{N})$ bands.

However, the novel X-Ray data on the crystal structure of all three isomers as well as the DFT calculations of IR spectra of the isolated molecules **5-7** (B3LYP, 6-31G (*d, p*)), enforced us to revise this assignment (Table 6).

Table 6 Selected fragments of theoretical and experimental IR spectral data of compounds **5-7**: frequencies (ν, cm^{-1}) and intensity (J)

	5		6		7	
C=N	Observed values Overlapping with «Amide I»	DFT 1661 (27)	Observed values Overlapping with «Amide I»	DFT 1661 (24)	Observed values 1653	DFT 1658 (20)
C(O)=O	1721	1728 (150)	1719	1728 (141)	1729	1719 (138)
«Amide I» $\nu \text{C(NH)=O}$	1640, 1656	1724 (307)	1638, 1653	1724(322)	1692	1726 (350)
«Amide II» $\delta \text{N-H}$	1544	1490 (333)	1543	1486 (334)	1527	1501 (517)
Py	1597, the second band overlapping with «Amide II»	1583 (17), 1549 (22)	1590, 1569	1579 (36), 1559 (13)	1591, 1571	1581 (27), 1564 (13)
νNH	3201, shoulder	3416 (12.9)	3209, 3177	3416 (18.8)	3319, 3289	3386 (25)

DFT calculations allowed us to identify unambiguously the $\nu(\text{C}=\text{O})$ bands of the ester moieties: 1721 and 1719 cm^{-1} for compounds **5**, **6**, respectively. High intensity bands revealed as doublets with two maxima ($1640, 1656\text{ cm}^{-1}$ for the *para*- and $1638, 1653\text{ cm}^{-1}$ for the *meta*-isomer) we have assigned to $\nu(\text{C}=\text{O})$ hydrazide moiety. The cleavage of these bands is probably caused by the differences in the crystallographic parameters of nonequivalent intermolecular hydrogen bonds $\text{N-H}\cdots\text{O}=\text{C}$ (A similar cleavage of $\text{C}=\text{O}$ bands in IR spectrum, caused by the presence of two independent molecules in the crystal observed authors²²). The shift of these frequencies relatively to the calculated values for the isolated molecules **5**, **6** (Table 6) is associated with the implementation of strong hydrogen bonds.

The low-intensity band $\nu(\text{C}=\text{N})$, is apparently inside of the band $\nu(\text{C}=\text{O})$ of hydrazide moiety. A shoulder at $\sim 3180\text{ cm}^{-1}$ on the peak $\nu(\text{N-H})$ 3201 cm^{-1} for the *para*-isomer **5** and on the peak $\nu(\text{N-H})$ 3209 cm^{-1} for the *meta*-isomer **6** we have previously attributed¹² to the overtones. But novel X-Ray data obtained for these compounds indicate that the geometrical parameters of the intermolecular hydrogen bonds $\text{N-H}\cdots\text{O}=\text{C}$ for molecules **A** and **B** of crystals **5** and **6** are different. This difference may lead to the splitting of the band $\nu(\text{N-H})$.

The frequencies, corresponding to the vibrations of the pyridine ring are in a good agreement with the calculated data and unambiguously identified (Table 6). High-intensity band “amide II” (deformation vibration of N-H bond) is shifted to higher frequencies due to the presence of strong intermolecular H-bonds.

A system of hydrogen bonds for the *ortho*-isomer in the crystal **7** differs from that one in **5** and **6**, which is reflected in IR spectrum (Fig. 10). The N-H bond in the molecule **A** of the crystal **7** participates only in intramolecular $\text{N-H}\cdots\text{N}$ interaction with the nitrogen atom of the pyridine cycle, while in the molecule **B** the two types of interactions are realized: the intramolecular interaction $\text{N-H}\cdots\text{N}(\text{Py})$ and weak intermolecular

hydrogen bond $\text{N-H}\cdots\text{O}=\text{C}$. The $\text{C}=\text{O}$ bond of the hydrazide group of the molecule **A** remains free. As a result, the maximum of the band $\nu(\text{C}=\text{O})$ 1692 cm^{-1} of the crystal **7** is observed in a higher frequencies region, than $\nu(\text{C}=\text{O})$ of the crystals **5** and **6**, and the $\nu(\text{N-H})$ absorption band splits and has maxima at 3319 and 3289 cm^{-1} .

It should be noted, that H-bonds for the *para*-isomer **5** and *meta*-isomer **6** are stronger, than in the *ortho*- isomer **7**, therefore the intensities of $\nu(\text{NH})$ for **5** and **6** is much higher than in the case of compound **7**, and the absorption bands $\nu(\text{NH})$ for them are observed in the lower frequencies region (at $\sim 3200\text{ cm}^{-1}$).

Conclusions

We have established a interesting feature of the crystallization of compounds **5-7** obtained from isosteviol and hydrazides of pyridinecarboxylic acids, namely, that they are crystallized in space group P2_1 with two independent molecules, the mutual disposition of which corresponds with the presence of local symmetry element – the glide plane, relative to which the key hydrogen bonding moiety fragment has either “pseudo-right” or “pseudo-left” conformation. Such type of crystal packing – H-bonded chains or dimers formed by $\text{N-H}\cdots\text{O}=\text{C}$ interaction through the glide plane – is a most typical packing in achiral compounds with a structural fragment of isoniazid and its isomers, as the CCDC analysis showed. Thus, the structures **5-7** represent the interesting example of transfer a robust supramolecular mirror-symmetry motive from racemic environment in the homochiral one, but inclusion of an “extra” molecule in a unitcell is a “cost” of such transferring.

Materials and methods

Compounds **5-7** were synthesized according to known protocol.¹² The physicochemical properties of these compounds agreed with those published.¹²

Single-Crystal X-Ray

The X-ray diffraction data for the crystals of **5** (low-temperature experiment), **6** and **7** were collected on a Smart Apex II automatic diffractometer using graphite monochromated radiation MoK α (λ 0.71073), room-temperature experiment for the crystal **5** was carried out on a Kappa Apex II automatic diffractometer using graphite monochromated radiation CuK α (λ 1.54178). Details of crystal data, data collection, and refinement are given in Table 1 and in Table S1. The structures were solved by direct method using the SHELXS²³ program and refined by full-matrix least-squares using SHELXL97²³ program. All the non-hydrogen atoms were refined with anisotropic atomic displacement parameters. H(C) atoms were constrained as riding atoms, with C-H set to 0.95 Å. The H(N) atoms were located from a difference Fourier map and refined isotropically in the final stages of refinement. All calculations were performed using WinGX²⁴ and APEX²⁵ programs. Search for additional (non)-crystallographic symmetry between residues through the program PLATON²⁶ (NONSYM option) has resulted in the detection of common features of crystals **5-7**: smallest angle of [RotAx] with plane normal (1. 0. 2.) Crystallographic data (excluding structure factors) for the structure **5, 6, 7** reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication, the corresponding CCDC numbers are given in the table 1 (low-temperature crystal data) and table S1 (room-temperature crystal data). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Powder XRD

The X-ray phase studies were performed on an automated D8 Advance X-ray diffractometer (Bruker) equipped with a Vario setup and a Vantec linear coordinate detector. The CuK α 1 radiation monochromated by the curved Johansson monochromator (λ = 1.5406 Å) was used, and the performance mode of the X-ray tube was 40 kV, 40 mA. Experiments were carried out at room temperature in the Bragg-Brentano geometry. Patterns were recorded in the 2θ range between 3 and 60°, in 0.008° steps, with a step time of 0.3s (samples of compound **6, 7**) and 1.5 s (sample of compound **5**). Powder samples were slightly pressed in a standard holder or on the glass plate before experiment.

For the calculation of theoretical diffraction patterns we used the data of X-Ray single crystal experiments performed at room temperature.

IR spectroscopy

The spectra were recorded in the range from 400 to 4000 cm⁻¹ on a Bruker Vector-22 spectrometer with Fourier transform from samples dispersed in mineral oil.

DFT calculations

Geometry optimizations and vibrational frequencies were carried out at basic DFT level using B3LYP^{27,28} 6-31G(*d,p*) basis set available in Gaussian-03 package.²⁹ These values were corrected using scale factor 0.9613 [DFT]³⁰ and the corrected frequencies and proposed assignments were summarized in Table 6 along with the observed values. These values indicate that there is a close agreement between the calculated values and observed values.

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Notes and references

^a A.E. Arbuzov Institute of Organic and Physical Chemistry of Kazan Scientific Center of Russian Academy of Sciences, Arbuzov Str. 8, 420088 Kazan, Russia. E-mail: lod_olga@mail.ru

[‡] Electronic Supplementary Information (ESI) available: room-temperature crystal data of crystal **5-7**. CCDC reference numbers 973306-973311. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x

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