Diastereoselective synthesis of 4,5-dihydroxyimidazolidin-2-ones (-thiones) and their structure

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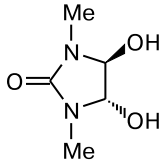
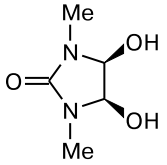
Studies on the synthesis of 4,5-dihydroxyimidazolidin-2-ones (-thiones) based on the condensation of ureas or thioureas with glyoxal or 1,2-dioxo-1,2-diphenylethane showed high diastereoselectivity in the formation of racemates (*trans*-diastereomers) of 4,5-dihydroxyimidazolidin-2-ones (-thiones) and *meso*-forms (*cis*-diastereomers) of 4,5-dihydroxy-4,5-diphenyl-1,3-dialkylimidazolidine-2-thiones; plausible mechanisms of their formation were suggested. X-ray diffraction studies confirmed structures of diastereomers for separate examples of racemates and *meso*-forms of 4,5-dihydroxyimidazolidin-2-ones (-thiones).

Key words: diastereoselective synthesis, 4,5-dihydroxyimidazolidin-2-ones (-thiones), X-ray diffraction studies.

Hydroxy groups in 4,5-dihydroxyimidazolidin-2-ones (-thiones) **1** and **2** (DHI and DHIT)* are known to have either *trans*- or *cis*-arrangement with respect to the imidazolidine ring[1—5] and hence different reactivity.[1] For example, while sodium metaperiodate[1] oxidizes only 62% of *trans*-isomer **1´a** during 24 h, *cis*-4,5-dihydroxy-1,3-dimethylimidazolidin-2-one **1″a** is completely oxidized already within 5—10 min, that is apparently due to their stereochemical distinctions.



1´a



1″a

However, so far stereochemical aspects of DHI and DHIT formation were not satisfactorily discussed in the literature, therefore, the purpose of the present work is to in detail study diastereoselectivity of the reactions of mono- and disubstituted at the nitrogen atoms ureas and thioureas with glyoxal and benzil, which have not been studied from this point of view, and to establish structure of the products obtained.

* Here and further, abbreviations DHI **1** and DHIT **2** correspond to the mixtures of racemates and *meso*-forms.

4,5-Dihydroxyimidazolidin-2-ones (-thiones) **1** and **2** are obtained by the reaction of ureas or thioureas with α-dicarbonyl compounds (mainly, with glyoxal and 1,2-dioxo-1,2-diphenylethane (benzil)), the hydroxy groups in DHI **1** and DHIT **2** can be *trans*- or *cis*-oriented with respect to the imidazolidine ring.[1—5] For the DHI and DHIT synthesized by the condensation of urea, 1,3-dimethylurea, thiourea, 1,3-dimethyl(diethyl)thioureas with glyoxal[1—4] and 1,3-diethylthiourea with benzil[5], such an isomerism was confirmed experimentally, with the individual isomers being isolated. Use of the notions *cis*- and *trans*-isomers of DHI and DHIT does not entirely reflect stereochemistry of these reagents. Since the carbon atoms C(4) and C(5) are chiral, the DHI and DHIT formed are diastereomers, with the *trans*-stereoisomers of DHI **1´** and DHIT **2´** being racemates, which can be separated to enantiomers independent on whether the nitrogen atoms have different or identical substituents. The carbon atoms in DHI **1″** and DHIT **2″** with *cis*-arrangement of the hydroxy groups have the opposite configuration, therefore, these compounds in the case of identical substituents at the nitrogen atoms have a plane of symmetry and are internal *meso*-forms. If in *cis*-stereoisomers substituents at the nitrogen atoms are different, *cis*-DHI and DHIT are racemates. Formation of diastereomers can proceed diastereoselectively.

Analysis of the literature data[1—5] showed that diastereoselectivity of the formation of DHI and DHIT can be

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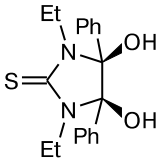
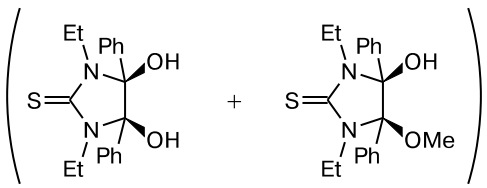
evaluated based on ^{1}H NMR spectra, in which signals for the protons at the carbon atoms C(4) and C(5) in *trans*-stereoisomers **1′** and **2′** are found more up-field than the signals for similar protons in *cis*-stereoisomers **1″** and **2″**. The reaction of glyoxal with urea leads predominantly to *trans*-stereoisomer **1′b**, while with 1,3-dimethylurea to a mixture of stereoisomers, with the ratio of *trans*- (**1′a**) and *cis*-stereoisomers (**1″a**) under acid-catalysis conditions being 95 : 5.[1,2] When 1-*tert*-butyl-3-methylurea was used, only *trans*-isomer **1′d** was isolated.[3] In the case of thioureas, DHIT **2a**,**b** were isolated as mixtures of *cis*- and *trans*-stereoisomers with predominance of *trans*-stereoisomers **2′a**,**b**, whereas preparation of DHIT **2c** predominantly gives *cis*-stereoisomer **2″c**.[4] Benzil with 1,3-diethylthiourea nearly exclusively forms *cis*-DHIT **2″d** both in the free form and as a cocrystallizate **3**.[5] X-ray diffraction studies showed that **1′b** is a conglomerate (a mixture of enantiomeric crystals, space group $P2_12_12_1$),[2,6] whereas **1′d** and **2′a** crystallize as racemates, which was confirmed by the space groups *Pbca* and $P\bar{1}$, respectively.[3,4] *cis*-DHIT **2″d**, being a *meso*-form, crystallizes also in the nonchiral space group $P\bar{1}$.[5]

1′a—d, 2′a—c

1″a—d, 2″a—c



2″d



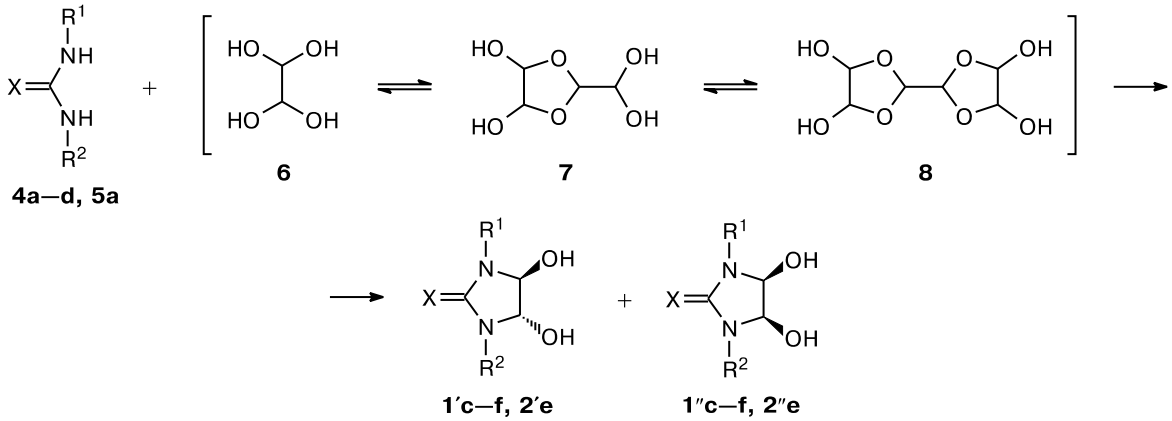
3

1′, **1″:** X = O, $R^1 = R^2$ = Me (**a**), H (**b**), Et (**c**), R^1 = Me, $R^2 = Bu^t$ (**d**)
2′, **2″:** X = S, $R^1 = R^2$ = H (**a**), Me (**b**), Et (**c**)

We effected condensation of 1,3-diethyl- (**4a**), 1-*tert*-butyl-3-methyl- (**4b**), 3-cyclohexyl-1-methyl- (**4c**), 1-cyclohexylureas (**4d**) and 1,3-diphenylthiourea (**5a**) with a freshly prepared aqueous solution of glyoxal trimeric dihydrate (Scheme 1). Glyoxal in aqueous solution normally exists as an equilibrium of hydrated forms:[3,7] bis-*gem*-diol **6**, dimeric dihydrate **7**, and trimeric dihydrate **8** (see Scheme 1). In the reactions with benzil **9**, we studied 1,3-dimethylurea (**4e**) and 1,3-dimethyl(diethyl)thioureas (**5b**,**c**) (Scheme 2), using reported procedures for the synthesis of DHI and DHIT,[3,5,8—12] including those developed by us earlier.[3,5,8]

A mixture of a racemate and a *meso*-form of 1,3-diethyl-DHI **1′c** and **1″c**, respectively (in 65% yield), was obtained in water at pH 4—5 and 50 °C during 7 h.[8] Diastereomers of 1-alkyl-3-methyl-DHI **1′d**,**e** and **1″d**,**e** were also obtained in water at pH 4—5 and 60 °C during 2 h (the yield of **1′d** and **1″d** was 35%, the yield of **1′e** and **1″e** was 52%).[3] The syntheses of 1-cyclohexyl-DHI **1′f** and **1″f** and 1,3-diphenyl-DHIT **2′e** and **2″e** are described in patents, and compounds are characterized only by melting points.[9,10] We succeeded in reproduction of the syn-

Scheme 1

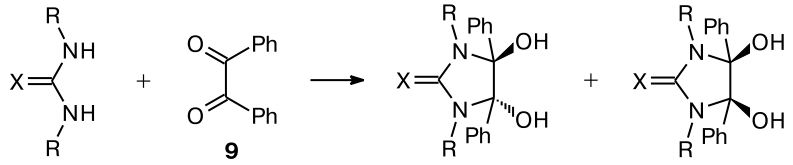


4a—d, 5a **6** **7** **8**

1′c—f, 2′e **1″c—f, 2″e**

1′, **1″:** X = O, $R^1 = R^2$ = Et (**c**), R^1 = Me, $R^2 = Bu^t$ (**d**), R^1 = Me, R^2 = *cyclo*-C_6H_{11} (**e**), R^1 = H, R^2 = *cyclo*-C_6H_{11} (**f**)
2′, **2″:** X = S, $R^1 = R^2$ = Ph (**e**)
4: X = O, $R^1 = R^2$ = Et (**a**), R^1 = Me, $R^2 = Bu^t$ (**b**), R^1 = Me, R^2 = *cyclo*-C_6H_{11} (**c**), R^1 = H, R^2 = *cyclo*-C_6H_{11} (**d**)
5: X = S, $R^1 = R^2$ = Ph (**a**)

Scheme 2



4e, 5b,c **9** **1′g, 2′d,f** **1″g, 2″d,f**

1′, **1″:** X = O, R = Me (**g**); **2′**, **2″:** X = S, R = Me (**f**), Et (**d**); **4:** X = O, R = Me (**e**); **5:** X = S, R = Me (**b**), Et (**c**)

thetic procedures: diastereomers **1′f** and **1″f** were obtained in isopropyl alcohol at pH 7.5 and 65 °C during 4 h (see Ref. 9) in 12% yield; diastereomers of 1,3-diphenyl-DHIT **2′e** and **2″e** were synthesized in a mixture of water—propan-2-ol (1 : 1) at pH 7.5 and reflux during 1 h (see Ref. 10) in 84% yield. Improving the literature procedures,[5,11,12] we carried out the reactions of 1,3-dimethylurea **4e** and 1,3-dimethyl(diethyl)thioureas **5b**,**c** with benzil **9** in methanol under alkali catalysis conditions (in the presence of KOH) upon reflux of the reaction mixtures during 2 and 5 h, that gave rise to diastereomers of DHI **1′g** and **1″g** (in 85% yield), as well as of DHIT **2′d**,**f** and **2″d**,**f** (in 83 and 37% yields, respectively).

The ratio of diastereomers in DHI **1c**—**g** and DHIT **2b**—**d** and completeness of their isolation from the reaction mixtures were evaluated based on the ^{1}H NMR spectra of solutions (in DMSO-d_6) of the diastereomer precipitates and concentrated to dryness filtrates. Analysis of the ^{1}H NMR spectra showed that the ratios of diastereomers DHI **1′c** : **1″c**, **1′d** : **1″d**, **1′e** : **1″e**, **1′f** : **1″f**, **1′g** : **1″g** are 12 : 1, 30 : 1, 20 : 1, 50 : 1, and 1 : 24, respectively, whereas for DHIT **2′d** : **2″d**, **2′e** : **2″e**, and **2′f** : **2″f** they are 1 : 99, 11 : 1, and 2 : 3, respectively. The ratios of diastereomers **1′c** and **1″c**, **1′d** and **1″d**, **1′e** and **1″e**, **1′f**, **1″f**, **2′e** and **2″e** were determined from the ratios of signal intensities for the protons of the CH—CH and OH groups (Table 1). The ratios of diastereomers **1′g** and **1″g**, **2′d** and **2″d**, **2′f** and **2″f** were evaluated from the ratios of signal intensities for the protons of the Ph groups (see Table 1). The variations in the yields (12—84%) and ratios of diastereomeric DHI and DHIT are explained by influence of the structure of the starting compounds on their ability to be involved into cyclization process.

In the ^{1}H NMR spectra of the reaction mixture residues, only traces of the signals for the protons of the DHI and DHIT predominant stereoisomers were observed, whereas no signals for the minor stereoisomers were observed at all. Based on the ^{1}H NMR spectroscopic data for isolated diastereomers, we concluded on high diastereoselectivity of the formation of racemic DHI **1′c**—**f** and DHIT **2′e** in the reactions of ureas **4a**—**d** and thiourea **5a** with glyoxal **6**—**8** and *meso*-forms of DHI **1″g** and DHIT **2″d** when urea **4e** and thiourea **5c** were reacted with benzil **9**. And only in the reaction of benzil **9** with 1,3-dimethylthiourea **5b**, the DHIT **2′f** and **2″f** are formed in the ratio 2 : 3 in high enough yield (83%).

The predominant isomers of DHI **1′c**,**d**,**e**,**f**, **1″g** and DHIT **2″d**,**f**, **2′e** were isolated by their crystallization from water (**1′c**,**d**,**e**, **1″g**), methanol (**2″d**,**f**), and a mixture of propan-2-ol—water (**1′f** and **2′e**). Physicochemical char-

Table 1. Chemical shifts (δ) of diastereomers **1′c**,**d**,**e**,**f**,**g** and **1″c**,**d**,**e**,**f**,**g**, **2′d**,**e**,**f** and **2″d**,**e**,**f** in the ^{1}H NMR spectra (DMSO-d_6)

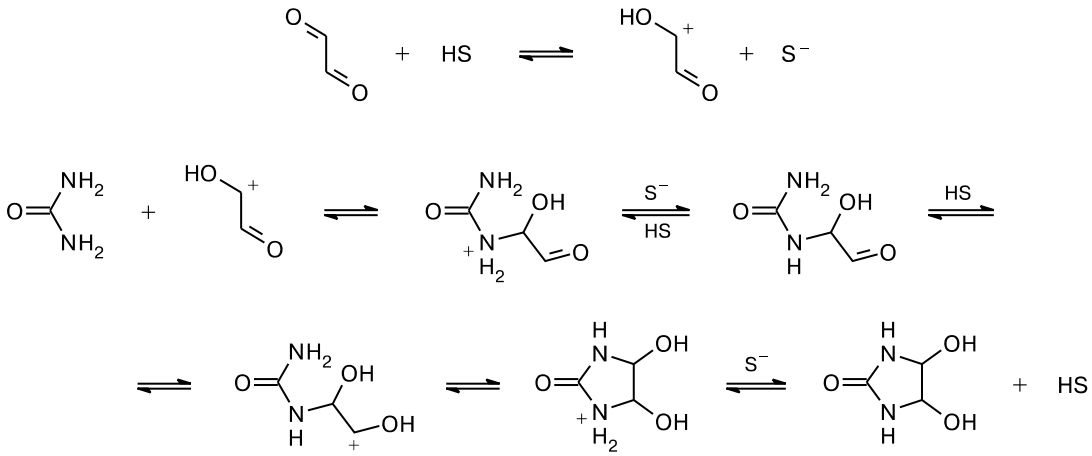
Group	δ
HC—CH	4.70* (s, **1′c**)[9]; 4.78* (s, **1″c**); 4.40 (m, **1′d**)[3]; 4.65 (m, **1′d**)[3]; 4.72 (m, **1″d**); 4.90 (m, **1″d**); 4.37 (m, **1′e**)[3]; 4.66 (m, **1′e**)[3]; 4.76 (m, **1″e**); 5.01 (m, **1″e**); 4.54 (d, *J* = 6.1 Hz, **1′f**); 4.65 (d, *J* = 7.3 Hz, **1′f**); 4.82 (d, *J* = 6.6 Hz, **1″f**); 4.97 (d, *J* = 7.1 Hz, **1″f**); 5.20 (d, *J* = 8.0 Hz, **2′e**); 5.62 (d, *J* = 6.5 Hz, **2″e**)
2 OH	5.83 (m, **1′d**); 6.00 (m, **1′d**)[3]; 5.67 (m, **1″d**); 5.77 (m, **1″d**); 5.90 (m, **1′e**); 6.05 (m, **1′e**)[3]; 5.66 (m, **1″e**); 5.82 (m, **1″e**); 7.08** (s, NH, **1′f**); 6.94** (s, NH, **1″f**); 7.11 (d, *J* = 8.2 Hz, **2′e**); 6.60 (d, *J* = 7.6 Hz, **2″e**)
2 Ph	7.13—7.35 (m, **1′g**); 6.84—7.05 (m, **1″g**)[12]; 7.20—7.40 (m, **2′d**); 7.01—7.14 (m, **2″d**)[5]; 7.14—7.36 (m, **2′f**); 6.80—7.00 (m, **2″f**)
Me	2.59 (s, **1′g**); 2.53 (s, **1″g**)[12]; 1.05 (t, *J* = 7.2 Hz, **2′d**); 1.33 (t, *J* = 7.1 Hz, **2″d**)[5]; 2.92 (s, **2′f**); 2.94 (s, **2″f**)
CH_2	3.30—3.41 (m, **2′d**); 3.26—3.38 (m, **2″d**), 3.85—3.97 (m, **2″d**)[5]

* In CD_3OD.

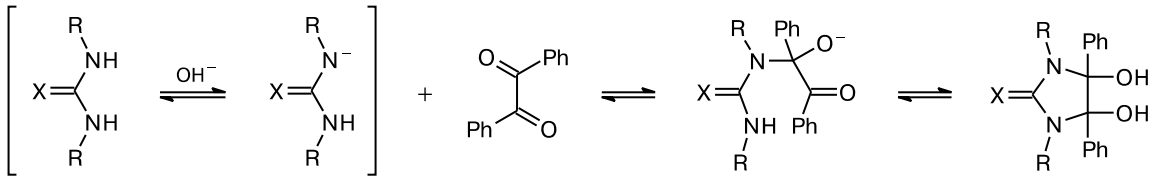
** In diastereomers, signals for the protons of the NH group are informative, since the signals for the protons of the OH group overlap with those of the Ph group (see Experimental).

Scheme 3

Mechanism 1



Mechanism 2



HS is an acid of medium strength.

acteristics of compounds **1′c**,**d**,**e**, **1″g** agree with those reported in the literature. There are no literature data on ^{1}H and ^{13}C NMR spectra for DHI **1′f** and DHIT **2″d**,**f**, **2′e**, therefore, they are given in the Experimental section. The minor diastereomers **1″c**,**d**,**e**,**f**, **1′g**, **2′d**,**f**, **2″e** were not isolated because of their very small amount, the diastereomers **1″f**, **2′d**,**f**, **2″e** are characterized only by ^{1}H NMR spectra.

The results obtained can be accounted for by different plausible mechanisms for the formation of DHI and DHIT from glyoxal and benzil.

The described earlier mechanisms for the formation of DHI and DHIT are still in dispute,[12—15] and they do not reflect stereochemical aspects (Scheme 3), therefore, they do not adequately explain the processes of diastereoselective formation of DHI and DHIT found by us.

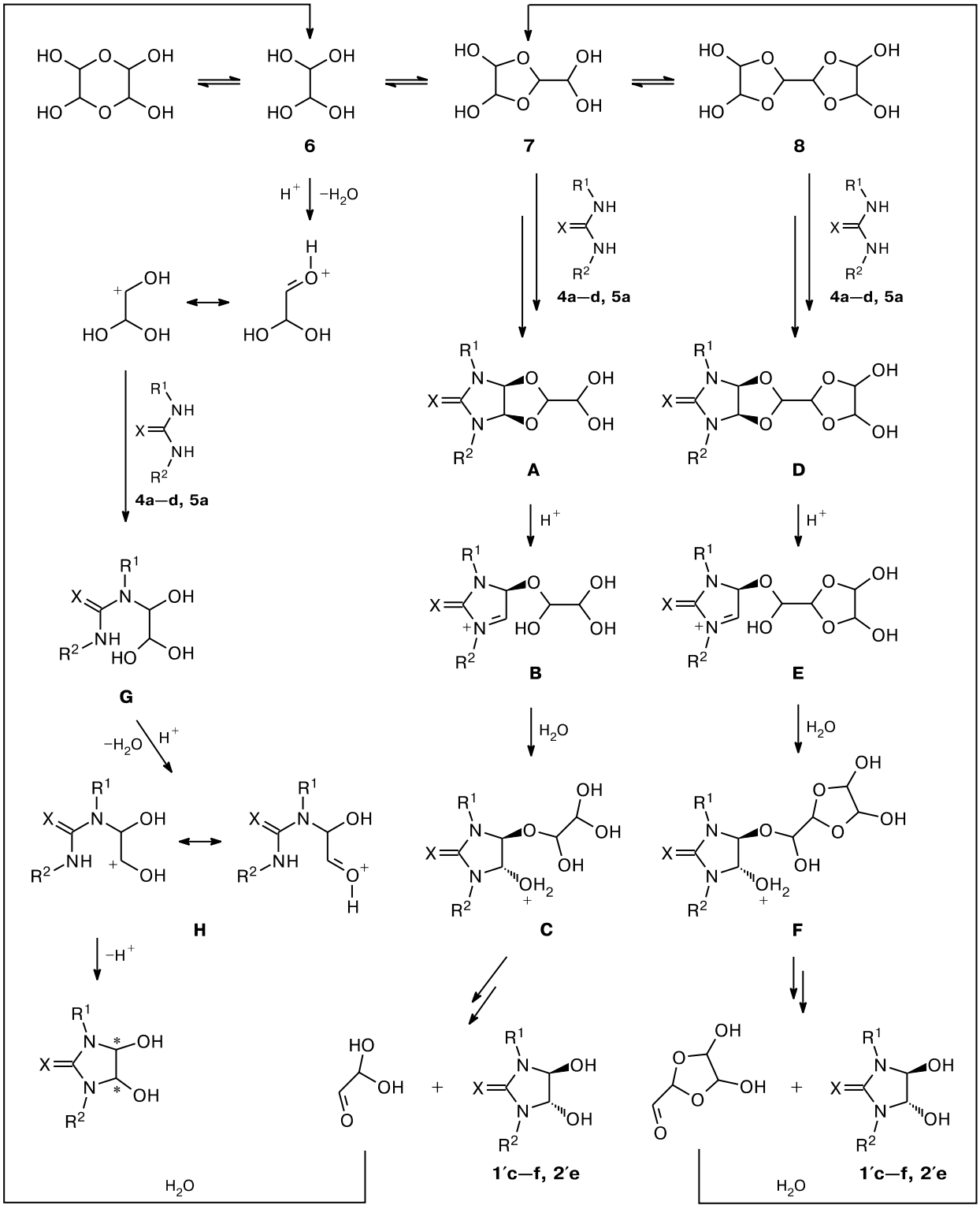
Proceeding from the data obtained, we suggest our own interpretation for the selective formation of racemates and *meso*-forms of DHI and DHIT (Schemes 4 and 5).

Since glyoxal exists in aqueous solutions in the equilibrium hydrated forms **6**—**8**, a predominant formation of racemates **1′c**—**f** and **2′e** occurs apparently due to the fact that the glyoxal forms **7** and **8** react with ureas **4a**—**d**, **5a**, because the intermediates **A**—**F**, which, apparently, facilitate intramolecular cyclization with predominant *trans*-orientation of the OH groups, can be formed only if these forms of glyoxal are present (see Scheme 4). As it is seen from the Scheme, possible involvement of bis-*gem*-diol **6** into the reactions with ureas **4a**—**d** and **5a** cannot explain selective preparation of diastereomers **1′c—f** and **2′e**, since the intermediates **G** and **H** formed cannot direct the reaction only to the side of diastereomers with *trans*-orientation of the hydroxy groups.

A predominant obtaining of *meso*-forms **1″g**, **2″d** and **2″f** is apparently explained by the ability of 1,3-dimethylurea **4e** and 1,3-dimethyl(diethyl)thioureas **5b**,**c** to form stable enough intermediates **I**—**K** (see Scheme 5).

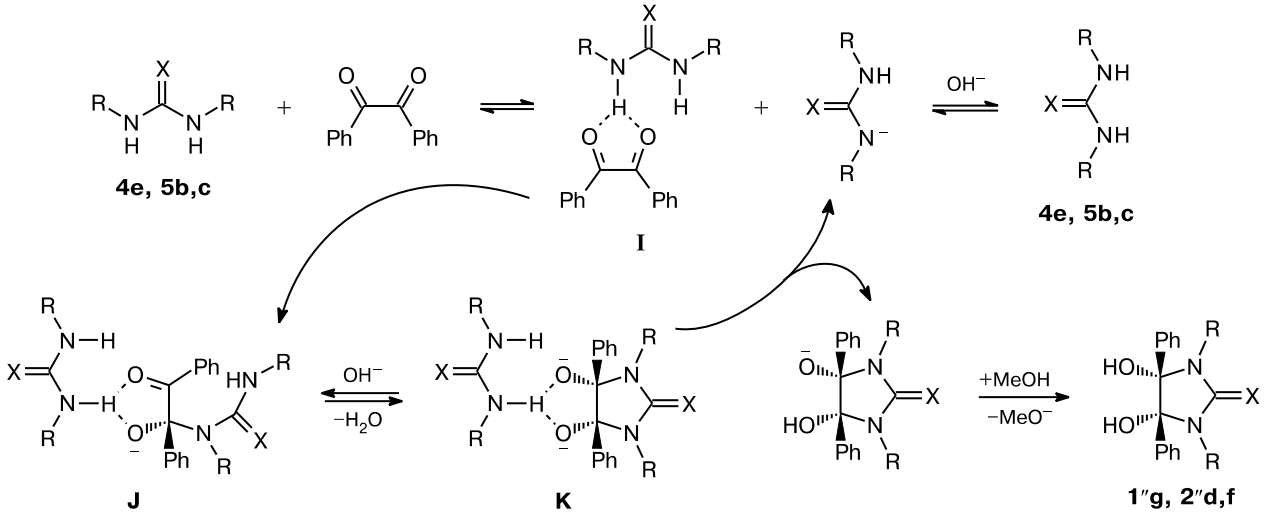
As it is seen from Scheme 5, urea **4e** and thioureas **5b**,**c** are not only reagents, but also catalysts of the reaction. To confirm their catalytic properties in this process, we collected additional data when excess of urea **4e** and thiourea **5b** (1.2 and 1.4 mol per 1 mol of benzil) were used in the reactions with benzil **9**. In the first case, the ratio of DHI diastereomers **1′g** and **1″g** remained unchanged and was 1 : 24, but the yield of diastereomers increased from 85 to 96%. In the second case, the ratio of diastereomers **2′f** : **2″f** changed from 2 : 3 to 1 : 11 and 1 : 13, with the yield increasing from 83 to 99%. It could have been suggested that the excess of thiourea **5b** facilitates isomerization of racemate **2′f** to *meso*-form **2″f**, but reflux of diastereomers **2′f**

Scheme 4



and **2″f** in the ratio 2 : 3 with 0.2 equiv. of thiourea during 15 and 30 min produced no changes in the diastereomeric composition. This indicates that no isomerization occurs. When the reaction is carried out during 2 h, diastereomers **2′f** and **2″f** are completely converted to thiohydantoin **10a**. The experiments performed showed that urea **4e**

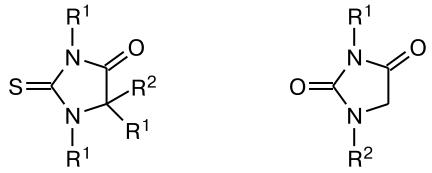
Scheme 5



X = O, S; R = Me, Et

and thiourea **5b** can catalyze formation of DHI and DHIT **1″g** and **2″f**.

Together with the synthesis of target compounds, all the processes under consideration were accompanied by side reactions, namely, by rearrangements of DHI and DHIT to the corresponding already known hydantoins **11a—e** (see Refs 3, 16, and 17) and thiohydantoins **10a—c** (see Refs 18—20), in which case the lower are the yields of diastereomers, the higher are the yields of compounds **10a**,**b** and **11a—f**, that is explained by influence of the structures of starting compounds on their reactivity.



10a—c **11a—e**

10: R^2 = Ph, R^1 = Me (**a**), Et (**b**), R^2 = H, R^1 = R^2 = Ph (**c**)
11: R^1 = R^2 = Et (**a**), R^1 = Me, R^2 = Bu^t (**b**), R^1 = Me, R^2 = *cyclo*-C_6H_{11} (**c**), R^1 = H, R^2 = *cyclo*-C_6H_{11} (**d**), R^1 = R^2 = Me (**e**)

For clarification of crystal structure of DHI **1´c**,**d**,**e**,**f**, **1″g**, DHIT **2″d**,**f**, **2´e**, and thiohydantoins **10a—c** and confirmation of their composition, we studied processes of crystallization of these compounds (see above), which resulted in obtaining crystals suitable for X-ray diffraction studies for compounds **1″g**, **2´f** and **2″f**. Crystals of compound **2´f** were found among crystals of **2″f** in the precipitate with the ratio of the products 2 : 3. In addition, we also succeeded in obtaining crystals for compounds **2´b** and **10d** synthesized earlier.[4,21]

Results of X-ray diffraction studies of compounds **1″g**, **2´f**, and **2″f** confirm the ^1H and ^{13}C NMR spectroscopic data. The torsional angles O—C(1)—C(3)—O in *cis*-DHI **1″g** and *trans*-DHIT **2´f** (Fig. 1) are 26.6(3) and 160.0(1)°, respectively. The imidazolidine ring has the *twist* conformation, with the atoms C(1) and C(3) coming out of the plane of other atoms by 0.33(1) and 0.13(1) Å in **1″g** and by 0.21(1) and 0.25(1) Å in **2´f**. In both cases, one of the nitrogen atoms is noticeablely pyramidalized: the sum of its bond angles is equal to 350.4(3) and 353.4(1)° in **1″g** and **2´f**, respectively (for the second nitrogen atom, 359.2(2) and 357.6(1)°). The differences in the mutual arrangement of the OH groups are responsible for different supramolecular organization in **1″g** and **2´f**. In the first case, the molecules are combined into infinite bands by the hydrogen bonds O—H...O (O...O 2.668(4) and 2.854(3) Å, the angle O—H—O 173(1) and 126(1)°), whereas in the second case, the hydrogen bonds O—H...S (O...S 3.2775(14) and 3.2970(14) Å, the angle O—H—S 166(1) and 145(1)°) provide formation of a three-dimensional framework; in both systems, a great number of weaker contacts C—H...O and C—H...π are effected (as well as C—H...C in **2´f**).

The *cis*-isomer **2″f** is distinguished by its ability to crystallize as a solvate with a methanol molecule (**2″f·MeOH**) (Fig. 2). The torsional angle O—C(4)—C(5)—O in compound **2″f** is 27.5(1)°. The heterocycle in the latter has the *twist* conformation, with the atoms C(4) and C(5) coming out of the plane by 0.28(1) and 0.18(1) Å, one of the nitrogen atoms is pyramidalized (the sum of the bond angles C—N—C is equal 358.2(2) and 352.6(1)°). In the crystal of **2″f·MeOH**, the molecules of **2″f** are combined with each other into infinite chains by the hydrogen bond O—H...S (O...S 3.2558(11) Å, the angle O—H—S 146(1)°),

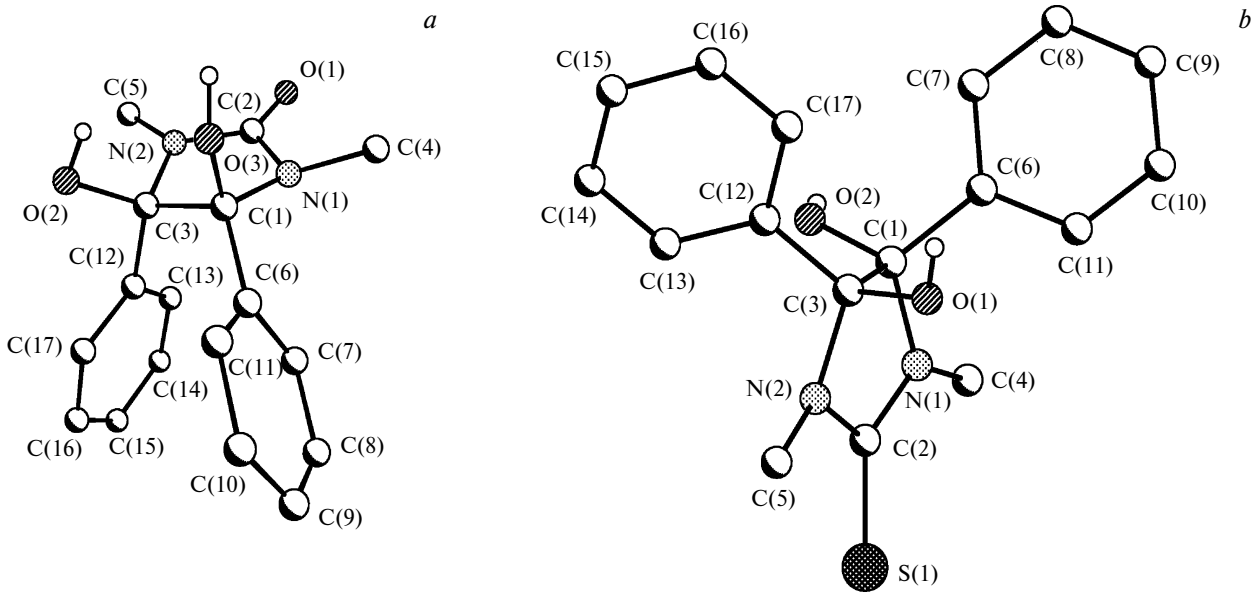


Fig. 1. General view of compounds **1″g** (*a*) and **2´f** (*b*).

as well as with the methanol molecules due to the hydrogen bonds O—H...O (O...O 2.6521(16) Å, the angle O—H—O 172(1)°) and O—H...S (O...S 3.2562(13) Å, the angle O—H—S 169(1)°) to form the H-bonded bands. These associates are hold in the crystal by weaker contacts of the type C—H...O, C—H...S, H...H, and O...π.

Because X-ray diffraction studies of DHIT **2´b** resulted in obtaining of earlier unpublished interesting data on the geometry of this molecule, we describe them in the present work. The molecule of **2´b** (Fig. 3) lies on the axis 2. As a result, its geometry significantly differs from that of DHI **1´a** studied earlier.[4] Though in both cases the hydroxyl groups are in *trans*-position with the close values of torsional angles O(1)—C(1)—C(1A)—O(1A) (133.3(1)° in **2´b** and 139.6(1)° in DHI **1´a** (see Ref. 4)), the imidazolidine ring in **2´b** is in the flattened *twist* conformation, with the atoms C(1) and C(1A) coming out of the plane of other atoms by 0.13(1) Å, whereas surrounding of the nitrogen atoms is ideally planar (the sum of their bond angles is equal to 360°). By analogy, the absence in **2´b** of NH groups leads to completely different supramolecular organization in the crystal. The OH groups, being a proton donors, are involved into the formation of hydrogen bonds with the atom S(1) (S...O 3.2292(11) Å, the angle O—H—S 162(1)°; see Fig. 3, *b*), binding molecules into infinite H-bonded bands. These associates are connected with each other by weaker contacts of the type O...C and C—H...O (the distances O...C are 3.142(1) and 3.664(1) Å, respectively) to form a three-dimensional framework.

During studies of crystallization processes for the synthesized thiohydantoins **10a—c** and the earlier obtained[21] thiohydantoin **10d**, we succeeded in growing crystals only for the latter and, since this group of compounds has some characteristic distinctions, we report here the X-ray diffraction data for thiohydantoin **10d** (Fig. 4). The heterocycle **10d** is planar in the crystal (the atoms come out of its mean-square plane on average by 0.01(1) Å). Introduction into it of a C=O group also led to a significant nonequivalence of the bonds C(2)—N (1.3305(19) and 1.3978(18) Å), that is characteristic of this class of compounds. The crystal packing of **10d** is distinguished by a very short contact S...S (3.563(1) Å; see Fig. 4, *b*), which combine the molecules into the centrosymmetric dimers; the contacts C—H...S (C...S 3.578(1)—3.763(1) Å) also contribute into

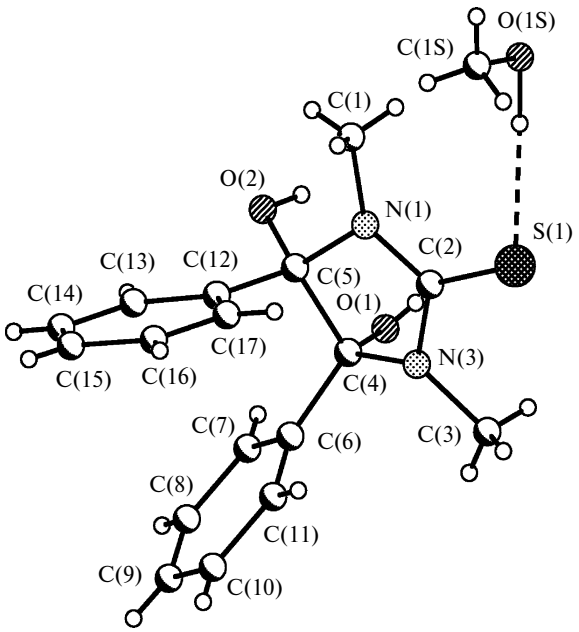


Fig. 2. General view of compound **2″f·MeOH**, illustrating formation of an H-bond with the methanol solvent molecule.

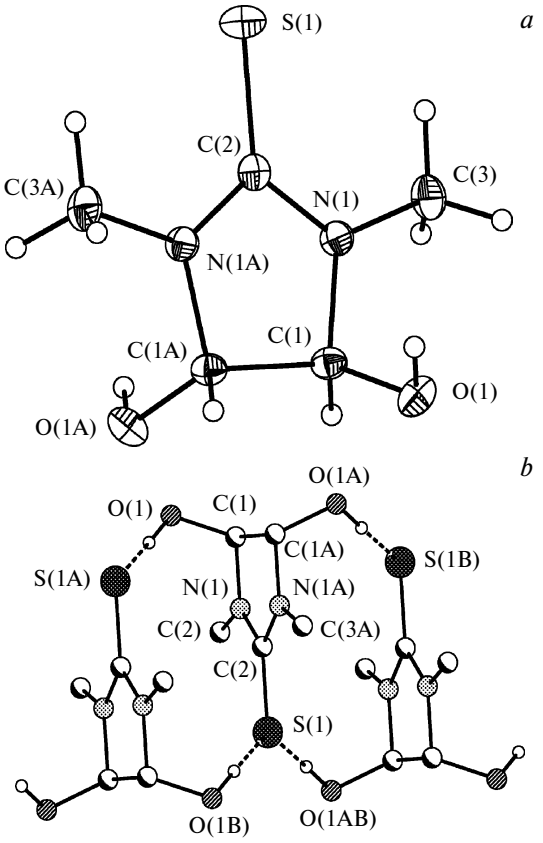


Fig. 3. General view of compound **2´b** in representation of atoms by ellipsoids of thermal vibrations ($p = 50\%$; *a*) and a fragment of an infinite H-bonded chain in the crystal (hydrogen atoms, except those from the OH groups, are not shown; *b*).

the stabilization of the latter. Formation of a three-dimensional framework is finished by the contacts of the type C—H...O and O...C.

In conclusion, while studying the reactions of ureas **4a**—**e** and thioureas **5a**—**c** with glyoxal **6**—**8** and benzil **9**, we considered stereochemical aspects of these reactions and for the first time observed high diastereoselectivity of the formation of racemates **1´c**—**f**, **2´e** and *meso*-forms **1″g**, **2″d**,**f**. Plausible mechanisms were suggested, accounting for their predominant formation. The structural features were discussed using results of X-ray diffraction studies.

Experimental

Ureas **4a**—**e**, thioureas **5a**—**c**, glyoxal trimeric dihydrate, and benzil **9** were commercially available from Acros. NMR spectra were recorded on Bruker AM-250 (^{1}H, 250 MHz) and Bruker AM-300 (^{13}C, 75.5 MHz) spectrometers in DMSO-d_6, chemical shift are given in the δ-scale using Me_4Si as an internal standard.

Melting points were determined on a Gallenkamp apparatus (Sanyo).

X-ray diffraction analyses of compounds **1″g**, **2´b** and **10d** were performed on a SMART 1000 CCD diffractometer (Mo-Kα irradiation, graphite monochromator, ω-scan technique), of compounds **2´f** and **2″f·MeOH** on a SMART APEX2 CCD diffractometer (Mo-Kα irradiation, graphite monochromator, ω-scan technique). The structures were solved by direct method and refined by the least square method in anisotropic full-matrix approximation on F^2_{hkl}. The hydrogen atoms of the OH groups in the structures **1″g**, **2´b**, **2´f**, and **2″f·MeOH** were localized from the differential Fourier-syntheses of electron density, whereas positions of the H(C) atoms were calculated geometrically. All the hydrogen atoms were refined in isotropic approximation using the riding model. The principal crystallographic data and parameters of refinement are given in Table 2. All the calculations were performed using the SHELXTL PLUS program package.[22]

Diastereomers **1´c**,**d**,**e**,**g and 1″c**,**d**,**e**,**g** were synthesized according to the known procedures, some aspects of their syntheses were discussed in the paper text. Since compounds **1´f** and **1″f**, **2´e** and **2″e** were obtained similarly to the patented procedures,[9,10]

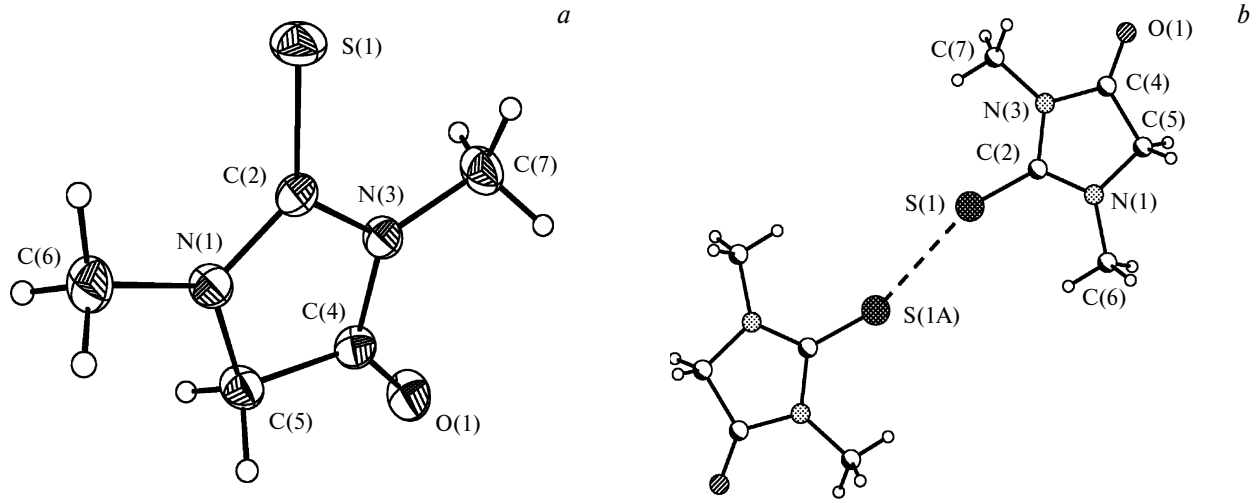


Fig. 4. General view of compound **10d** in representation of atoms by ellipsoids of thermal vibrations ($p = 50\%$, *a*) and a dimer formed by a shortened contact S...S in the crystal (*b*).

Table 2. Principal crystallographic data and parameters of refinement for the structures **1″g**, **2´b**, **2´f**, **2″f·MeOH**, and **10d**

Parameter	**1″g**	**2´b**	**2´f**	**2″f·MeOH**	**10d**
Molecular formula	$C_{17}H_{18}N_2O_3$	$C_5H_{10}N_2O_2S$	$C_{17}H_{18}N_2O_2S$	$C_{18}H_{22}N_2O_3S$	$C_5H_8N_2OS$
Molecular weight	298.33	162.21	314.39	346.44	144.19
T/K	120	120	100	100	120
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$C2/c$	$Pna2_1$	$P2_1/c$	$P2_1/c$
Z 4	4	4	4	4	
a/Å	15.090(4)	12.8251(13)	11.6699(18)	10.8063(9)	7.8361(7)
b/Å	6.1497(16)	7.6602(8)	15.832(3)	6.2845(5)	12.1398(10)
c/Å	16.285(4)	7.3448(7)	8.2679(12)	25.764(2)	7.2031(6)
β/deg	104.055(5)	96.615(2)	90.00	96.755(2)	100.442(5)
V/Å^3	1466.0(7)	716.77(12)	1527.5(4)	1737.5(2)	673.87(10)
d_{calc}/g cm^{-3}	1.352	1.503	1.367	1.324	1.421
μ/cm^{-1}	0.94	3.91	2.21	2.05	3.95
F(000)	632	344	664	736	304
$2\theta_{max}$/deg	55	57	54	58	58
Number of measured reflections	13790	3799	6642	18198	5396
Number of independent reflections	3532	951	3193	4622	1773
Number of reflections with $I > 2\sigma(I)$	2062	852	2803	3579	1439
Number of refined parameters	201	48	201	220	84
R_1 ($I > 2\sigma(I)$)	0.0785	0.0348	0.0300	0.0473	0.0366
wR_2 (all the reflections)	0.2079	0.0945	0.0673	0.1187	0.0882
GOOF	1.003	1.006	1.049	1.002	1.002
Residual electron density/e Å^{-3}, ρ_{max}/ρ_{min})	0.541/−0.446	0.519/−0.342	0.153/−0.192	0.472/−0.268	0.360/−0.257

we describe these procedures in our work. For the synthesis of DHIT **2´d** and **2″d**, we used a modified procedure developed by us earlier,[5] since we need no cocrystallizate **3** in this study. For DHIT **2´f** and **2″f**, we optimized a published[12] procedure.

Synthesis of (4*R,5*R**)-1-cyclohexyl-4,5-dihydroxyimidazolidin-2-one (1´f) and (4*R**,5*S**)-1-cyclohexyl-4,5-dihydroxyimidazolidin-2-one (1″f).** A freshly prepared 30% aqueous glyoxal trimeric dihydrate (0.033 mol) and K_2CO_3 (to pH 7—7.5) were added to a solution of cyclohexylurea **4d** (0.1 mol) in Pr^{i}OH (100 mL). The reaction mixture was heated to 65 °C, kept for 4 h, and left in air to crystallize. A precipitate formed within 4 days was filtered off (side products). A precipitate of **1´f** and **1″f** was formed from the filtrate after 2 days, which was filtered off and dried in air. The ratio of isomers was determined as 50 : 1. Precipitate **1´f** was isolated after recrystallization from Pr^{i}OH.

Compound **1´f.** The yield was 10%. M.p. 148—150 °C.[9] Found (%): C, 54.01; H, 7.99; N, 13.87. $C_9H_{16}N_2O_3$. Calculated (%): C, 53.98; H, 8.05; N, 13.69. ^{1}H NMR, δ: 0.95—1.32* (m, 3 H, CH_2); 1.4—1.81* (m, 7 H, CH_2); 3.32—3.43 (m, 1 H, CH); 4.82 (d, 1 H, CH, J = 6.6 Hz); 4.97 (d, 1 H, CH, J = 7.1 Hz); 5.82 (d, 1 H, OH, J = 6.5 Hz); 5.86 (d, 1 H, OH, J = 7.5 Hz); 7.08 (s, 1 H, NH). ^{13}C NMR, δ: 25.30, 25.57; 25,71; 29.95; 32.61 (5 CH_2, *cyclo*-C_6H_{11}); 50.59 (CH, *cyclo*-C_6H_{11}); 82.03, 85.53 (2 CH); 158.31 (CO).

Compound **1″f.** ^{1}H NMR, δ: 0.95—1.32* (m, 3 H, CH_2); 1.4—1.81* (m, 7 H, CH_2); 3.15—3.18 (m, 1 H, CH); 4.54 (d, 1 H, CH, J = 6.1 Hz); 4.65 (d, 1 H, CH, J = 7.3 Hz); 5.49 (d, 1 H, OH, J = 5.8 Hz); 5.54 (d, 1 H, OH, J = 7.9 Hz); 6.94 (s, 1 H, NH).

Synthesis of (4*R,5*R**)-4,5-dihydroxy-1,3-diphenylimidazolidine-2-thione (2´e) and (4*R**,5*S**)-4,5-dihydroxy-1,3-diphenylimidazolidine-2-thione (2″e).** Potassium carbonate was added in portions to a solution of 1,3-diphenylthiourea **5a** (0.1 mol) and glyoxal trimeric dihydrate **6**—**8** (0.033 mol) in a mixture of H_2O (50 mL) and Pr^{i}OH (50 mL) to pH 7.5, and the mixture was refluxed for 1 h. Thin needle-like yellowish brown crystals of **2´e** and **2″e** were formed on cooling, which were filtered off and dried in air. The ratio of isomers was determined as 11 : 1. Precipitate of **2´e** was isolated after recrystallization from the Pr^{i}OH—water mixture (1 : 1).

Compound **2´e.** The yield was 70%. M.p. 176—178 °C. Found (%): C, 62.94; H, 5.00; N, 9.81; S, 11.01. $C_{15}H_{14}N_2O_2S$. Calculated (%): C, 62.92; H, 4.93; N, 9.78; S, 11.20. ^{1}H NMR for **2´e**, δ: 5.20 (d, 2 H, CH, J = 8.0 Hz); 7.12 (d, 2 H, OH, J = 8.2 Hz); 7.31* (t, 2 H, Ph, J = 7.2 Hz); 7.44* (t, 4 H, Ph, J = 7.6 Hz); 7.50—7.57*) (m, 4 H, Ph). ^{13}C NMR, δ: 89.66 (CH); 126.75, 127.68, 128.47 (CH, Ph); 139.05 (s, Ph); 179.71 (CS).

Compound **2″e.** ^{1}H NMR, δ: 5.62 (d, 2 H, CH, J = 6.5 Hz); 6.60 (d, 2 H, OH, J = 7.6 Hz); 7.31* (t, 2 H, Ph, J = 7.2 Hz); 7.44* (t, 4 H, Ph, J = 7.6 Hz); 7.50—7.57* (m, 4 H, Ph).

Synthesis of (4*R,5*R**)-1,3-diethyl-4,5-dihydroxy-4,5-diphenylimidazolidine-2-thione (2´d) and (4*R**,5*S**)-1,3-diethyl-4,5-dihydroxy-4,5-diphenylimidazolidine-2-thione (2″d).** A solution of KOH (0.005 mol) in water (1 mL) was added in portions to a solution of 1,3-diethylthiourea **5c** (0.01 mol) and benzil **9** (0.01 mol) in MeOH (10 mL). The reaction mixture was refluxed for 5 h, cooled to ~20 °C, and diluted with water (7 mL). Benzil **9** formed was filtered off, a precipitate of **2″d** was imme-

* Signals for the protons in the ^{1}H NMR spectra of diastereomers **1´f**, **1″f**, **2´e**, **2″e** overlap.

* Signals for the protons in the ^{1}H NMR spectra of diastereomers **1´f**, **1″f**, **2´e**, **2″e** overlap.

diately formed from the filtrate, which was filtered off. The filtrate was concentrated to dryness, the precipitate was washed with water and dried. The ratio of diastereomers **2´d** and **2″d** was determined as 1 : 4. Together with the filtered precipitate of **2″d**, the overall ratio of diastereomers **2´d** and **2″d** was 1 : 99.

Compound **2´d**. ^{1}H NMR, δ: 1.05 (t, 6 H, Me, J = 7.2 Hz); 3.30—3.41 (m, 4 H, CH_2); 7.20—7.29 (m, 4 H, Ph); 7.30—7.40 (m, 6 H, Ph).

Compound **2″d**. The yield was 37%, m.p. 162—164 °C.[5] Found (%): C, 66.72; H, 6.45; N, 8.22; S, 9.33. $C_{19}H_{22}N_2O_2S$. Calculated (%): C, 66.64; H, 6.48; N, 8.18; S, 9.36.

Synthesis of (4*R,5*R**)-4,5-dihydroxy-1,3-dimethyl-4,5-diphenylimidazolidine-2-thione (2´f) and (4*R**,5*S**)-4,5-dihydroxy-1,3-dimethyl-4,5-diphenylimidazolidine-2-thione (2″f).** A solution of KOH (0.03 mol) in water (5 mL) was added to a solution of benzil (0.05 mol) and 1,3-dimethylthiourea **5b** (0.05 mol) in methanol (50 mL). The reaction mixture was refluxed with stirring for 2 h, then concentrated to dryness. A precipitate of **2´f** and **2″f** was washed with water on the filter and dried. The ratio of diastereomers **2´f** and **2″f** was determined as 2 : 3.

Diastereoselective synthesis of (4*R,5*S**)-4,5-dihydroxy-1,3-dimethyl-4,5-diphenylimidazolidine-2-thione (2″f).** A solution of KOH (0.03 mol) in water (5 mL) was added to a solution of benzil (0.05 mol) and 1,3-dimethylthiourea **5b** (0.06 mol) in methanol (50 mL). The reaction mixture was refluxed with stirring for 2 h, then cooled to ~20 °C. Two days after, a precipitate of **2″f** was filtered off. The filtrate was concentrated to dryness, a precipitate of **2´f** and **2″f** was washed with water on the filter and dried. The ratio of diastereomers **2´f** and **2″f** was determined as 1 : 8. Together with the filtered precipitate of **2″f**, the overall ratio of diastereomers **2´f** and **2″f** was 1 : 11.

When 0.07 mol of 1,3-dimethylthiourea **5b** was used in a similar experiment, the ratio of diastereomers **2´f** and **2″f** changed to 1 : 13.

Compound **2´f**. ^{1}H NMR, δ: 2.94 (s, 6 H, Me); 7.14—7.19 (m, 4 H, Ph); 7.32—7.36 (m, 6 H, Ph).

Compound **2″f**. M.p. 170—172 °C. ^{1}H NMR, δ: 2.91 (s, 6 H, Me); 6.80—6.93 (m, 4 H, Ph); 6.98—7.08 (m, 6 H, Ph). ^{13}C NMR, δ: 30.16 (Me); 95.07 (s, Ph); 126.76, 127.30, 127.48 (CH, Ph); 137.71 (s, Ph); 183.63 (CS). Found (%): C, 64.97; H, 5.75; N, 8.92; S, 10.26. $C_{17}H_{18}N_2O_2S$. Calculated (%): C, 64.94; H, 5.77; N, 8.91; S, 10.20.

1,3-Dimethyl-5,5-diphenyl-2-thioxoimidazolidin-2-one (10a). A solution of KOH (0.03 mol) in water (5 mL) was added to a solution of diastereomers **2´f**—**2″f** (2 : 3) (0.05 mol) and 1,3-dimethylthiourea **5b** (0.01 mol) in methanol (50 mL). The reaction mixture was refluxed for 2 h and concentrated to dryness. A precipitate of **10a** was recrystallized from Et_2O. The yield was 95%. M.p. 142—143 °C.[12] ^{1}H NMR, δ: 2.84 (s, 6 H, 2 Me); 6.78—7.09 (m, 10 H, 5 Ph). Found (%): C, 68.82; H, 5.41; N, 9.46; S, 10.86. $C_{17}H_{16}N_2OS$. Calculated (%): C, 68.89; H, 5.44; N, 9.45; S, 10.82.

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