Cyclothiomethylation of carboxylic acid hydrazides with aldehydes and H_2S

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The cyclothiomethylation of carboxylic acid hydrazides $RCONHNH_2$ (R = C_5H_4N, Ph, 2-$MeOC_6H_4$, or 4-$HOC_6H_4CH_2$) with formaldehyde and H_2S at 70 °C affords predominantly the corresponding *N*-(1,3,5-dithiazinan-5-yl)amides, whereas this reaction at 0—−50 °C gives a mixture of the latter compounds with 3-acyl-1,3,4-thiadiazolidines. *N*-(1,3,5-Dithiazinan-5-yl)-amides were selectively synthesized by the reaction of carboxylic acid hydrazides with formaldehyde and H_2S in the presence of BuONa in BuOH.

Key words: cyclothiomethylation, carboxylic acid hydrazides, 1,3,5-dithiazinanes, 1,3,4-thiadiazolidines, formaldehyde, acetaldehyde, hydrogen sulfide, X-ray diffraction study.

Cyclic acid amides and hydrazides, including cyclic peptides, have found use as antibiotics.[1,2] Sulfur-containing cyclic amides exhibit also antituberculosis, radioprotective, antidepressant, diuretic,[3] and antibacterial properties.[2]

1,3,4-Thiadiazolidine derivatives have antifungal activity against *Candida spp.*,[4] and substituted 1,3,5-dithiazinanes are effective sorbents for platinum, gold, and silver.[5]

Previously,[6,7] we have described the selective synthesis of 5-acyl-1,3,5-dithiazinanes by the cyclothiomethylation of carboxamides with CH_2O and H_2S in aqueous butanol in the presence of BuONa. By contrast, the cyclothiomethylation of *p*-toluenesulfonic acid hydrazide with CH_2O and H_2S affords a mixture of 1,3,4-thiadiazolidine, 1,3,5-dithiazinane, and 1,5,3,7-dithiadiazaoctane regardless of the reaction conditions used (pH, the temperature mode).[8] Before we started our research, carboxylic acid hydrazides have not been subjected to cyclothiomethylation with aldehydes and H_2S.

In the present study, with the aim of performing the selective synthesis of *N*-acyl-1,3,4-thiadiazolidines and *N*-(1,3,5-dithiazinan-5-yl)amides, we investigated the condensation of carboxylic acid hydrazides, *viz.*, isonicotinic acid hydrazide (**1a**), benzhydrazide (**1b**), *o*-methoxybenzhydrazide (**1c**), and *p*-hydroxybenzhydrazide (**1d**), with the CH_2O—H_2S thiomethylating mixture(see Ref. 9) under different conditions, and also investigated the cyclothioalkylation with acetaldehyde and propionaldehyde for isonicotinic acid hydrazide **1a**.

Results and Discussion

By analogy with sulfonic acid hydrazides,[8] carboxylic acid hydrazides would be expected to undergo heterocyclization with CH_2O and H_2S at the β-nitrogen atom, as well as at both the α- and β-nitrogen atoms of hydrazides. Actually, the cyclothiomethylation of isonicotinic acid hydrazide (**1a**) affords a mixture of 4-(isonicotinoyl)-1,3,4-thiadiazolidine (**2a**) and *N*-(1,3,5-dithiazinan-5-yl)isonicotinamide (**3a**) (Scheme 1, Table 1). It should be noted that at 0, −10, and −50 °C, the yield of 3-acyl-1,3,4-thiadiazolidine **2a** increases, whereas at 70 °C the reaction produces predominantly *N*-(1,3,5-dithiazin-

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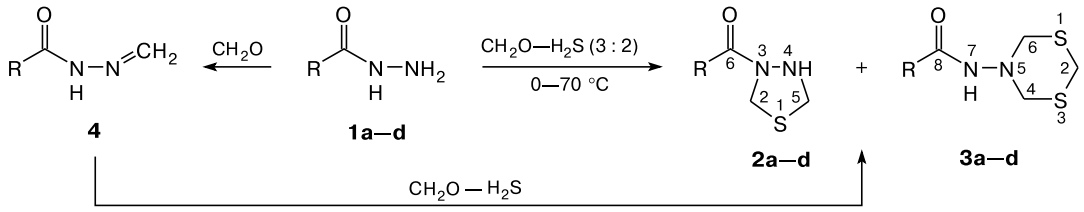
Scheme 1



R = C_5H_4N (**a**), Ph (**b**), 2-$MeOC_6H_4$ (**c**), 4-$HOC_6H_4CH_2$ (**d**)

anyl)amide **3a**. However, the cyclothiomethylation of benzhydrazide (**1b**) in the temperature range of 0—70 °C gives *N*-(1,3,5-dithiazinan-5-yl)benzamide (**3b**) as the major product, whereas the cyclothiomethylation of *o*-methoxybenzhydrazide (**1c**) and *p*-hydroxybenzhydrazide (**1d**) yields mixtures of the corresponding 3-acyl-1,3,4-thiadiazolidines **2c,d** and *N*-(1,3,5-dithiazinanyl)amides **3c,d** (see Scheme 1 and Table 1). A change in the order of mixing of the reagents (the reaction of **1a** with CH_2O) results in the formation of imine **4** (90%), and the subsequent bubbling of H_2S (20 °C) through a mixture of imine **4** and CH_2O affords a mixture of compounds **2a** and **3a** in a ratio of 2 : 3.

It should be noted that, in some cases, this reaction under reflux conditions in ethanol (70—80 °C) occurs with a higher selectivity. Thus, isonicotinic acid hydrazide (**1a**) and benzhydrazide (**1b**) were selectively transformed into the corresponding dithiazinanes **3a,b** (see Table 1).

Table 1. Influence of the temperature and the nature of the reaction medium on the yield and the composition of the cyclothiomethylation products of acid hydrazides **1a—d** with CH_2O and H_2S

Hydrazide	*T*/°C	Medium	Yield (%)	
			2	**3**
1a	−50	H_2O	56	22
	−10	H_2O	53	23
	0	H_2O	44	35
	70	H_2O	22	58
	70	EtOH—H_2O	—	62
1b	−10	H_2O	21	46
	0	H_2O	18	55
	70	H_2O	16	60
	70	EtOH—H_2O	—	57
1c	−10	H_2O	34	47
	0	H_2O	39	51
	70	H_2O	18	55
	70	EtOH—H_2O	35	48
1d	−10	H_2O	36	49
	0	H_2O	37	51
	70	H_2O	10	61
	70	EtOH—H_2O	31	47

Previously, the reaction temperature,[10] as well as the nature and the arrangement of the substituents in the aromatic rings of anilines,[11,12] have been found to have a similar effect on the cyclothiomethylation pathway.

Therefore, the heterocyclization of carboxylic acid hydrazides **1a—d** with CH_2O and H_2S involves two competitive reactions. One reaction occurs at both N atoms of the hydrazide group and affords 1,3,4-thiadiazolidines **2**, whereas another reaction proceeds with the involvement of the NH_2 group of the hydrazide moiety and gives 1,3,5-dithiazinanes **3**, the pathway of cyclothiomethylation being dependent on the nature of the solvent and the reaction temperature.

Compounds **2a—d** and **3a—d** were separated by column chromatography on silica gel.

In the ^{13}C NMR spectra of thiadiazolidines **2a,c,d**, the signals for the carbon atoms of the rings are magnetically nonequivalent. The 2D HMBC spectra show cross-peaks corresponding to the C(2)—H(5) (C(5)—H(2)) coupling. The ^1H NMR spectra have, in addition to the signals of the rings and the aromatic substituent, signals for the protons of the secondary amino group of 1,3,4-thiadiazolidines (δ 9.33—10.54).

The mass spectra of compounds **2a—d** and **3a—d** contain the corresponding molecular ion peaks $[M]^+$ and peaks of fragmentation ions produced by the successive elimination of CH_2S and CH_2SCH_2S fragments from $[M]^+$.

The structures of 1,3,5-dithiazinanes **3a—d** were established by ^1H and ^{13}C NMR spectroscopy and X-ray diffraction. Thus, the signals for the carbon atoms of the methylene fragments S—CH_2—S and S—CH_2—N are observed at δ 30.90—33.57 and 53.30—57.86, respectively. The chemical shifts are similar to those described in the literature[13] for other 1,3,5-dithiazinane derivatives. Analogously, the ^1H NMR spectra of compounds **3a—d** show signals for the methylene groups as broadened singlets due to the rapid heterocyclic ring inversion on the NMR time scale. The crystal structures of compounds **3a—c** were studied by X-ray diffraction (Figs 1—5).

In dithiazinane **3a**, the Py—CO—NH fragment is nonplanar. The dihedral angle between the planes of the pyridine ring and CONH is 35.4°. The dithiazinane ring is twisted around the N(1)—N(2) bond by 87.5°, *i.e.*, the

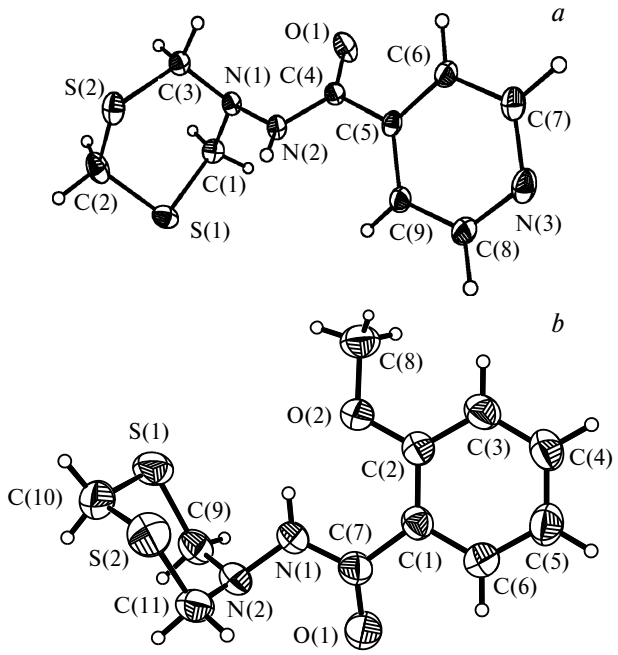


Fig. 1. Molecular structures of *N*-(1,3,5-dithiazinan-5-yl)-isonicotinamide (**3a**) (*a*) and *N*-(1,3,5-dithiazinan-5-yl)-*o*-methoxybenzamide (**3c**) (*b*) in the crystals (displacement ellipsoids are drawn at the 50% probability level).

aromatic substituent is in the axial position. The ring adopts the classical chair conformation slightly flattened at the N(1) atom (the deviations of the C(2) and N(1) atoms from the mean plane of the ring are 0.90 and 0.64 Å, respectively). The dihedral angles between the bottom of the chair (C(1)—S(1)—S(2)—C(3)) and the N(1)C(1)C(3) and C(2)S(1)S(2) planes are 55.2 and 63.7°, respectively (see Fig. 1). In the crystal structure, the molecules are linked through the N(2)—H(2N)...N(1) (H(2N)...N(1), 2.18 Å) and S(2)...H(3)—C(3)

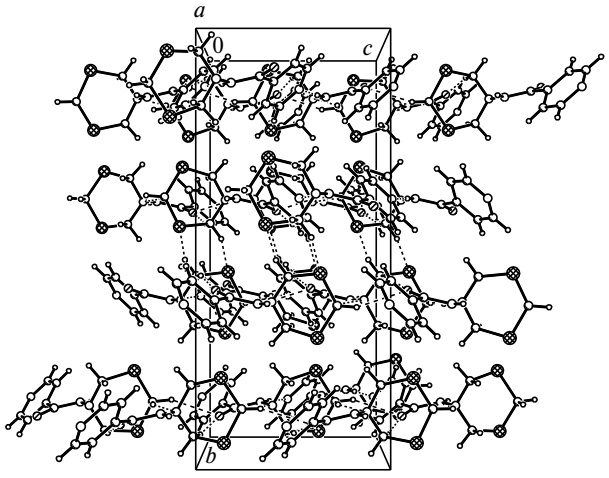


Fig. 2. Double layers in the crystal packing of **3a**.

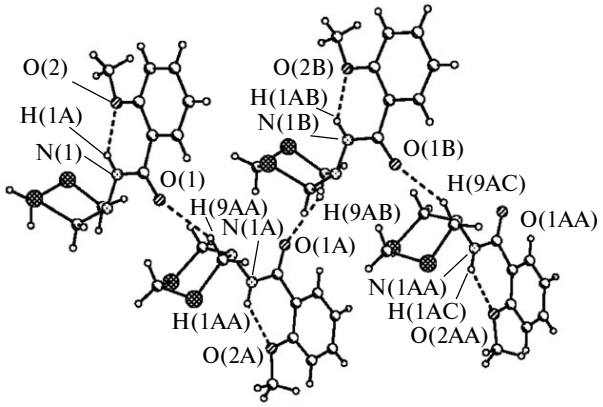


Fig. 3. Molecular chains in the crystal structure of **3c**.

(S(2)...H(3), 2.93 Å) hydrogen bonds to form double layers parallel to the *ac* plane (see Fig. 2).

In molecule **3c**, the Ph—CO—NH fragment is strongly flattened, as opposed to molecule **3a** (the flattening is associated with the formation of the strong intramolecular N(1)—H(1N)...O(2)Me hydrogen bond with the methoxy group (H(1N)...O(2), 2.003 Å)). The similar bond was found in 18 structures of hydrazones containing the *o*-methoxy group[14] (H...N, 1.79—2.02 Å). The dithiazinane ring is twisted around the N(1)—N(2) bond line by 92.6° and adopts the conformation identical to that observed in **3a**. The angles between the bottom of the chair

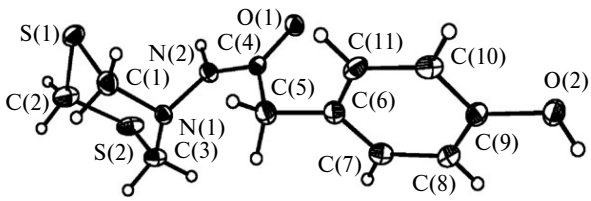


Fig. 4. Molecular structure of *N*-(1,3,5-dithiazinan-5-yl)-*p*-hydroxybenzamide (**3d**) in the crystal.

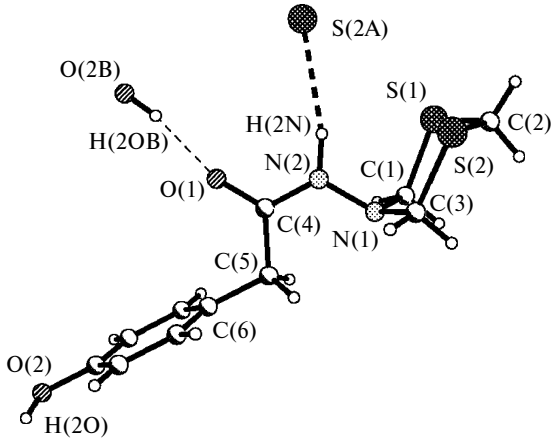


Fig. 5. Hydrogen bonds in the crystal structure of **3d**.

(C(1)—S(1)—S(2)—C(3)) and the N(2)C(11)C(9) and C(10)S(1)S(2) planes are 56.0 and 62.3°, respectively (the deviations of the C(10) and N(2) atoms from the mean plane are 0.89 and 0.65 Å, respectively) (see Fig. 1).

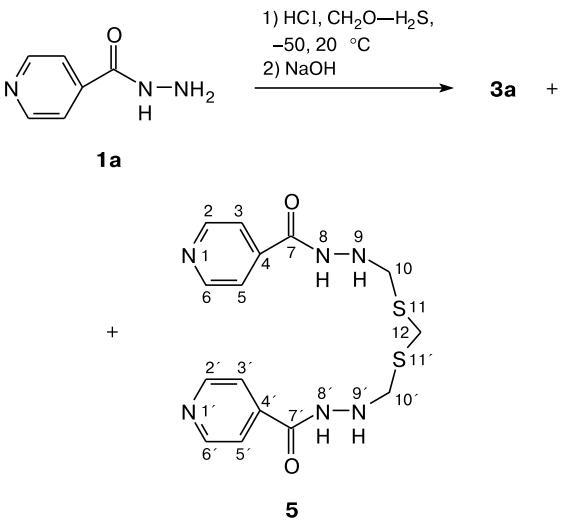
In the crystal structure, molecules **3c** are linked to each other through the weak C(9)—H(9a)...O(1) hydrogen bonds (H(9a)...O(1), 2.36 Å) to form zigzag chains running along the *a* axis (see Fig. 3).

The NH—CO group in molecule **3d**, unlike those in **3a,c**, has a fixed *cis* conformation (see Fig. 4). This is associated with the formation of the strong O(2)—H(2O)...O(1) (H(2O)...O(1), 1.90 Å) and N(1)—H(1N)...S(2) (H(1N)...S(2), 2.52 Å) hydrogen bonds (see Fig. 5). The N(1)N(2)C(4)O(1) group is planar and orthogonal to the dithiazinane ring (the dihedral angle is 88.7°). The conformation of the dithiazinane rings is identical to that in compounds **3a,c**. The angles between the bottom of the chair (C(1)—S(1)—S(2)—C(3)) and the N(1)C(1)C(3) and C(2)S(1)S(2) planes are 55.4 and 63.8°, respectively (the deviations of the C(2) and N(1) atoms from the mean plane are 0.90 and 0.64 Å, respectively).

The bond lengths are given in Table 2. As can be seen from the above-considered data, the molecules have similar geometric characteristics, which are close to the standard values.

We found that the reaction of hydrazide **1a** with CH_2O and H_2S in the presence of HCl (−50—20 °C) occurs with the involvement of the NH_2 group of protonated form **1a**. As a result, 1,3,5-dithiazinane **3a** and linear oligomer **5** were obtained after the neutralization of the reaction mixture (NaOH) (Scheme 2, Table 3). Compounds **3a** and **5** were separated by column chromatography.

Scheme 2



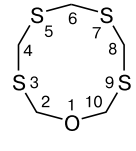
The HMBC spectrum of linear product **5** contains cross-peaks between the C(10) (C(10′)) atoms and the protons of the S—CH_2—S fragment. The mass spectrum of compound **5** shows a molecular ion peak $[M]^-$ at *m/z* 378 and a characteristic fragmentation pattern corresponding to the successive elimination of the $CH_2CH_2NNHCOC_5H_4N$ (*m/z* 184) and $CH_2NNHCOC_5H_4N$ (*m/z* 148) fragments.

Table 2. Selected bond lengths (*d*) and torsion angles (τ) in molecules **3a,c,d** and **8**

Parameter	**3a**	**3c**	**3d**	**8**
Bond		*d*/Å		
N—N	1.410(3)	1.406(3)	1.402(2)	1.389(3), 1.384(4), 1.389(3), 1.397(3)
N—C(=O)	1.351(4)	1.341(3)	1.341(3)	1.333(4), 1.342(4), 1.326(4), 1.331(4)
C=O	1.220(3)	1.217(3)	1.232(3)	1.235(3), 1.231(3), 1.241(3), 1.234(4)
C—S*	1.833(2), 1.829(3)	1.826(3), 1.824(3)	1.828(2), 1.827(2)	—
C—S**	1.820(3), 1.829(4)	1.812(3), 1.800(3)	1.812(2), 1.809(2)	—
Angle		τ/deg		
N—N—C—O	0.0(4)	2.5(4)	−5.9(2)	−4.2(5), −3.9(4), −1.0(4), −4.1(4)

* The bottom of the chair.
** The SCH_2S fragment.

Liquid chromatography mass spectrometry (LCMS) of a mixture of reaction products **3a** and **5** also revealed the cyclic oligomer of formaldehyde and CH_2S, *viz.*, 1,3,5,7,9-oxatetrathiecane **6** (~10%).



6

The selective cyclothiomethylation of hydrazides **1a—d** to dithiazinylamides **3a—d** was carried out with the use of the CH_2O—H_2S thiomethylating mixture in the presence of BuONa in BuOH (see Table 3) by analogy with the cyclothiomethylation of carboxamides.[6,7] The activation of hydrazide **1a** with sodium metal in refluxing benzene[15] followed by the thiomethylation with the CH_2O—H_2S system affords the mixture **2a** + **3a**.

Alkyl-substituted nitrogen- and sulfur-containing heterocyclic systems were synthesized by the cyclothioalkylation of hydrazide **1a** with acetaldehyde or propionaldehyde and H_2S. Unlike the reactions with CH_2O and H_2S, the reaction of **1a** with these aldehydes under usual conditions (20 °C in ethanol) produces exceptionally Schiff bases **7** and **8** in 72 and 50% yields, respectively (Scheme 3).

Table 3. Influence of the reaction temperature and the pH of the reaction mixture on the yield and the composition of the cyclothioalkylation products of carboxylic acid hydrazides **1a—d**

Hydrazide	*T* /°C	Aldehyde	Medium	Reagent ratio	Yield (%)			
					2a	**3a**	**5**	**9**
1a	20	CH_2O	HCl	1 : 2 : 1	—	39	11	—
	20	CH_2O	HCl	1 : 2 : 3	—	56	14	—
	–50	CH_2O	HCl	1 : 2 : 3	—	40	12	—
	40	CH_2O	BuONa/BuOH	1 : 3 : 3	—	68	—	—
	40	MeCHO	BuONa/BuOH	1 : 3 : 3	—	—	—	41
	20	CH_2O	Na/C_6H_6	1 : 3 : 1	24	35	—	—
1b	40	CH_2O	BuONa/BuOH	1 : 3 : 3	—	57	—	—
1c	40	CH_2O	BuONa/BuOH	1 : 3 : 3	—	59	—	—
1d	40	CH_2O	BuONa/BuOH	1 : 3 : 3	—	55	—	—

Imines **7** and **8** were identified by ^1H and ^{13}C NMR spectroscopy. The structure of compound **8** was established also by X-ray diffraction (Fig. 6).

It should be noted that the Py—CO—NH fragment in molecule **8** is structurally similar to that in dithiazinane **3a**. This fragment is nonplanar; the dihedral angle between the planes of the pyridine ring and CONH is 32.4°.

The reaction of imine **7** with MeCHO and H_2S affords a mixture of the heterocycles *N*-(2,4,6-trimethyl-1,3,5-dithiazinan-5-yl)isonicotinamide (**9**) and 1,1-bis[4-(isonicotinoyl-2,5-dimethyl-1,3,4-thiadiazolidin-3-yl)ethylsulfanyl]ethane (**10**) in a ratio of ~5 : 1 both upon refluxing in ethanol and in the presence of BuONa/BuOH (see Scheme 3).

The liquid chromatography mass spectra show molecular ion peaks $[M - H]^-$ at *m/z* 283 and 591 for compounds **9** and **10**, respectively, and fragmentation ion peaks. For molecule **10**, the characteristic elimination of two $CHCH_3SCHCH_3$ fragments from $[M - H]^-$ (*m/z* 413) and the successive fragments $C_5H_4NCONCHCH_3SCHCH_3NCHCH_3SCHCH_3S$ (*m/z* 281) and $C_5H_4NCONCHCH_3SCHCH_3N$ (*m/z* 223) were observed.

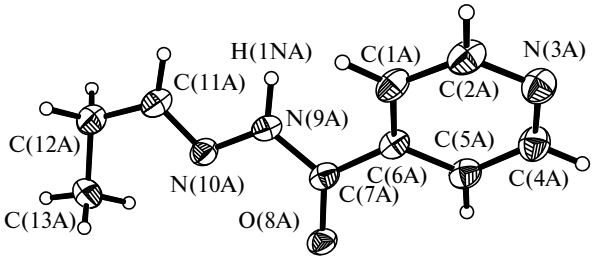
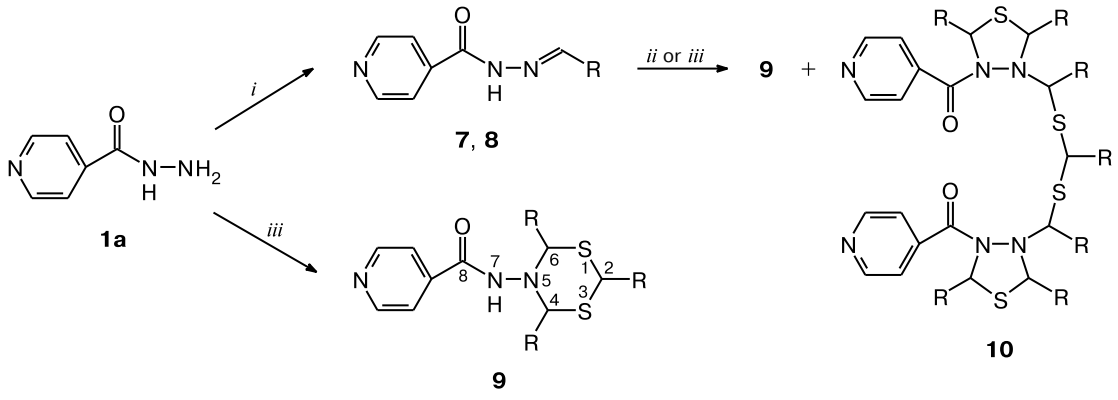


Fig. 6. Molecular structure of *N´*-(propylidene)isonicotinic acid hydrazide (**8**) (displacement ellipsoids are drawn at the 50% probability level).

The stereoselective synthesis of (*cis*,*cis*-2,4,6-trimethyl-1,3,5-dithiazinan-5-yl)isonicotinamide (**9**) was carried out in the presence of BuONa/BuOH (pH 11.25) at 40 °C (see Scheme 3 and Table 3).

The ^{13}C and ^1H NMR spectra of compound **9** contain one set of signals. A comparison of the ^{13}C NMR spectra of compound **9** with the corresponding data for two stereoisomers of 2-methyl-1,3-dithiane[16] showed that the methyl group at the C(2) atom in the dithiazinane ring is in the equatorial position, because its chemical shift (δ 19.72) agrees well with the corresponding chemical shift (δ 20.80) of the equatorial methyl group of 2-methyl-1,3-dithiane, whereas the corresponding resonance of the axial isomer should appear at much lower field (δ 25.4). It is also known[17] that under these reaction conditions, the condensation of *N*-nitrosodimethylamine, acetaldehyde, and NaSH affords the 2,4,6-*cis*,*cis* stereoisomer. Hence, it can be said with certainty that heterocycle **9** is the stereo-

Scheme 3



Reagents and conditions: *i*. RCHO—H_2S (3 : 2), 20 °C, EtOH. *ii*. RCHO—H_2S (3 : 2), EtOH, refluxing. *iii*. RCHO—H_2S (3 : 2), 1) BuONa/BuOH, 2) HCl.

isomer with the 2,4,6-*cis*,*cis* configuration of the methyl substituents.

To sum up, the cyclothiomethylation of carboxylic acid hydrazides with aldehydes (CH_2O, MeCHO) and H_2S in the presence of BuONa/BuOH (pH 11.25) selectively gives *N*-(1,3,5-dithiazin-5-yl)amides of carboxylic acids in 55—68% yields. 3-Acyl-1,3,4-thiadiazolidines were synthesized by the reactions of carboxylic acid hydrazides with formaldehyde and H_2S at 0—−50 °C in 21—56% yields.

Experimental

Experiments were carried out with the use of the starting compounds with a purity of 95%. The solvents were purified, dried, and distilled according to known procedures.[18]

The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer operating at 400.13 and 100.62 MHz, respectively, in DMSO-d_6 (δ_C, 39.50) and $CDCl_3$ (δ_C, 77.10). The IR spectra were measured on a Specord 75 IR spectrometer as Nujol mulls. The LC-mass-spectrometric analysis of compounds **2b** and **3b** was carried out on a Finnigan 4021 instrument (50000×0.25 mm glass capillary column, HP-5 stationary phase, helium as the carrier gas, temperature-programmed from 50 to 300 °C at a rate of 5 deg min^{-1}, the temperature of the vaporizer was 280 °C, the temperature of the ion source was 250 °C). Compounds **2a,c,d**, **3a,c,d**, and **4—10** were analyzed on a Shimadzu LCMS-2010 EV instrument by atmospheric pressure chemical ionization (APCI) mass spectrometry; the maximum temperature of the APCI probe was 500 °C; the temperature of the heating source was 200 °C, the temperature of the vaporizer was 250 °C; nitrogen that was produced by an NM18L ultra-high purity nitrogen generator was used as the nebulizing gas; the liquid flow rate was 0.05 mL min^{-1}, the nebulizing gas flow rate was 2.5 mL min^{-1}; the ion source voltage was as follows: (+), 4.5 kV; (−), 3 kV.

The elemental analysis was carried out on a Carlo Erba (model 1106) elemental analyzer. The melting points were determined on a PHMK 80/2617 instrument; the refractive index of compound **9** was measured on an IRF-22 refractometer; the pH values of solutions were measured and adjusted using a pH-340 pH-meter.

Cyclothioalkylation of acid hydrazides with aldehydes and H_2S (general procedure). A solution of aldehyde (2 or 3 mol) was saturated with H_2S by bubbling for 30 min until the required aldehyde : H_2S ratio (2 : 1 or 3 : 2) was achieved. Then a solution of isonicotinic acid hydrazide (1 mol) in water (method *A*), in EtOH (method *B*), in aqueous 37% HCl (**1** : HCl = 1 : 3) (method *C*), or in BuONa/BuOH (**1** : BuONa = 1 : 3) (method *D*) was added dropwise to the thiomethylating mixture, and the reaction solution was stirred for 5 h at a specified temperature (−50, −10, 0, 20, or 70 °C). In the method *C*, the mixture was neutralized with NaOH; in the method *D*, with HCl. The reaction products were extracted with chloroform and separated by column chromatography on silica gel ($CHCl_3$—AcOEt—EtOH, 5 : 1 : 1 (**2a**, **3a**), diethyl ether—AcOEt, 5 : 1 (**2b**, **3b**), $CHCl_3$—AcOEt—acetone, 10 : 1 : 1 (**2c**, **3c**), and $CHCl_3$—AcOEt, 10 : 1 (**2d**, **3d**) as the eluents).

Cyclothiomethylation of isonicotinic acid hydrazide (1a) with H_2S and CH_2O by the reverse mixing procedure. Paraformaldehyde (1 mol), isonicotinic acid hydrazide (**1a**) (1 mol), and benzene (15 mL) were placed into a reactor at room temperature. The reaction mixture was refluxed with stirring for 2 h and then divided into two aliquots. Imine **4** was isolated from one aliquot. Another aliquot was saturated with hydrogen sulfide for 5 h. After bubbling with H_2S, the products were extracted with chloroform and separated by column chromatography on silica gel ($CHCl_3$—AcOEt—EtOH, 5 : 1 : 1, as the eluent; compounds **2a** and **3a**).

Cyclothiomethylation of isonicotinic acid hydrazide (1a) with H_2S and CH_2O in the presence of the Na/C_6H_6 system. Isonicotinic acid hydrazide (**1a**) (1 mol), benzene (20 mL), and sodium metal (1 mol) were mechanically stirred in a reactor until a homogeneous cream-like substance was obtained. Then paraformaldehyde (1 mol) was added. The mixture was stirred at 70 °C for 3 h, and then hydrogen sulfide was bubbled through the reaction mixture for 4 h. The benzene was decanted, and a mixture of heterocycles **2a** and **3a** was isolated from the residue by extraction with $CHCl_3$.

4-(Isonicotinoyl)-1,3,4-thiadiazolidine (2a). The yield was 56% (method *A*), m.p. 185—187 °C, R_f 0.35 ($CHCl_3$—AcOEt—EtOH, 5 : 1 : 1). IR, ν/cm^{-1}: 690, 900, 1080, 1270, 1440—1520, 1660, 2900, 3385. ^1H NMR (DMSO-d_6), δ: 4.35 (s, 2 H, C(2)H_2); 4.53 (s, 2 H, C(5)H_2); 7.64—7.70 (d, 2 H, C(10)H, C(12)H, J = 5.6 Hz); 8.68—8.75 (d, 2 H, C(9)H, C(13)H, J = 5.6 Hz); 10.09 (s, 1 H, N(3)H). ^{13}C NMR (DMSO-d_6), δ: 55.5 (t, C(2)); 74.0 (t, C(5)); 121.6 (d, C(9), C(11)); 140.8 (d, C(7)); 150.2 (d, C(8), C(12)); 163.7 (s, C(6)). MS, m/z (I_{rel} (%)): 196 $[M + 1]^+$ (10); 151 $[M - CH_2S]^+$ (100); 120 $[M - CH_2SCH_2NH]^+$ (15); 106 $[M - CH_2SCH_2NHN]^+$ (12). Found (%): C, 49.83; H, 4.64; N, 21.87; S, 16.67. $C_8H_9N_3OS$. Calculated (%): C, 49.23; H, 4.62; N, 21.54; S, 16.41.

4-Benzoyl-1,3,4-thiadiazolidine (2b). The yield was 21% (method *A*), m.p. 223—225 °C, R_f 0.40 (diethyl ether—AcOEt, 5 : 1, as the eluent). IR, ν/cm^{-1}: 670, 1100, 1265, 1360—1450, 1620, 1670, 2900, 3315. ^1H NMR (DMSO-d_6), δ: 4.63 (s, 2 H, C(5)H_2); 5.05 (s, 2 H, C(2)H_2); 7.60—7.80 (m, 4 H, Ph); 9.83 (s, 1 H, N(3)H). ^{13}C NMR (DMSO-d_6), δ: 55.0 (t, C(5)); 73.5 (t, C(2)); 127.7 (d, C(8), C(12)); 128.6 (d, C(9), C(11)); 132.0 (d, C(10)); 132.8 (d, C(7)); 166.2 (s, C(6)). MS, m/z (I_{rel} (%)): 194 $[M]^+$ (2); 149 $[M - CH_2S]^+$ (43); 119 $[M - CH_2SCH_2NH]^+$ (61); 105 $[PhCO]^+$ (100); 45 $[CH_2S]^+$ (17). Found (%): C, 56.48; H, 5.74; N, 14.87; S, 15.97. $C_9H_{10}N_2OS$. Calculated (%): C, 55.65; H, 5.19; N, 14.42; S, 16.51.

4-(*o*-Methoxybenzoyl)-1,3,4-thiadiazolidine (2c). The yield was 34% (method *A*), m.p. 110—112 °C, R_f 0.09 ($CHCl_3$—AcOEt—acetone, 10 : 1 : 1, as the eluent). IR, ν/cm^{-1}: 740, 1005, 1165, 1280, 1470—1480, 1595, 1640, 2840, 2950, 3295. ^1H NMR (DMSO-d_6), δ: 3.65 (br.s, 3 H, C(13)H_3); 3.92 (s, 2 H, C(5)H_2); 4.25 (s, 2 H, C(2)H_2); 7.10—7.95 (m, 4 H, Ph); 9.33 (s, 1 H, N(3)H). ^{13}C NMR (DMSO-d_6), δ: 56.0 (s, C(13)); 56.5 (t, C(5)); 74.0 (t, C(2)); 112.1 (d, C(12)); 120.8 (d, C(11)); 121.7 (d, C(10)); 131.2 (d, C(9)); 133.5 (d, C(8)); 157.5 (d, C(7)); 164.4 (s, C(8)). MS, m/z (I_{rel} (%)): 225 $[M + 1]^+$ (50); 193 $[M - S]^+$ (10); 180 $[M - SCH_2]^+$ (100); 165 $[M - SCH_2N]^+$ (20); 136 $[M - CH_2SCH_2NNH]^+$ (10); 93 $[M - CH_2SCH_2NNHCO,Me]^+$ (15). Found (%): C, 53.58; H, 5.29; N, 14.87; S, 15.18. $C_{10}H_{12}N_2O_2S$. Calculated (%): C, 53.57; H, 5.36; N, 12.50; S, 14.29.

4-(4-Hydroxybenzylcarbonyl)-1,3,4-thiadiazolidine (2d). The yield was 36% (method *A*), m.p. 183—185 °C, R_f 0.15 ($CHCl_3$—AcOEt, 10 : 1, as the eluent). IR, ν/cm^{-1}: 670, 1100,

1265, 1360—1450, 1620, 1670, 2900, 3315. ^{1}H NMR (DMSO-d_6), δ: 4.56 (s, 1 H, OH(13)); 4.15 (s, 2 H, C(5)H_2); 4.81 (s, 2 H, C(2)H_2); 6.71—7.00 (m, 4 H, Ph); 9.35 (s, 1 H, N(3)H). ^{13}C NMR (DMSO-d_6), δ: 55.9 (t, C(5)); 70.9 (t, C(2)); 115.1 (s, C(9), C(11)); 126.5 (d, C(10)); 130.0 (d, C(8), C(12)); 155.9 (d, C(7)); 169.9 (s, C(6)). MS, *m/z* (I_{rel} (%)): 224 $[M]^+$ (15); 180 $[M - SCH_2]^+$ (100); 150 $[M - CH_2SCH_2NH]^+$ (11); 135 $[M - CH_2SCH_2NNH]^+$ (5). Found (%): C, 53.47; H, 5.29. $C_{10}H_{12}N_2O_2S$. Calculated (%): C, 53.55; H, 5.39.

***N*-(1,3,5-Dithiazinan-5-yl)isonicotinamide (3a).** The yield was 62% (method *B*), 68% (method *D*), m.p. 200—202 °C, R_f 0.35 ($CHCl_3$—AcOEt—EtOH, 5 : 1 : 1). IR, ν/cm^{-1}: 700, 1070, 1270, 1460—1540, 1650, 2905, 3390. ^{1}H NMR (DMSO-d_6), δ: 4.59 (s, 2 H, C(2)H_2); 5.06 (s, 4 H, C(4)H_2, C(6)H_2); 8.12—8.17 (d, 2 H, C(11)H, C(13)H, *J* = 4.7 Hz); 9.14—9.19 (d, 2 H, C(10)H, C(14)H, *J* = 4.7 Hz); 9.74 (s, 1 H, N(7)H). ^{13}C NMR (DMSO-d_6), δ: 30.9 (t, C(2)); 57.7 (t, C(4), C(6)); 121.5 (d, C(11), C(13)); 141.2 (d, C(9)); 150.3 (d, C(10), C(14)); 163.2 (s, C(8)). MS, *m/z* (I_{rel} (%)): 242 $[M]^+$ (5); 150 $[M - SCH_2SCH_2]^+$ (100); 122 $[M - CH_2SCH_2SCH_2N]^+$ (13); 108 $[M - CH_2SCH_2SCH_2NHN]^+$ (6). Found (%): C, 46.18; H, 4.74; N, 17.97; S, 25.97. $C_9H_{11}N_3OS_2$. Calculated (%): C, 44.81; H, 4.56; N, 17.43; S, 26.55.

***N*-(1,3,5-Dithiazinan-5-yl)benzamide (3b).** The yield was 57% (method *B*), 57% (method *D*), m.p. 240—242 °C, R_f 0.43 (diethyl ether—AcOEt, 5 : 1, as the eluent). IR, ν/cm^{-1}: 700, 1070, 1250, 1360—1450, 1615, 1670, 2900, 3310. ^{1}H NMR (DMSO-d_6), δ: 4.20 (s, 2 H, C(2)H_2); 4.66 (s, 4 H, C(4)H_2, C(6)H_2); 7.60—7.80 (m, 4 H, Ph); 8.86 (s, 1 H, N(7)H). ^{13}C NMR (DMSO-d_6), δ: 30.9 (t, C(2)); 58.1 (t, C(4), C(6)); 127.3 (d, C(11), C(13)); 128.8 (d, C(10), C(14)); 131.9 (d, C(12)); 148.5 (d, C(9)); 155.6 (s, C(8)). MS, *m/z* (I_{rel} %): 240 $[M]^+$ (25); 162 $[M - SCH_2S]^+$ (5); 121 $[M - PhCONH]^+$ (6); 105 $[PhCO]^+$ (100); 45 $[CH_2S]^+$ (10). Found (%): C, 49.47; H, 4.99; N, 11.84; S, 25.37. $C_{10}H_{12}N_2OS_2$. Calculated (%): C, 49.97; H, 5.03; N, 11.66; S, 26.68.

***N*-(1,3,5-Dithiazinan-5-yl)-*o*-methoxybenzamide (3c).** The yield was 59% (method *D*), m.p. 105—107 °C, R_f 0.50 ($CHCl_3$—AcOEt—acetone, 10 : 1 : 1, as the eluent). IR, ν/cm^{-1}: 740, 1005, 1100, 1265, 1370—1445, 1595, 1640, 2840, 2900, 3340. ^{1}H NMR (DMSO-d_6), δ: 3.51 (br.s, 3 H, C(15)H_3); 4.05 (s, 2 H, C(2)H_2); 4.54 (s, 4 H, C(4)H_2, C(6)H_2); 7.11 (t, 1 H, C(11)H, *J* = 7.6 Hz); 7.15 (d, 1 H, C(10)H, *J* = 8.6 Hz); 7.57 (t, 1 H, C(12)H, *J* = 7.4 Hz); 7.99 (d, 1 H, C(13)H, *J* = 7.4 Hz); 10.23 (s, 1 H, N(7)H). ^{13}C NMR (DMSO-d_6), δ: 30.9 (t, C(2)); 56.7 (t, C(4), C(6)); 58.1 (s, C(15)); 112.6 (d, C(13)); 120.5 (d, C(12)); 121.1 (d, C(11)); 131.2 (d, C(14)); 136.1 (d, C(10)); 157.1 (d, C(9)); 164.4 (s, C(8)). MS, *m/z* (I_{rel} (%)): 271 $[M + 1]^+$ (100); 179 $[M - SCH_2SCH_2]^+$ (72); 151 $[M - SCH_2SCH_2N]^+$ (8); 135 $[M - SCH_2SCH_2NNH]^+$ (13). Found (%): C, 49.42; H, 5.57; N, 10.37; S, 24.28. $C_{11}H_{14}N_2O_2S_2$. Calculated (%): C, 48.88; H, 5.19; N, 10.37; S, 23.70.

***N*-(1,3,5-Dithiazinan-5-yl)-2-(hydroxyphenyl)acetamide (3d).** The yield was 55% (method *D*), m.p. 209—210 °C, R_f 0.52 ($CHCl_3$—AcOEt, 10 : 1, as the eluent). IR, ν/cm^{-1}: 700, 1070, 1250, 1360—1450, 1615, 1670, 2900, 3310. ^{1}H NMR (DMSO-d_6), δ: 3.89 (s, 2 H, C(2)H_2); 4.44 (s, 4 H, C(4)H_2, C(6)H_2); 6.63—6.73 (d, 2 H, C(12)H, C(14)H, *J* = 8.5 Hz); 7.04—7.14 (d, 2 H, C(11)H, C(15)H, *J* = 8.5 Hz); 8.94 (s, 1 H, N(7)H); 9.26 (s, 1 H, OH(15)). ^{13}C NMR (DMSO-d_6), δ: 31.2 (t, C(2)); 57.9 (t, C(4), C(6)); 115.2 (d, C(11), C(13)); 126.0 (d, C(12)); 130.2 (d, C(10), C(14)); 156.1 (d, C(9)); 168.4 (s, C(8)). MS, *m/z* (I_{rel} (%)): 271 $[M + 1]^+$ (49); 179 $[M - SCH_2SCH_2]^+$ (100); 151 $[M - SCH_2SCH_2N]^+$ (9); 107 $[M - CH_2SCH_2SNNCH_2]^+$ (12). Found (%): C, 49.12; H, 5.47; N, 10.39; S, 24.28. $C_{11}H_{14}N_2O_2S_2$. Calculated (%): C, 48.86; H, 5.22; N, 10.36; S, 23.72.

***N´*-(Methylidene)isonicotinic acid hydrazide (4).** The yield was 90% (method *A*), m.p. 156—158 °C, R_f 0.58 ($CHCl_3$—EtOH, 5 : 1, as the eluent). IR, ν/cm^{-1}: 1060, 1160, 1300, 1530, 1650, 2905, 3150, 3250. ^{1}H NMR (DMSO-d_6), δ: 4.20 (br.s, 2 H, C(10)H); 7.67 (d, 2 H, C(2)H, C(6)H, *J* = 5.6 Hz); 8.72 (d, 2 H, C(3)H, C(5)H, *J* = 5.6 Hz); 10.33 (s, 1 H, N(8)H). ^{13}C NMR (DMSO-d_6), δ: 121.6 (d, C(2), C(6)); 140.60 (d, C(4)); 149.7 (d, C(10)); 150.4 (d, C(3), C(5)); 163.9 (s, C(7)). MS, *m/z* (I_{rel} (%)): 150 $[M]^+$ (100); 138 $[M - CH_2]^+$ (20); 123 $[M - CH_2N]^+$ (10). Found (%): C, 56.11; H, 4.71; N, 27.85. $C_7H_7N_3O$. Calculated (%): C, 56.37; H, 4.73; N, 28.17.

Bis[4-(isonicotinoylaminohydrazino)methylsulfanyl]methane (5a). The yield was 14% (method *C*), R_f 0.05 ($CHCl_3$—AcOEt—EtOH, 10 : 1 : 1, as the eluent). IR, ν/cm^{-1}: 740, 1020, 1190, 1280, 1370—1410, 1500, 1590, 1650, 2905, 3280. ^{1}H NMR (DMSO-d_6), δ: 3.97 (s, 2 H, C(12)H_2); 4.27 (s, 4 H, C(10)H_2, C(10´)H_2); 7.49 (s, 1 H, N(9)H, N(9´)H); 7.78 (d, 4 H, C(2)H, C(2´)H, C(6)H, C(6´)H, *J* = 4.4 Hz); 8.83 (d, 4 H, C(3)H, C(3´)H, C(5)H, C(5´)H), *J* = 4.4 Hz); 9.29 (s, 2 H, N(8)H, N(8´)H). ^{13}C NMR (DMSO-d_6), δ: 33.7 (t, C(12)); 56.6 (t, C(10), C(10´)); 120.6 (d, C(2), C(2´), C(6), C(6´)); 140.9 (d, C(4), C(4´)); 151.5 (d, C(3), C(3´), C(5), C(5´)); 162.9 (s, C(7), C(7´)). MS, *m/z* (I_{rel} (%)): 378 $[M]^-$ (50); 184 $[M - CH_2SCH_2NHNHCOC_5H_4N]^-$ (100); 148 $[M - CH_2SCH_2SCH_2NHNHCOC_5H_4N]^-$ (37). Found (%): C, 48.58; H, 4.54; N, 20.17; S, 17.23. $C_{15}H_{18}N_6O_2S_2$. Calculated (%): C, 47.60; H, 4.79; N, 22.21; S, 16.94.

1,3,5,7,9-Oxatetrathiecane (6). The yield was 10%. MS, *m/z* (I_{rel} (%)): 217 $[M]^+$ (87); 201 $[M - CH_2]^+$ (100); 185 $[M - CH_2O]^+$ (44); 182 $[M - S]^+$ (87); 138 $[M - CH_2SCH_2O]^+$ (87).

***N´*-(Ethylidene)isonicotinic acid hydrazide (7).** The yield was 72% (method *A*), m.p. 150—151 °C, R_f 0.69 ($CHCl_3$—EtOH, 5 : 1, as the eluent). IR, ν/cm^{-1}: 1020, 1120, 1290, 1455—1540, 1610, 1650, 2900, 3050, 3210. ^{1}H NMR ($CDCl_3$), δ: 1.94 (m, 3 H, C(11)H_3); 7.67 (d, 2 H, C(2)H, C(6)H, *J* = 6.0 Hz); 7.78 (q, 1 H, C(10)H, *J* = 5.2 Hz); 8.61 (d, 2 H, C(3)H, C(5)H, *J* = 6.0 Hz); 10.97 (s, 1 H, N(8)H). ^{13}C NMR ($CDCl_3$), δ: 18.6 (s, C(11)); 121.0 (d, C(2), C(6)); 140.4 (d, C(4)); 150.3 (d, C(3), C(5)); 150.9 (t, C(10)); 162.7 (s, C(7)). MS, *m/z* (I_{rel} (%)): 164 $[M]^+$ (100); 138 $[M - CH_3CH]^+$ (20); 121 $[M - CH_3CHN]^+$ (17); 78 $[M - CH_3CHNHNCO]^+$ (8). Found (%): C, 58.18; H, 5.71; N, 25.97. $C_8H_9N_3O$. Calculated (%): C, 58.88; H, 5.56; N, 25.75.

***N´*-(Propylidene)isonicotinic acid hydrazide (8).** The yield was 50% (method *A*), m.p. 134—135 °C, R_f 0.73 ($CHCl_3$—EtOH, 5 : 1, as the eluent). IR, ν/cm^{-1}: 1000, 1130, 1295, 1450—1530, 1615, 1650, 2905, 3035, 3190. ^{1}H NMR ($CDCl_3$), δ: 1.04 (m, 3 H, C(12)H_3); 2.27 (m, 2 H, C(11)H_2); 7.70 (d, 2 H, C(2)H, C(6)H, *J* = 4.4 Hz); 7.77 (t, 1 H, C(10)H, *J* = 5.2 Hz); 8.61 (d, 2 H, C(3)H, C(5)H, *J* = 4.4 Hz); 10.06 (s, 1 H, N(8)H). ^{13}C NMR ($CDCl_3$), δ: 10.6 (s, C(12)); 26.0 (s, C(11)); 121.5 (d, C(2), C(6)); 140.4 (d, C(4)); 150.3 (d, C(3), C(5)); 156.0 (t, C(10)); 162.8 (s, C(7)). MS, *m/z* (I_{rel} (%)): 178 $[M]^+$ (100); 150 $[M - CH_3CH_2]^+$ (6); 135 $[M - CH_3CH_2CH]^+$ (79); 121 $[M - CH_3CH_2CHN]^+$ (6). Found (%): C, 61.18; H, 6.34; N, 24.07. $C_9H_{11}N_3O$. Calculated (%): C, 61.00; H, 6.26; N, 23.71.

***N*-(2,4,6-Trimethyl-1,3,5-dithiazinan-5-yl)isonicotinamide (9).** The yield was 32% (method *C*), 41% (method *D*), n_D^{20} 1.4990, R_f 0.78 ($CHCl_3$—AcOEt—EtOH, 5 : 1 : 1, as the eluent). IR, ν/cm^{-1}: 700, 1050, 1255, 1450—1510, 1600, 1695, 2935, 3370. ^{1}H NMR ($CDCl_3$), δ: 1.39 (m, 3 H, C(15)H$_3$); 1.64 (m, 6 H, C(16)H$_3$, C(17)H$_3$); 3.54 (s, 2 H, C(2)H$_2$); 4.28 (s, 4 H, C(4)H$_2$, C(6)H$_2$); 7.30 (d, 2 H, C(11)H, C(13)H), J = 4.2 Hz); 7.66 (d, 2 H, C(10)H, C(14)H, J = 4.2 Hz); 8.71 (s, 1 H, N(7)H). ^{13}C NMR ($CDCl_3$), δ: 19.5 (s, C(15)); 23.6 (s, C(16), C(17)); 44.2 (s, C(2)); 68.9 (s, C(4), C(6)); 121.1 (d, C(11), C(13)); 140.2 (d, C(9)); 150.6 (d, C(10), C(14)); 164.9 (s, C(8)). MS, m/z (I_{rel} (%)): 284 [M + 1]$^+$ (100); 224 [M – $CH_3CHSCHCH_3$]$^+$ (5); 164 [M – $SCHCH_3SCHCH_3$]$^+$ (25); 107 [M – – $CH_3CHSCHCH_3SCHCH_3$]$^+$ (7). Found (%): C, 50.52; H, 6.09; N, 14.57; S, 22.78. $C_{12}H_{17}N_3OS_2$. Calculated (%): C, 50.85; H, 6.05; N, 14.83; S, 22.63.

1,1-Bis[4-(isonicotinoyl-2,5-dimethyl-1,3,4-thiadiazolidin-3-yl)ethylsulfanyl]ethane (10). The yield was 6% (method *C*). MS, m/z (I_{rel} (%)): 591 [M – H]$^-$ (53); 531 [M – $SCHCH_3$]$^-$ (100); 515 [M – $CHCH_3SCHCH_3$]$^-$ (58); 413 [M – 2 $CHCH_3SCHCH_3$]$^-$ (41); 281 [M – $C_5H_4NCONCHCH_3SCHCH_3NCHCH_3SCHCH_3$]$^-$ (29); 223 [M – $C_5H_4NCONCHCH_3SCHCH_3NCHCH_3SCHCH_3$]$^-$ (24); 190 [M – $C_5H_4NCONCHCH_3SCHCH_3NCHCH_3SCHCH_3SCHCH_3$,S]$^-$ (29).

X-ray diffraction study of compounds 3a,c,d and 8. Crystals of **3a** were grown by crystallization from a 5 : 1 : 1 $CHCl_3$—AcOEt—EtOH mixture; crystals of **3c**, by crystallization from a 10 : 1 : 1 $CHCl_3$—AcOEt—acetone mixture; crystals of **3d**, by crystallization from a 10 : 1 $CHCl_3$—AcOEt mixture; crystals of **8**, by crystallization from a 5 : 1 $CHCl_3$—EtOH mixture.

The X-ray diffraction data sets for compounds **3a**,**c**,**d** and **8** were collected on Bruker SMART CCD Area Detector (**3c**,**d**, **8**) and Bruker APEX 2 CCD Area Detector (**3a**) diffractometers (Mo-Kα radiation) at 100, 295, 100, and 120 K for compounds **3a**,**c**,**d** and **8**, respectively. For compounds **3a**,**c**,**d**, semiempirical absorption corrections were applied; the transmission coefficients T_{max} and T_{min} were determined using the SADABS program.[19] The structures were solved by direct methods. All non-hydrogen atoms were located in different electron density maps and refined based on F^2_{hkl} with anisotropic displacement parameters. The hydrogen atoms of the NH and OH groups were located in difference electron density maps. The H(C) atoms were positioned geometrically. All hydrogen atoms were refined using a riding model with U(H) = 1.2U(Ci), where U(X) are the

Table 4. Crystallographic characteristics and the structure refinement statistics for **3a,c,d** and **8**

Parameter	**3a**	**3c**	**3d**	**8**
Molecular formula	$C_9H_{11}N_3OS_2$	$C_{11}H_{14}N_2O_2S_2$	$C_{11}H_{14}N_2O_2S_2$	$C_9H_{11}N_3O$
M	241.33	270.36	270.36	177.21
Space group	*Pccn*	*Pbca*	$P2_1/c$	$P\bar{1}$
a/Å	12.083(1)	8.778(1)	12.754(3)	9.893(2)
b/Å	20.398(2)	12.143(1)	7.864(2)	14.219(2)
c/Å	9.0115(9)	23.483(3)	13.496(3)	15.123(2)
α/deg	90	90	90	93.022(4)
β/deg	90	90	111.675(6)	106.224(3)
γ/deg	90	90	90	109.655(3)
V/Å^3	2221.1(4)	2502.9(5)	1258.0(5)	1898.1(5)
Z	8	8	4	8
d_{calc}/g cm^{-3}	1.443	1.435	1.428	1.240
Crystal color and shape	Colorless prism			
Crystal dimensions/mm	0.25×0.20×0.20	0.40×0.30×0.20	0.20×0.20×0.15	0.25×0.21×0.18
μ/mm^{-1}	0.456	0.417	0.414	0.085
Absorption correction	SADABS			—
T_{min}/T_{max}	0.896/0.914	0.851/0.921	0.923/0.940	—
$2\theta_{max}$/deg	56	58	58	56
Number of reflections	23456	14083	7927	19578
Number of independent reflections (R_{int})	2658 (0.0803)	3284 (0.0397)	3333 (0.0559)	9133 (0.0582)
R_1 (based on F for reflections with $I > 2\sigma(I)$)	0.0509 (1932)	0.0525 (2143)	0.0485 (2186)	0.0671 (3829)
wR_2 (based on F^2 for all reflections)	0.1341	0.1555	0.1048	0.2206
Number of refined parameters	136	155	154	490
Weighting scheme	$w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$, $P = 1/3(F_o^2 + 2F_c^2)$			
A	0.0533	0.0313	0.0350	0.0918
B	4.8523	2.5802	0.2000	0.2650
GOOF	1.000	1.023	1.000	1.001
F(000)	1008	1136	568	752

equivalent thermal parameters of the corresponding parent atoms; for the hydrogen atoms of the methyl groups, $U(H) = 1.5U(Ci)$. All calculations were carried out with the use of the SHELXTL PLUS 5.10 program package.[14]

Principal X-ray data collection and refinement statistics are given in Table 4. The atomic coordinates, bond lengths, bond angles, and thermal parameters were deposited with the Cambridge Crystallographic Data Centre (CCDC 716620—716623) and can be obtained, free of charge, on application to www.ccdc.cam.uk/conts/retrieving.html (or CCDC, 12 Union Road, Cambridge CB2 1EZ; fax: +44 1223 335 033; or deposit@ccdc.cam.ac.uk).

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