Synthesis and Stereochemical Studies of 6-Substituted 1*H*,3*H*,6*H*,7a*H*-3,3-Dimethylimidazo-[1,5-*c*]thiazol-5-one-7-thiones

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The reaction of (4*S*)-5,5-dimethyl-4-thiazolidine-carboxylic acid **1** with alkyl and aryl isothiocyanates **2** gave bicyclic thiohydantoins **3**. The (2*R*,4*S*)- and (2*S*,4*S*)-mixtures of 2-substituted 5,5-dimethyl-4-thiazolidine-carboxylic acids **4** and **8** containing two centers of chirality in the analogous reaction afforded thiohydantoins **7** and **10**, respectively, with (1*R*)-configuration. In some cases we managed to isolate the thioureido acid intermediates **6** and **9** or their triethylamine salts which afforded the corresponding bicycles **7** and **10** under thermal cyclization or acidification. The stereochemistry has been elucidated by high resolution nmr studies, optical rotation measurements and X-ray crystallography.

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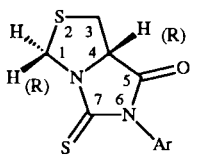
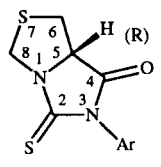
The study of the reaction of amino acids with isothiocyanates obtained a special importance in the routine sequence analysis of peptides by Edman-degradation [1-6]. In case of the cyclic amino acid, for example proline or pipecolic acid, in analogous manner the 2-(aryl)thiohydantoin formed invariably [7]. The studies of the stereochemistry of thiazolidine carboxylic acids as cyclic amino acids [8], prompted us to investigate the reaction of these compounds with isothiocyanates, in order to determine the stereochemistry of cyclization and the possibility of isolation of the intermediates.

It was known, that thiohydantoins formed through the Edman degradation reaction without racemization at *p*H 9 [9], but the authors [10,11,12] gave no data of the optical purity of the 1*H*,3*H*,6*H*,7a*H*-imidazo[1,5-*c*]thiazol-5-one-7-thiones [**A**] formed (other name: 7-thia-1,3-diazabicyclo[3.3.0]octan-4-one-2-thiones [**B**]) from (4*R*)-thiazolidinecarboxylic acid and isothiocyanates (Scheme 1).

Scheme 1



A



B

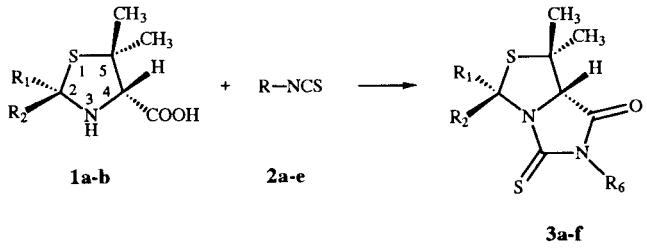
Russian and French authors investigated the cyclization of ethyl (4*R*)-thiazolidinecarboxylate and ethyl 1,4-tetrahydrothiazine-3-carboxylate with phenyl isothiocyanate and phenyl isocyanate [13-16]. The Mitsubishi Chemical Industries patented the synthesis of 6-aryl-dihydro-6*H*,7a*H*-imidazo[1,5-*c*]thiazole-5,7-dione derivatives by thermal cyclization of ureido-acid intermediates which are active against *Botrytis cinerea* [17].

First of all we were interested to ascertain that unsubstituted (4*S*)-thiazolidinecarboxylic acid can be used for cyclization instead of its ester not using strongly basic conditions, because the Dutch authors showed, that under such conditions, two molecules of isothiocyanates could take part in the reaction [8]. (4*S*)-Thiazolidinecarboxylic acids, containing one center of chirality, cyclized with aryl isothiocyanates in alcoholic solution at reflux temperature and afforded 3,3-dimethyl-1*H*,3*H*,6*H*,7a*H*-imidazo[1,5-*c*]thiazol-5-one-7-thione derivatives **3** in yields of 70-85% as shown in Table 1. The products are stereohomogenous from data of optical rotation and by the 4-H signal at ~4.8 ppm. These experiments indicated that thiohydantoins **3** can be synthesized without using the esters of **1** under basic conditions (Scheme 2).

The problem became more complicated when 2-substituted 4-thiazolidinecarboxylic acids **1** in which R_1 and R_2 were not equal were used resulting in two chiral centers in the molecule.

It was shown in our earlier communications [9,18,19] that from D-penicillamine (3-mercapto-D-valine, 3-dimethyl-D-cysteine) we could obtain 4(*S*)-5,5-dimethyl-2-aryl-4-thiazolidinecarboxylic acids containing (2*R*,4*S*)- or (2*S*,4*S*)-diastereoisomers in different proportions depending on the substituent at position 2 which could be transformed by

Scheme 2



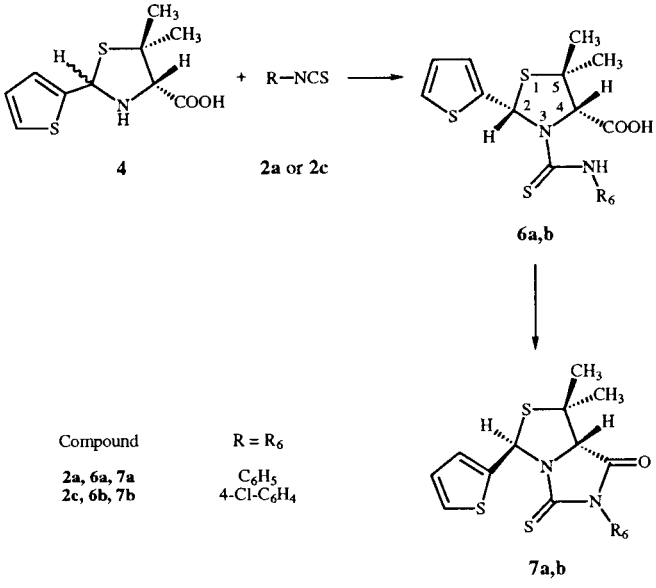
1a-b 2a-e 3a-f

Compound	$R_1 = R_2$	Compound	R	Compound	R_6	$R_1 = R_2$
1a	H	2a	C_6H_5	3a	C_6H_5	H
1b	CH_3	2b	2,4,6-$(Cl)_3$-C_6H_2	3b	C_6H_5	CH_3
		2c	4-Cl-C_6H_4	3c	2,4,6-$(Cl)_3$-C_6H_2	H
		2d	CH_3	3d	4-Cl-C_6H_4	H
		2e	4-NO_2-C_6H_4	3e	CH_3	H
				3f	4-NO_2-C_6H_4	H

recyclization following the ring opening one to the other. We showed that from these mixtures of diastereomers it is possible to synthesize (2*R*,4*S*)- or (2*S*,4*S*)-3-acyl-2-aryl-4-thiazolidinecarboxylic acids in a diastereoselective manner choosing the proper conditions of acylation [9,18,19,20,21].

The study of thiohydantoin formation was extended for such acids in which the substituent at position 2 are 2-thienyl (**4**) [22] and carboxy (**9**) [23]. For the product **9** the proportion of (2*R*,4*S*)- and (2*S*,4*S*)-diastereomers is 4:1 (Scheme 3).

Scheme 3



Compound	R = R_6
2a, 6a, 7a	C_6H_5
2c, 6b, 7b	4-Cl-C_6H_4

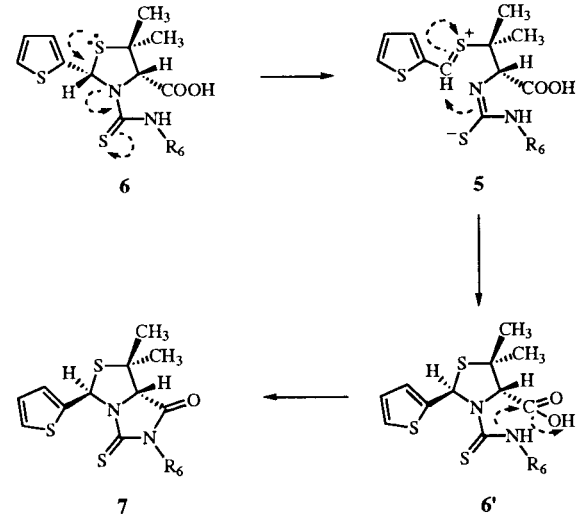
We managed to transform **4** with isothiocyanates **2a** and **2c** under such conditions when we could isolate thioureido-compounds **6a** and **6b** in the free acid form as primary products. These acids **6a** and **6b** were cyclized to **7a** and **7b** under thermal condition. The same products **7a** and **7b** were obtained directly by the reaction of **4** with **2a** or **2c**, respectively, in hot ethanol.

The chirality (by numbering **A**, Scheme 1) of carbon atom C-1 could be determined from optical rotation measurements according to our previous studies [18-20]. Compounds with configuration of (2*R*,4*S*) show a strong positive rotation whereas compounds with (2*S*,4*S*) configuration show a moderately negative rotation. Our compounds **6a** and **6b** showing a moderate negative rotation correspond to (2*S*,4*S*) derivatives. This stereochemistry was supported by NOE measurements (see below).

The cyclization of thioureido derivatives **6a** and **6b** (see Experimental) afforded thiohydantoins with a high positive specific rotation value. This observation suggests the following explanation: in the process leading to the ring closure of bicycle **7** compound **6** must undergo a ring opening and subsequent epimerization/ring closure and as a result it leads exclusively to the less strained fused ring system with (2*R*,4*S*) configuration (Scheme 4).

This configurational change was also supported by ^1H nmr and X-ray crystallographic studies.

Scheme 4

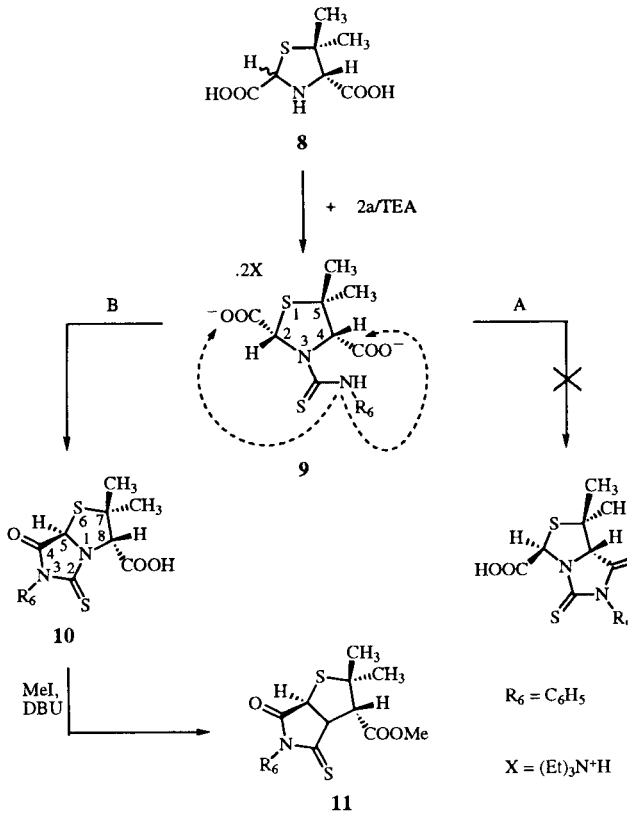


An analogous observation was made in the reaction of (4*S*)-5,5-dimethyl-thiazolidine-2,4-dicarboxylic acid (**8**) with isothiocyanates since we obtained optically pure, single thioureido derivative as the triethylamine salt **9**.

The cyclization of product **9** started during acidification, therefore it could not be isolated as free acid and bicycle **10** was obtained.

Theoretically the cyclization of **9** may be accomplished by two distinct routes (Scheme 5) **A** and **B** [16]. Route **B** was confirmed by the ^1H nmr study, therefore the monocarboxylic acid **10** could be obtained by cyclization of **8**. In contrary the French authors [16] reported that the (4*R*)-5,5-desmethyl derivative of **8** gave the appropriate bicyclic product by route **A**.

Scheme 5



determined by 1D difference NOE experiments. In **7** and **10**, the irradiation of the high-field 5-CH_3 signal resulted in a *ca.* 20% NOE enhancement of the H-2 signal, whereas the low-field 5-CH_3 protons showed a *ca.* 30% NOE with H-4. In addition, a 1-2% NOE was observed between H-2 and H-4. These NOEs suggest that in **7** and **10**, H-2 and H-4 are at the opposite side of the thiazolidine ring, (2*R*,4*S*), *i.e.* in *trans* arrangement. Note that the X-ray study (see later) of compound **7b** has also corroborated the nmr derived stereochemical assignment. A strikingly different NOE pattern was observed for compounds **6** and **9**, indicating a different spatial arrangement of the relevant protons. When the low-field methyl (5-CH_3) signal was saturated both H-2 and H-4 signal intensities were enhanced by 5% and 17%, respectively. The irradiation of high-field 5-CH_3 signal, however, gave NOE enhancement at only H-4 (4%). These NOEs are in agreement with a *cis* arrangement of H-2 and H-4, (2*S*,4*S*), *i.e.* they are at the same side of the ring.

In order to establish the stereochemistry of ring closure (path **A** or **B** in Scheme 4), selective steady-state heteronuclear NOE experiments were carried out. Selective irradiation of H-2 and H-4, respectively, enabled the assignment of the neighboring carbonyl carbons. The carbon signal at 168.6 ppm could be assigned to CO attached to C-4 based on its 80% intensity enhancement observed upon irradiation of H-4 proton. As expected, a heteronuclear NOE enhancement (32%) was also detected at C-5

Table 1

Optical Rotation and ^{1}H-NMR data of Monochiral 1*H*,3*H*,6*H*,7a*H*-Imidazo[1,5-*c*]thiazol-5-one-7-thiones

Compound	$[\alpha]_D$	δ (200.13 MHz, DMSO-d_6, δ in ppm, J in Hz)
3a	+47.0 [a]	1.32 (3H, s, CH_3), 1.61 (3H, s, CH_3), 4.73 (1H, d, J = 9.2, H-1), 4.81 (1H, s, H-4), 5.14 (1H, d, J = 9.2, H-1), 7.2-7.6 (5H, m, C_6H_5)
3b	+63.4 [a]	1.48 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.86 (3H, s, CH_3), 2.24 (3H, s, CH_3), 5.28 (1H, s, H-4), 7.2-7.5 (5H, m, C_6H_5)
3c	+21.2 [b]	1.39 (3H, s, CH_3), 1.61 (3H, s, CH_3), 4.78 (1H, d, J = 9.5, H-1), 5.05 (1H, d, J = 9.5, H-1*), 5.20 (1H, s, H-4), 7.9-8.0 (2H, m, $(Cl)_3C_6H_2$)
3d	-7.5 [b]	1.31 (3H, s, CH_3), 1.60 (3H, s, CH_3), 4.72 (1H, d, J = 9.5, H-1), 4.80 (1H, s, H-4), 5.12 (1H, d, J = 9.5, H-1*), 7.34, 7.59 (4H, d, J = 8.8, 4-(Cl)-C_6H_4)
3e	+85.0 [b]	1.12 (3H, s, CH_3), 1.56 (3H, s, CH_3), 3.10 (3H, s, NCH_3), 4.64 (1H, d, J = 9.5, H-1), 4.65 (1H, s, H-4), 5.05 (1H, d, J = 9.5, H-1*)
3f	-29.0 [c]	1.34 (3H, s, CH_3), 1.62 (3H, s, CH_3), 4.76 (1H, d, J = 9.9, H-1), 4.85 (1H, s, H-4), 5.14 (1H, d, J = 9.9, H-1*), 7.66, 8.38 (4H, d, J = 8.8, 4-NO_2-C_6H_4)

[a] In chloroform. [b] In methanol. [c] In dimethylformamide.

NMR Structural Studies of the Compounds Synthesized.

The ^{1}H nmr assignments were straightforward and based on simple chemical shift considerations. All ^{1}H nmr data of the relevant compounds are listed in the Tables 1 and 2. Note that in the following discussion the numbering of atoms in the relevant molecules corresponds to that of the thiazolidine ring allowing a unified presentation of the nmr data.

The relative configuration of the chiral carbons C-2 and C-4 of the thiazolidine ring in compounds **6**, **7**, **9** and **10** was

(59.5 ppm), indicating the spatial proximity of the relevant nuclei. Saturation of H-2 gave a NOE enhancement (60%) at CO of 170.9 ppm, thus this signal could be safely assigned to CO bound to C-2. Irradiation of H-2 gave NOE enhancement (45%) at the other carbonyl carbon (168.6 ppm) which is also consistent with the *trans* position of H-2 and H-4 established by homonuclear NOE study. In order to distinguish between the carbonyls, carbonyl belonging to the free COOH group or that incorpo-

Table 2

Optical Rotation and ^{1}H-NMR Data of Bichiral Thiohydantoins and Intermediates

Compound	$[\alpha]_D$	Chirality	δ (200.13 MHz, DMSO-d_6, δ in ppm, J in Hz)
6a	-60.1 [a]	2*S*,4*S*	1.39 (3H, s, CH_3), 1.64 (3H, s, CH_3), 4.96 (1H, s, H-4), 7.12 (1H, s, H-2), 6.8-7.6 (8H, m, C_6H_5, C_4SH_3), 9.02 (1H, s, NH)
6b	-60.9 [a]	2*S*,4*S*	1.38 (3H, s, CH_3), 1.63 (3H, s, CH_3), 4.94 (1H, s, H-4), 7.10 (1H, s, H-2), 6.8-7.7 (7H, m, *p*-Cl-C_6H_4, C_4SH_3), 9.12 (1H, s, NH)
7a	+346.7 [a]	2*R*,4*S*	1.41 (3H, s, CH_3), 1.68 (3H, s, CH_3), 5.05 (1H, s, H4), 6.90 (1H, s, H-2), 7.0-7.6 (8H, m, C_6H_5, C_4SH_3),
7b	+341.7 [a]	2*R*,4*S*	1.39 (3H, s, CH_3), 1.67 (3H, s, CH_3), 5.04 (1H, s, H-4), 6.88 (1H, s, H-2), 7.05, 7.41, 7.59 (3H, m, C_4SH_3), 7.35, 7.59 (each 2H, d, J = 8.7, 4-(Cl)-C_6H_4)
9	-29.8 [a]	2*S*,4*S*	1.41 (3H, s, CH_3), 1.53 (3H, s, CH_3), 4.99 (1H, s, H-4), 5.95 (1H, s, H-2), 7.0-7.5 (5H, m, C_6H_5), 9.31 (1H, s, NH)
10	+136.3 [a]	2*R*,4*S* [b]	1.61 (3H, s, CH_3), 1.66 (3H, s, CH_3), 4.98 (1H, s, H-4), 6.24 (1H, s, H-2), 7.3 (5H, m, C_6H_5), 11.5 (1H, broad signal COOH)

[a] In chloroform. [b] Note that the numbering of atoms in the relevant molecule corresponds to that of thiazolidine ring allowing a unified presentation of the nmr data.

rated in the newly formed ring, the solvent dependence of carbon chemical shifts was determined. The largest shift (+0.4 ppm) observed for the carbonyl signal at 168.6 ppm upon addition of pyridine to the DMSO solution indicates that the carbonyl bound to C-4 belongs to the free carboxylic group. Note that all other signals showed less than 0.1 ppm solvent induced shifts. The esterification of the free COOH group (compound **11**) resulting in -1.1 ppm shift of the signal at 168.6 ppm provided further evidence to the carbonyl assignment. These results, however, unambiguously confirm that the ring closure takes place with the COOH at C-2 according to path **B** in Scheme 5.

Discussion of Crystallographic Results of **7b**.

Numbering of the atoms is shown in Figure 1. A stereo view of the molecule is given in Figure 2. Crystal data, conditions of measurement and of refinement are listed in Table 3. Table 4 contains positional parameters and equivalent isotropic temperature factors.

The thiazolidine ring has a twisted envelope conformation ^{4}T3, while the imidazole ring is almost planar due to the sp^2 hybridized carbon atoms C5 and C7. The mean planes of the two fused five membered rings enclose an angle of 37°.

Compound **7b** contains five C-S bonds, which fall into three categories. The longest, S2-C1 = 1.845(7) and S2-C3 = 1.851(7) are single bonds, the shortest, S7-C7 = 1.639(7)Å, is a double bond and the C-S bonds of the thiophene ring, S12-C11 = 1.673(8)Å and C12-C8 = 1.683(8)Å are conjugated double bonds. The expected values given in the International Tables [24] are 1.81(±1), 1.71(±2), and 1.73(±2)Å for the three kinds of bonds, respectively. The single bonds are longer than the expected value, probably due to the strain on the five membered ring and tendency to reduce crowding caused by the bulky substituents on C1 and C3. The shorter than expected C-S bonds of the thiophene ring and elongated C8-C9 and C9-C10 bonds may point to a small amount of rotational disorder of 180° about the C1-C8 bond. The phenyl and thiophene rings are planar as expected. Between the phenyl ring and the imidazole ring an angle of 60° was found and the thiophene ring encloses an angle of 107° degrees with the thiazolidine ring.

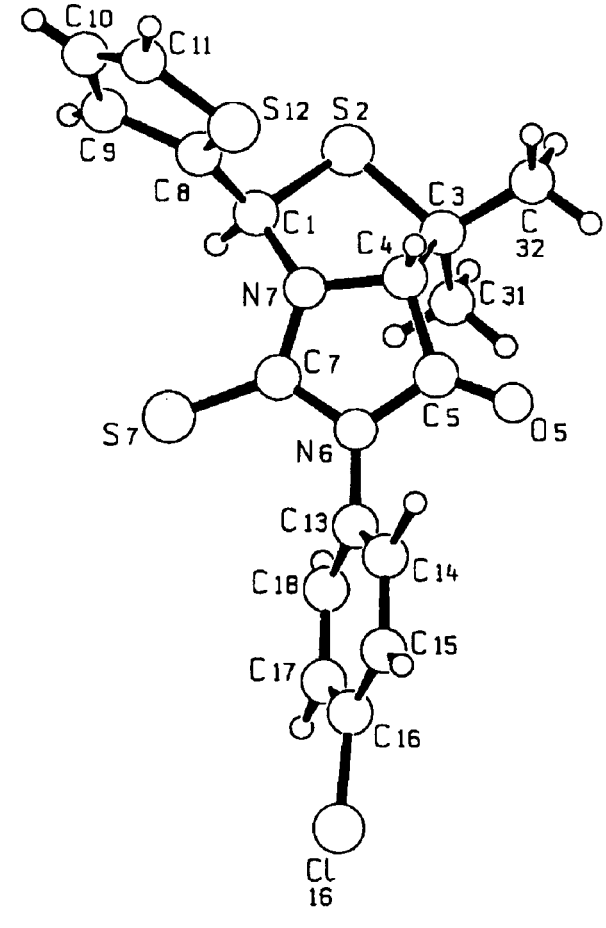


Figure 1. A view of the molecular structure **7b**, showing the atomic numbering.

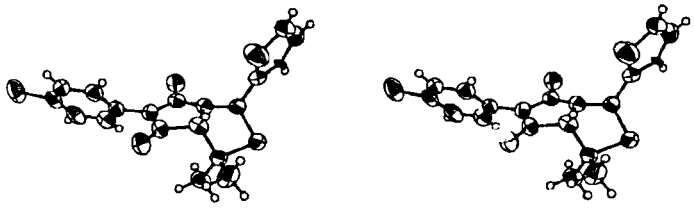


Figure 2. A stereo view of the molecule **7b**.

Table 3

Crystal Data and Structure Refinement for **7b**

Empirical formula	$C_{17}H_{15}ClN_2OS_3$
Formula weight	394.94
Temperature	293(2) K
Wavelength	1.54180 Å
Crystal system	monoclinic
Space group	C2
Unit cell dimensions	a = 15.908(4) Å alpha = 90.00(3) deg.
	b = 6.431(3) Å beta = 96.16(2) deg.
	c = 17.928(4) Å gamma = 90.00(3) deg.
Volume	1823.5(10) A^3
Z	4
Density (calculated)	1.439 Mg/m^3
Absorption coefficient	5.119 mm^{-1}
F(000)	816
Crystal size	0.85 x 0.13 x 0.08 mm
Theta range for data collection	4.96 to 64.01 deg.
Index ranges	-18<=h<=18, -7<=k<=0, 0<=1<=20
Reflections collected	1745
Independent reflections	1662 [R(int) - 0.0248]
Refinement method	Full-matrix least-squares on F
Data/restraints/parameters	1662/1/219
Goodness-of-fit on F	1.046
Final R indices (I>2sigma(I)]	R1 = 0.0566, wR2 = 0.1734
R indices (all data)	R1 = 0.0653, wR2 = 0.1785
Absolute structure parameter	-0.01(4)
Largest diff. peak and hole	0.842 and -0.631 e. A^3

Table 4

Atomic Coordinates (x 10^4) and Equivalent isotropic displacement parameters (A^2 x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor

	x	y	z	U(eq)
C(1)	1721(4)	7441(12)	3523(3)	49(2)
S(2)	809(1)	8704(4)	3890(1)	61(1)
C(3)	279(4)	9453(13)	2959(4)	51(2)
C(31)	-324(5)	7796(19)	2626(5)	77(3)
C(32)	-163(8)	11530(18)	3036(6)	92(3)
C(4)	1033(4)	9684(10)	2506(3)	44(1)
C(5)	852(4)	9345(11)	1665(4)	44(1)
O(5)	420(3)	10375(9)	1229(3)	59(1)
N(6)	1296(3)	7566(9)	1511(3)	44(1)
N(7)	1613(3)	8012(8)	2726(3)	42(1)
C(7)	1730(4)	6694(10)	2151(3)	42(1)
S(7)	2268(1)	4516(3)	2217(1)	56(1)
C(8)	2530(4)	8116(12)	3928(3)	46(2)
C(9)	3023(3)	6845(11)	4575(3)	35(1)
C(10)	3743(5)	8408(18)	4804(4)	70(2)
C(11)	3769(5)	10091(19)	4424(4)	76(3)
S(12)	2977(2)	10401(5)	3739(2)	93(1)
C(13)	1327(4)	6782(11)	771(3)	45(1)
C(14)	1623(4)	8058(12)	236(4)	51(2)
C(15)	1668(5)	7287(13)	-487(4)	56(2)
C(16)	1416(4)	5255(15)	-650(4)	58(2)
C(16)	1549(2)	4284(5)	-1536(1)	90(1)
C(17)	1105(5)	4051(12)	-139(4)	63(2)
C(18)	1048(5)	4787(11)	584(4)	52(2)

Table 5 shows the geometric parameters: bond lengths and bond angles. Torsional angles of the nonhydrogen atoms are listed in Table 6.

Table 5

Bond Lengths (Å) and Angles (deg)

C(4)-N(7)	1.443(8)	C(9)-C(10)	1.545(11)
C(4)-C(5)	1.521(9)	C(10)-C(11)	1.28(2)
C(5)-O(5)	1.185(8)	C(11)-S(12)	1.673(8)
C(5)-N(6)	1.388(9)	C(13)-C(14)	1.384(9)
N(6)-C(7)	1.392(8)	C(13)-C(18)	1.387(10)
N(6)-C(13)	1.424(9)	C(14)-C(15)	1.397(10)
N(7)-C(7)	1.363(8)	C(15)-C(16)	1.389(13)
C(7)-S(7)	1.639(7)	C(16)-C(17)	1.334(12)
C(8)-C(9)	1.560(8)	C(16)-Cl(16)	1.740(7)
C(8)-S(12)	1.683(8)	C(17)-C(18)	1.393(11)
N(7)-C(1)-C(8)	114.3(5)	C(32)-C(3)-C(4)	111.1(7)
N(7)-C(1)-S(2)	102.9(4)	C(31)-C(3)-S(2)	112.4(6)
C(8)-C(1)-S(2)	111.9(5)	C(32)-C(3)-S(2)	108.5(6)
C(1)-S(2)-C(3)	95.3(3)	C(4)-C(3)-S(2)	101.3(4)
C(31)-C(3)-C(32)	112.0(8)	N(7)-C(4)-C(5)	102.2(5)
C(31)-C(3)-C(4)	111.2(6)	N(7)-C(4)-C(3)	107.4(5)
C(5)-C(4)-C(3)	115.9(5)	C(5)-N(6)-C(7)	112.7(5)
O(5)-C(5)-N(6)	126.9(6)	C(5)-N(6)-C(13)	123.1(5)
O(5)-C(5)-C(4)	127.5(7)	C(7)-N(6)-C(13)	124.1(6)
N(6)-C(5)-C(4)	105.6(5)	C(7)-N(7)-C(4)	113.1(5)
C(7)-N(7)-C(1)	124.7(5)	C(11)-S(12)-C(8)	92.8(5)
C(4)-N(7)-C(1)	117.2(5)	C(14)-C(13)-C(18)	120.3(7)
N(7)-C(7)-N(6)	106.1(5)	C(14)-C(13)-N(6)	119.0(6)
N(7)-C(7)-S(7)	126.1(5)	C(18)-C(13)-N(6)	120.7(6)
N(6)-C(7)-S(7)	127.8(5)	C(13)-C(14)-C(15)	119.3(7)
C(1)-C(8)-C(9)	123.7(6)	C(16)-C(15)-C(14)	119.1(7)
C(1)-C(8)-S(12)	121.6(5)	C(17)-C(16)-C(15)	121.5(7)
C(9)-C(8)-S(12)	114.7(4)	C(17)-C(16)-Cl(16)	120.5(7)
C(10)-C(9)-C(8)	98.9(6)	C(15)-C(16)-Cl(16)	117.9(7)
C(11)-C(10)-C(9)	118.2(7)	C(16)-C(17)-C(18)	120.5(7)
C(10)-C(11)-S(12)	115.2(7)	C(13)-C(18)-C(17)	119.3(7)

Table 6

Torsion Angles (deg)

N(7)-C(1)-S(2)-C(3)	9.2(5)	C(1)-S(2)-C(3)-C(4)	-28.5(5)
C(8)-C(1)-S(2)-C(3)	132.3(5)	C(31)-C(3)-C(4)-N(7)	-79.3(7)
C(1)-S(2)-C(3)-C(31)	90.3(6)	C(32)-C(3)-C(4)-N(7)	155.3(7)
C(1)-S(2)-C(3)-C(32)	-145.4(6)	S(2)-C(3)-C(4)-N(7)	40.3(6)
C(31)-C(3)-C(4)-C(5)	34.1(9)	C(13)-N(6)-C(7)-S(7)	-7.2(9)
C(32)-C(3)-C(4)-C(5)	-91.2(8)	N(7)-C(1)-C(8)-C(9)	-145.4(6)
S(2)-C(3)-C(4)-C(5)	153.7(5)	S(2)-C(1)-C(8)-C(9)	98.2(7)
N(7)-C(4)-C(5)-O(5)	-178.0(6)	N(7)-C(1)-C(8)-S(12)	36.7(9)
C(3)-C(4)-C(5)-O(5)	65.6(9)	S(2)-C(1)-C(8)-S(12)	-79.7(6)
N(7)-C(4)-C(5)-N(6)	2.3(6)	C(1)-C(8)-C(9)-C(10)	-175.3(6)
C(3)-C(4)-C(5)-N(6)	-114.1(6)	S(12)-C(8)-C(9)-C(10)	2.7(6)
O(5)-C(5)-N(6)-C(7)	-178.7(6)	C(8)-C(9)-C(10)-C(11)	-3.1(10)
C(4)-C(5)-N(6)-C(7)	1.0(6)	C(9)-C(10)-C(11)-S(12)	2.3(11)
O(5)-C(5)-N(6)-C(13)	3.7(9)	C(10)-C(11)-S(12)-C(8)	-0.3(8)
C(4)-C(5)-N(6)-C(13)	-176.5(5)	C(1)-C(8)-S(12)-C(11)	176.4(6)
C(5)-C(4)-N(7)-C(7)	-5.1(6)	C(9)-C(8)-S(12)-C(11)	-1.7(5)

Table 6 (continued)

C(3)-C(4)-N(7)-C(7)	117.3(6)	C(5)-N(6)-C(13)-C(14)	57.1(8)
C(5)-C(4)-N(7)-C(1)	-161.2(5)	C(7)-N(6)-C(13)-C(14)	-120.2(7)
C(3)-C(4)-N(7)-C(1)	-38.8(7)	C(5)-N(6)-C(13)-C(18)	-121.4(7)
C(8)-C(1)-N(7)-C(7)	100.7(7)	C(7)-N(6)-C(13)-C(18)	61.3(8)
S(2)-C(1)-N(7)-C(7)	-137.8(5)	C(18)-C(13)-C(14)-C(15)	-2.5(10)
C(8)-C(1)-N(7)-C(4)	-106.1(7)	N(6)-C(13)-C(14)-C(15)	179.0(6)
S(2)-C(1)-N(7)-C(4)	15.4(6)	C(13)-C(14)-C(15)-C(16)	-0.1(10)
C(4)-N(7)-C(7)-N(6)	5.8(6)	C(14)-C(15)-C(16)-C(17)	2.4(10)
C(1)-N(7)-C(7)-N(6)	159.9(5)	C(14)-C(15)-C(16)-Cl(16)	175.6(5)
C(4)-N(7)-C(7)-S(7)	-173.6(4)	C(15)-C(16)-C(17)-C(18)	-2.0(10)
C(1)-N(7)-C(7)-S(7)	-19.6(8)	Cl(16)-C(16)-C(17)-C(18)	176.0(5)
C(5)-N(6)-C(7)-N(7)	-4.1(6)	C(14)-C(13)-C(18)-C(17)	2.9(10)
C(13)-N(6)-C(7)-N(7)	173.4(5)	N(6)-C(13)-C(18)-C(17)	-178.6(6)
C(5)-N(6)-C(7)-S(7)	175.3(4)	C(16)-C(17)-C(18)-C(13)	-0.7(10)

EXPERIMENTAL

Melting points were determined on a PHMK hot plate apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Microanalyses were performed on a Carlo Erba EA1108 Elemental Analyzer. For tlc purposes Merck DC Alurolle Kieselgel $60F_{254}$ was used.

All ^1H and ^{13}C experiments were performed at ambient temperature on a Bruker WP 200 SY (200.13 MHz for ^1H, 50.3 MHz for ^{13}C) spectrometer equipped with an Aspect 2000 computer; 20-30 mg of samples were dissolved in 0.5 ml of DMSO-d_6 for ^1H measurements; *ca.* 100 mg of compound **10** dissolved in 0.5 ml of DMSO-d_6 was used for the selective heteronuclear NOE experiment. The chemical shifts were referenced to the solvent signal (2.49 ppm for ^1H, 39.5 ppm for ^{13}C) Both homo- and heteronuclear NOE experiments were carried out in difference mode using the frequency jumping line selective saturation of proton transitions [25,26]. The selective proton pulses (6-8 Hz) were obtained through the decoupler.

The crystal structure was determined by X-ray diffraction. Data were collected on a Stoe four circle diffractometer with CuK_α radiation. Crystal data, conditions of measurement and of refinement are listed in Table 3. The data were corrected for absorption.

General Procedure for Synthesis of Thiohydantoins **3a-f** and **7a,b**.

Method A.

(4*S*)-5,5-Dimethylthiazolidine-4-carboxylic acid derivative **1** (5 mmoles) or (4*S*)-2-(2-thienyl)-5,5-dimethylthiazolidine-4-carboxylic acid **4** (5 mmoles) and 5 mmoles of **2a** or **2b** in 10 ml of ethanol were refluxed for 2-3 hours. The reaction was followed by tlc (benzene:diethyl ether = 1:9 or benzene:ethyl acetate:acetic acid = 7:3:1) After cooling the white crystals precipitated. The optical rotation data and ^1H nmr are shown in Tables 1 and 2. The following compounds were synthesized in this way.

(4*S*)-3,3-Dimethyl-6-phenyl-1*H*,3*H*,6*H*,7a*H*-imidazo[1,5-*c*]thiazol-5-one-7-thione (**3a**).

The yield was 72%, mp 125-126°.

Anal. Calcd. for $C_{13}H_{14}N_2OS_2$: C, 56.08; H, 5.07; N, 10.06; S, 23.30. Found: C, 56.28; H, 5.31; N, 9.86; S, 23.44.

(4*S*)-1,1,3,3-Tetramethyl-6-phenyl-1*H*,3*H*,6*H*,7a*H*-imidazo-[1,5-*c*]thiazole-5-one-7-thione (**3b**).

The yield was 82%, mp 178-180°.

Anal. Calcd. for $C_{15}H_{18}N_2OS_2$: C, 58.78; H, 5.92; N, 9.14; S, 20.92. Found: C, 58.61; H, 5.77; N, 8.90; S, 20.87.

(4*S*)-3,3-Dimethyl-6-(2,4,6-trichloro)phenyl-1*H*,3*H*,6*H*,7a*H*-imidazo[1,5-*c*]thiazol-5-one-7-thione (**3c**).

The yield was 72%, mp 137-140°.

Anal. Calcd. for $C_{13}H_{11}Cl_3N_2OS_2$: C, 40.90; H, 2.91; N, 7.34; S, 16.80. Found: C, 40.97; H, 3.06; N, 7.50; S, 16.76.

(4*S*)-3,3-Dimethyl-6-(4-chloro)phenyl-1*H*,3*H*,6*H*,7a*H*-imidazo-[1,5-*c*]thiazol-5-one-7-thione (**3d**).

The yield was 85%, mp 129-131°.

Anal. Calcd. for $C_{13}H_{13}ClN_2OS_2$: C, 49.90; H, 4.19; N, 8.96; S, 20.50. Found: C, 50.16; H, 4.30; N, 8.66; S, 20.32.

(4*S*)-3,3-Dimethyl-6-methyl-1*H*,3*H*,6*H*,7a*H*-imidazo[1,5-*c*]thiazol-5-one-7-thione (**3e**).

The yield was 98%, mp 42°.

Anal. Calcd. for $C_8H_{12}N_2OS_2$: C, 44.41; H, 5.59; N, 12.95; S, 29.64. Found: C, 44.16; H, 5.80; N, 12.67; S, 29.55.

(4*S*)-3,3-Dimethyl-6-(4-nitro)phenyl-1*H*,3*H*,6*H*,7a*H*-imidazo[1,5-*c*]thiazol-5-one-7-thione (**3f**).

The yield was 90%, mp 192-194°.

Anal. Calcd. for $C_{13}H_{13}N_3O_3S_2$: C, 48.28; H, 4.05; N, 12.99; S, 19.83. Found: C, 48.30; H, 3.95; N, 12.99; S, 19.87.

(1*R*,4*S*)-3,3-Dimethyl-6-phenyl-1-(2-thienyl)-1*H*,3*H*,6*H*,7a*H*-imidazo[1,5-*c*]thiazol-5-one-7-thione (**7a**).

The yield was 53%, mp 165°.

Anal. Calcd. for $C_{17}H_{16}N_2OS_3$: C, 56.63; H, 4.47; N, 7.76; S, 26.67. Found: C, 56.58; H, 4.39; N, 7.68; S, 26.71.

(1*R*,4*S*)-3,3-Dimethyl-6-(4-chloro)phenyl-1-(2-thienyl)-1*H*,3*H*,6*H*,7a*H*-imidazo[1,5-*c*]thiazol-5-one-7-thione (**7b**).

The yield was 55%, mp 152°.

Anal. Calcd. for $C_{17}H_{15}ClN_2OS_3$: C, 51.69; H, 3.83; N, 7.09; S, 24.35. Found: C, 51.43; H, 3.79; N, 7.10; S, 24.28.

Method B.

Five mmoles of (2*S*,4*S*)-2-(2-thienyl)-3-phenylthiocarbamoyl-5,5-dimethylthiazolidine-4-carboxylic acid **6a** or (2*S*,4*S*)-2-(2-thienyl)-3-(4-chloro)phenylthiocarbamoyl-5,5-dimethyl-thiazolidine-4-carboxylic acid **6b** in 10 ml of ethanol were refluxed for 10 minutes. After cooling the white crystals precipitated. The products **7a** and **7b** were prepared under the same conditions as by method A.

General Procedure for the Synthesis of **6a** and **6b**.

Five mmoles of **4** and 5 mmoles of triethylamine were dissolved in 20 ml of ethanol. To this solution 5 mmoles of **2a** or **2b** were added. After stirring for 2-3 hours the reaction mixture was acidified to *p*H = 2 with 10% aqueous hydrochloric acid. The white powder precipitated. The optical data rotation and ^1H nmr are shown in Table 2.

(2*S*,4*S*)-5,5-Dimethyl-3-phenylthioureido-2-(2-thienyl)thiazolidine-4-carboxylic Acid (**6a**).

The yield was 55%, mp 115°.

Anal. Calcd. for $C_{17}H_{18}N_2O_2S_3$: C, 53.94; H, 4.79; N, 7.46; S, 25.41. Found: C, 53.85; H, 4.82; N, 7.42; S, 25.38.

(2*S*,4*S*)-5,5-Dimethyl-3-(4-chloro)phenylthioureido-2-(2-thienyl)thiazolidine-4-carboxylic Acid (**6b**).

The yield was 57%, mp 97°.

Anal. Calcd. for $C_{17}H_{17}ClN_2O_2S_3$: C, 49.44; H, 4.15; N, 6.78; S, 23.25. Found: C, 49.35; H, 4.08; N, 6.72; S, 23.38.

Preparation of Di(triethylammonium)(2*S*,4*S*)-3-Phenylthioureido-5,5-dimethyl-2,4-dicarboxylate (**9**).

Five mmoles of **8** and 10 mmoles of triethylamine were dissolved in 20 ml of ethanol. To this solution 5 mmoles of **2a** was added. After stirring for 3 hours the white powder precipitated. The optical rotation data and ^1H nmr are shown in Table 2. The yield was 72%, mp 145°.

Anal. Calcd. for $C_{14}H_{16}N_2S_2O_4 \cdot 2C_6H_{15}N$: C, 57.52; H, 8.54; N, 10.32; S, 11.81. Found: C, 57.48; H, 8.46; N, 10.24; S, 11.70.

Preparation of (5*R*,8*S*)-[1*H*,3*H*,6*H*,7a*H*]-3-Phenyl-7,7-dimethyl-8-carboxyimidazo[5,1-*b*]thiazol-4-one-2-thione (**10**).

Five mmoles of **9** was dissolved in 20 ml of water. The reaction mixture was acidified to *p*H = 1 with 10% aqueous hydrochloric acid. After stirring for 1 hour the product was filtered. The optical rotation data and ^1H nmr are shown in Table 2. The yield was 74%, mp 209°.

Anal. Calcd. for $C_{14}H_{14}N_2S_2O_3$: C, 52.15; H, 4.37; N, 8.69; S, 19.89. Found: C, 52.20; H, 4.25; N, 8.58; S, 20.02.

Preparation of (5*R*,8*S*)-[1*H*,3*H*,6*H*,7a*H*]-3-Phenyl-7,7-dimethyl-8-carboxymethylimidazo[5,1-*b*]thiazol-4-one-2-thione (**11**).

One mmole of **10** was dissolved in 1.5 ml of DMF and the solution was stirred at room temperature. To this solution 0.15 ml of DBU and 0.07 ml of methyliodide were added. After 90 minutes the reaction mixture was diluted with water and the product was isolated by extraction with ether. The organic solution was washed with water, dried (sodium sulfate) and evaporated to yield syrupy **11**. The yield was 83%, $[\alpha]_D$ = +202.0 (in methanol).

Anal. Calcd. for $C_{15}H_{16}N_2S_2O_3$: C, 53.54; H, 4.79; N, 8.32; S, 19.06. Found: C, 54.02; H, 4.68; N, 8.28; S, 18.92.

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