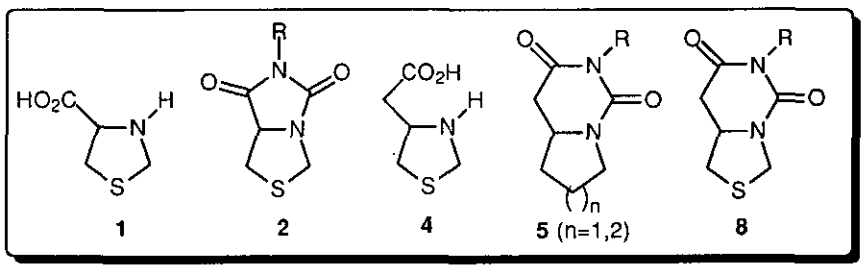
SYNTHESIS OF HOMOHYDANTOIN-THIAZOLIDINE BICYCLIC COMPOUNDS

Mostafa Hatam, Sabine Köpper, and Jürgen Martens*

Fachbereich Chemie, Universität Oldenburg, P. O. Box 2503, D-26111 Oldenburg, Germany

Abstract- Preparation of various homohydantoin-thiazolidine bicyclic compounds from 3-thiazolines is described. The reaction of C2-mono-substituted 3-thiazolines proceeds with considerable diastereoselectivity. The assignment for relative configuration of the prepared compounds was carried out unequivocally by nmr spectroscopical analysis.

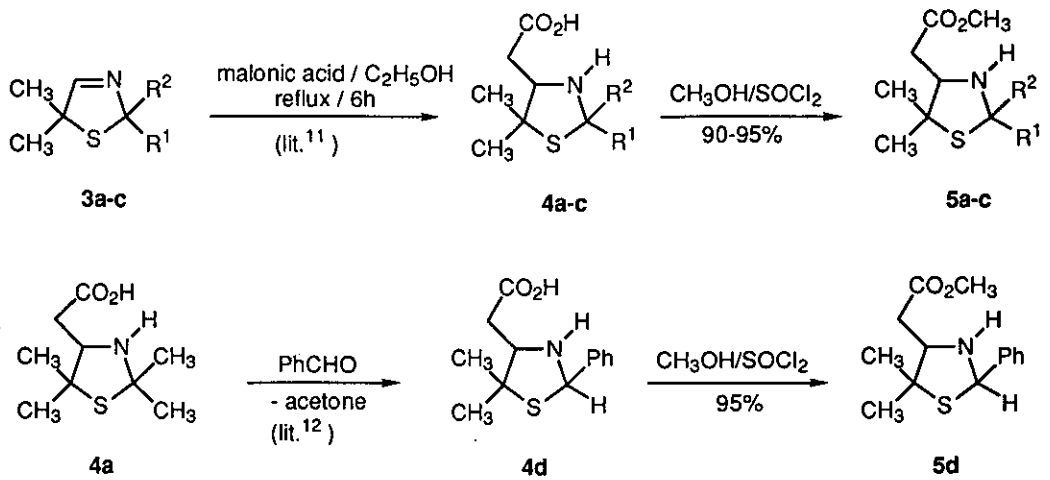
Sulfur containing cyclic α-amino acids like thiazolidine-4-carboxylic acid (**1**) and related compounds are of interest since they reveal many biologic activities as detoxicating agents in ethanol intoxication,[1] protection of mice against acetaminophene hepatoxicity,[2] antiallergic effects,[3] etc. Furthermore, they can be cyclocondensed with isocyantes to give hydantoin structures[4] like **2**, which in turn have interesting pharmaceutical properties[5] and are known to be useful backbone building blocks for hplc separation of enantiomers[6] (Scheme 1).



1 **2** **4** **5** (n=1,2) **8**

Scheme 1

On the other hand, thiazolidine-4-acetic acids (**4**) are direct precursors of β-lactams,[7] important as antibiotics and also used for peptide modifications.[8] With the best of our knowledge, synthesis of homohydantoin analogues, *i. e.* ***8***, *has not yet been reported, although their homocyclic analogues, i. e.* ***5*** have been prepared and in part revealed outstanding biological activities.[9] As a part of our previous studies on heterocyclic imines[10] and their derivatives we were interested in the synthesis of the homohydantoins (**8**).For this purpose, we should first prepare thiazolidine-4-acetic acids. The thiazolidine-4-acetic acids (**4a-c**) were synthesized by the reaction of 3-thiazolines (**3a-c**) with malonic acid in refluxing ethanol[11] whereas **4d** was obtained by transacetalization of **4a** with benzaldehyde[12] (Scheme 2).



3, 4, 5	R^1	R^2
a	CH_3	CH_3
b	—$(CH_2)_5$—	
c	H	isopropyl
d	H	phenyl

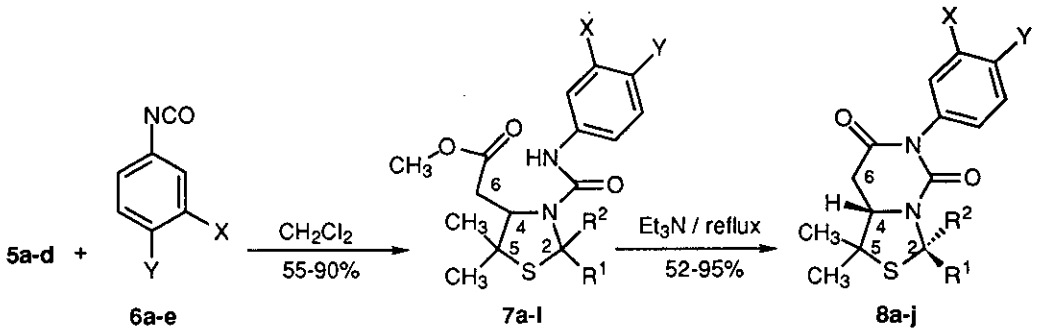
Scheme 2

Cyclization of β-amino acids with isocyanates has been carried out at different conditions , namely, in concentrated hydrochloric acid,[13] sodium hydroxide solution,[14] nonpolar hot solvents such as toluene,[15] ligroine[16] or in weak basic solvents like pyridine.[17] However, due to ring opening reactions in thiazolidines at both acidic and basic conditions or the predominant formation of self condensation products of isocyanates, these methods could not afford the desired products in satisfactory yields. In some cases, they suffered also from difficulties in separation and purification steps. Therefore, we tried to carry out the reaction under mild conditions. Thus, the β-amino acids (**4a-d**) were esterified quantitatively to their appropriate β-amino ester (**5a-d**) in the presence of thionyl chloride. The esterification of **4a** has been accomplished previously with concentrated hydrochloric acid, however, it suffered from the low yield of reaction[18] (Scheme 2).

The β-amino esters (**5a-d**) reacted with isocyanates (**6a-e**) in dry dichloromethane in an exothermic manner (in most cases the reaction temperatures increased ≤ 10°C) and the carbamoyl compounds (**7a-l**) were formed in 55-90% yields as colorless crystals (Scheme 3). Compounds (**7e,f**) and (**7j-l**) were completely identified, whereas the structure of the others was confirmed by derivatization to their homohydantoin analogues.

Efforts devoted to the cyclization of amidoesters (**7**) in dichloromethane at both ambient temperatures and refluxing conditions were unsuccessful and only the starting materials were recovered. However, heating of the amidoesters (**7a-j**) in triethylamine under reflux for 2 h resulted in the formation of the appropriate

homohydantoins (**8a-j**) as colorless crystals in 54-95% yields. Attempts to cyclize **7k-l** in both refluxing triethyl amine and *n*-C_4H_9Li were unsuccessful. Table 1 summarizes selected physical data of **8a-j**.



6	X	Y
a	H	H
b	Cl	H
c	H	Cl
d	Cl	Cl
e	CF_3	H

Scheme 3

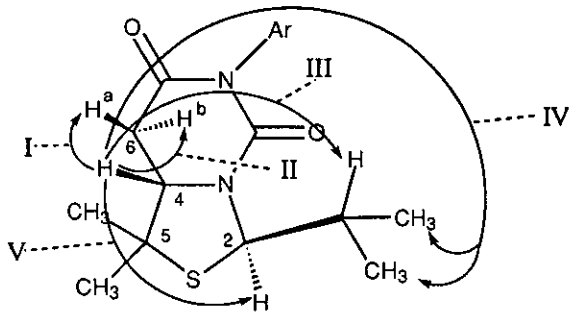
7,8	R^1	R^2	X	Y
a	CH_3	CH_3	Cl	H
b	CH_3	CH_3	H	Cl
c	CH_3	CH_3	CF_3	H
d	CH_3	CH_3	Cl	Cl
e	—$(CH_2)_5$—		CF_3	H
f	—$(CH_2)_5$—		H	Cl
g	H	isopropyl	Cl	H
h	H	isopropyl	H	Cl
i	H	isopropyl	CF_3	H
j	H	isopropyl	H	H
k	H	isopropyl	Cl	Cl
l	H	Ph	Cl	H

Table 1: Some selected data of **8a-j**

8	mp(°C)[a]	Yield[b]	dr[c]	Mass(100%)[d]
a	225	63	-	339
b	141	95	-	339
c	121	93	-	373
d	197	90	-	373
e	131	52	-	413
f	142	69	-	379
g	138	83	>95:5	353
h	146	89	>95:5	353
i	193	85	>95:5	387
j	134	~ 54	>95:5	319

[a] Uncorrected. [b] Based on **7**. [c] The diastereomeric ratio (dr) was detected based on the intensity of H-2 in the nmr spectra of the isolated products. [d] Cl, isobutane, *m/z* [MH^+].

Table 2: Selected NOE contacts of **8h,i** in % relative to the diagonal peak of H-2.



8h,i

	I	II	III	IV	V
8h	2.9	3.2	3.2	19.3	<1.0
8i	2.9	3.2	3.2	19.3	<0.6

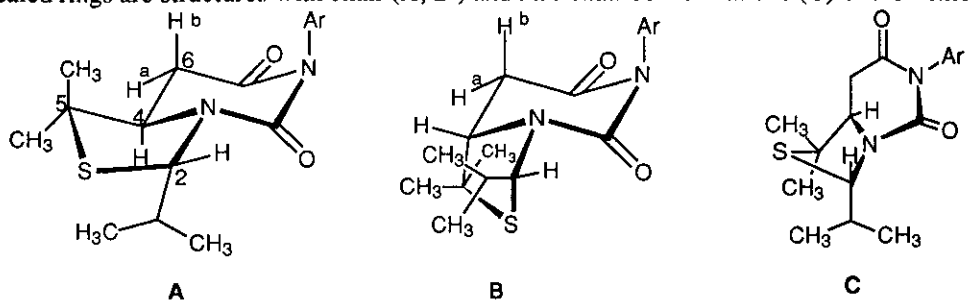
The absence of the methoxy signals in ^{1}H- and ^{13}C -nmr spectra as well as a change in the coupling constants of H-4 with both H-6 from acyclic compounds (**7**) to their cyclic analogues demonstrated that cyclization had taken place.

In the course of the synthesis of β-amino acids (**4a-d**) a chiral center is generated at position 4. Therefore two diastereomers are possible in **4c** and **4d**. The C2-asymmetric β-amino acid (**4c**) was formed in a *trans:cis* ratio[14] of about 1.9 whereas **4d**[15] in 1.5. Without stereochemical influence compounds (**8g-j**) should be obtained in similar diastereomeric ratios. However, the lack of duplication of nmr signals reflects the fact that only one diastereomer is formed in the course of reaction. This outcome is in agreement with preceeding observations of 1,3-induction in the course of reactions with 3-thiazolines having an asymmetric center at C2-position.[10]

Assignment of the relative configuration at positions 2 and 4 in the C2-monosubstituted homohydantoins (**8**) was possible by study the nmr spectroscopy of **8h** and **8i**. NOE spectra of these compounds showed only very small contacts between the two crucial protons H-4 and H-2. Due to their size, these contacts could not be taken as a conclusive indication for the configuration. Two-dimensional NOESY spectroscopy showed a number of additional contacts between various protons of the two rings. There was especially a strong contact between H-4 and the methyl protons of the isopropyl group in position 2 both in **8h** and **8i** (Table 2). The evaluation of this array of NOE contacts in comparison to possible configurations and conformations of the two annealed rings in the cyclic derivatives finally led to the assignment of the stereochemical configuration as well as the solution conformation of the bicyclic C2-monosubstituted homohydantoins (**8**).

Whereas the five membered rings of the hydantoins have nearly flat pentahedron structures as judged from X-ray crystallography,[19] the six membered structures of homohydantoins can adopt more puckered rings as

deduced from molecular models (applying SYBYL software). Possible stereochemical configurations of the two annealed rings are structures with chair (**A**, **B**) and half-chair conformations (**C**) of the homohydantoin



Scheme 4: Stereochemical configurations of homohydantoines (**8g-l**).

ring, in which the second ring can be annealed either *endo* or *exo* in position 4 (see **A** and **B** in scheme 4). Due to the existence of similar scalar coupling constants from proton H-4 to both methylene protons in position 6 ($J_{4,6a} = J_{4,6b} = 7.7$ and 7.8 Hz in **8h** and **8i** , resp.), chair conformations of the homohydantoin ring with a diaxial configuration of H-4 and H-6b (i. e. **A** in scheme 4) can be excluded. On the other hand, skew and half-chair arrangements in the homohydantoin ring force the thiazolidine ring to adopt conformations with C5 in *exo* position of the homohydantoin ring: either in a $_5$E- or a $_5T^S$ confor-mation. These conformations do not show short enough distances in either *cis* or *trans* isomers to produce strong NOE contacts from H-4 to C<u>H</u>Me$_2$ as well as to both the methyl protons of the isopropyl group.

All other observed NOE contacts are in agreement with a structure like **B**. Compounds (**8h**) and (**8i**) exhibit a *trans* configuration for the H-2 and H-4 protons and adopt solution conformations with a flattened $^4C_{N8}$-chair of the homohydantoin ring and twist or envelope conformations of the thiazolidine ring that hold position 2 in an *exo* orientation. With respect to the preferred *exo* orientation of the position 2, these results agree with the solution conformations that were deduced for five membered rings of hydantoins.[20]

The spiro and C2-dimethyl substituted compounds (**8**) were not studied by NOE spectroscopy, because they do not possess an asymmetric center at C2. Nevertheless, compounds (**8e,f**) do adopt a different solution conformation than **8h-i**. The coupling constants in **8a-f** strongly evidence *anti* and *gauche* orientations of H-4 to the protons at position 6 and therefore support chair like conformation **A** or the half chair and twist conformations of the homohydantoin ring.

EXPERIMENTAL

Melting points were determined in an open capillary tube on a Dr. Linström instrument and were uncorrected. The elemental analyses were carried out on a Carlo Erba (MOD 1104). The nmr spectra were recorded either on a Bruker AM300 or a ARX500 spectrometer at 300 and 500 MHz for ^{1}H and 121 MHz and 75 MHz, respectively, for ^{13}C. NOE measurements were performed at the ARX500 instrument in $CDCl_3$ as 2D NOESY spectroscopy applying standard Bruker software. Mixing times of 400 and 800 ms were used, the data given in table 2 correspond to a mixing time of 800 ms. Molecular Modeling was performed on Iris Indigo Silicon Graphics computers with the programme package SYBYL. Mass

spectroscopy was peformed on a Finnigan MAT 212 (data system SS 300) apparatus. The 3-thiazolines **3a-c** were prepared according to the literature.[13] The β-amino acids (**4a-c**) were prepared by refluxing an equimolar mixtures of the appropriate 3-thiazolines and malonic acid in ethanol[14] whereas **4d** was synthesized by transacetalization of **4a** with benzaldehyde.[15]

General procedure for the preparation of the β-aminoesters 5a-d(GP1):
The thiazolidines-4-carboxylic acids (**4a-d**) (20 mmol) were suspended in absolute methanol at 0°C. Thionyl chloride (3 ml, ca. 40 mmol) was dropwise added to the mixture, then left to stir at room temperature overnight and finally heated under reflux for 1 h. The solvent distilled off under reduced pressure and the residue of thionyl chloride was removed completely by three times addition of absolute methanol (30 ml) followed by distillation off at reduced pressure. The resulting oily materials were poured into a mixture of diethyl ether (50 ml) and saturated sodium bicarbonate (50 ml) and stirred for 5 min. The aqueous layer was extracted with diethyl ether (2×20 ml) and the recombined organic layers were dried ($MgSO_4$) and evaporated. The ester (**5b**) was crystalized rapidly on cooling to room temperature. The other esters were obtained as colorless oil. The esters were further utilizied without characterization. Yield: 90-95%.

The *N*-amidothiazolidine-4-carboxylic acid methyl esters (7a-l); General procedure (GP2): The methyl esters of thiazolidine-4-acetic acids (5 mmol) were dissolved under dry conditions in absolute dichloromethane (20 ml) at room temperature and a solution of the isocyanates (**6a-e**) (7 mmol) in dry dichloromethane (20 ml) was added in one portion with stirring. In almost all cases an exothermic reaction was observed sometimes up to 30°C. Stirring was continued overnight after which a solution of hydrochloric acid (2N, 30 ml) was added followed by stirring for another 15 min. The organic layer was seperated and the aqueous layer was washed with dichloromethane (3×30 ml). The recombined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The resulted oily materials were crystallized from ether (4 ml) and petroleum ether 40/60 (2 ml) at 4°C. The thiazolidine-*N*-amido-4-acetic acid methyl esters (**7e,f**) and (**7j-l**) were fully characterized whereas **7a-c** and **7g-h** were characterized by derivatization to the appropriate homohydantoin analogues.

[2,2-Dimethyl-4-(3-trifluoropmethylphenylcarbamoyl)-1-thia-4-azaspiro[4.5]dec-3-yl]acetic acid methyl ester (**7e**). mp: 78°C (from ether/petroleum ether). Yield: 55%. ^{1}H-Nmr($CDCl_3$/δ): 1.31, 1.64(2s, 6H, 2×CH_3); 1.23-1.80, 2.17, 2.59-2.66, 2.92, 3.16-3.78(m, 12 H, 6×CH_2); 3.77(s, 3H, CH_3O); 4.28(dd, $J_{4,6b}$ = 7.8 Hz, $J_{4,6a}$ = 2.8 Hz, 1H, H-4); 7.21-7.78(m, 5H, Ar-CH and NH) ppm. ^{13}C-Nmr($CDCl_3$/δ): 23.24, 32.67(2×CH_3); 21.51, 24.35, 25.29, 26.02, 35.36, 38.25, 39.16, 42.03(6× CH_2, C5, CF_3); 51.35(CH_3O); 68.89(C4); 80.66(C2); 116.06, 119.17, 122.46, 122.99, 129.30, 139.76 (Ar-C); 152.35, 172.75(2×C=O) ppm. Anal. Calcd for $C_{21}H_{27}N_2O_3F_3S$: C, 56.74; H, 6.13; N, 6.31. Found: C, 56.89; H, 6.21; N, 6.10. Ms (CI, Isobutane): *m/z* (%) = 445 (100)[MH^+].

[4-(4-Chlorophenylcarbamoyl)-2,2-dimethyl-1-thia-4-azaspiro[4.5]dec-3-yl]acetic acid methyl ester (**7f**): mp: 83°C (from ether/petroleum ether). Yield: 80%.^{1}H-Nmr($CDCl_3$/δ): 1.26, 1.62(2s, 6H, 2×CH_3); 0.84-1.89, 2.16, 2.56-2.63, 2.84(m, 10H, cyclohexyl-CH_2); 2.75-2.87, 3.14-3.22(2m, 2H, H_{6a}, H_{6b}); 4.27(s,

3H, OCH_3); 4.25(dd, $J_{4,6b}$ = 7.9 Hz, $J_{4,6a}$ = 2.5 Hz, 1H, H-4); 7.18-7.26, 7.39-7.42(m, 5H, Ar-CH and NH) ppm. ^{13}C-Nmr($CDCl_3$/δ): 23.22, 32.70(2×CH_3); 21.54, 24.39, 25.45, 26.03, 35.33, 38.26, 39.04, 49.03(6×CH_2 and C5); 52.57 (OCH_3); 68.80(C4); 80.57(C2); 121.08, 121.36, 127.90, 128.72, 128.99, 137.89(Ar-C); 152.39, 173.70 (2×C=O) ppm. Anal. Calcd for $C_{20}H_{27}N_2O_3ClS$(410.2): C, 58.52; H, 6.63; N, 6.83. Found: C, 58.28; H, 6.36; N, 7.01. MS(CI, Isobutane): *m/z* (%) = 411(100)[MH^+].

5,5-Dimethyl-2-isopropyl-3-phenylcarbamoylthiazolidine-4-acetic acid methyl ester[21] (**7j**). mp: 72°C (from ether/petroleum ether). Yield: 55% (diastereomeric ratio *dr* = 75:25). ^{1}H-Nmr($CDCl_3$ /δ): 0.90, 0.95[2d, ^3J = 6.7 Hz, 2×6H, 2×$CH(C\underline{H}_3)_2$]; 1.38, 1.42 and 1.41, 1.43(4s, 2×6H, 2×C5-CH_3); 1.94-1.99, 2.52-2.59[m, 2×1H, 2×$C\underline{H}(CH_3)_2$]; 2.71-2.83, 2.94-3.08(m, 2×2H, H_{6a}, H_{6b}); 3.75, 3.79(2×s, 2×3H, 2×OCH_3); 4.31, 4.34 (2m, 2×1H, 2×H-4); 5.34(d, ^3J = 8.6 Hz, 1H, H-2_{trans}); 5.54(d, ^3J = 6.7 Hz, 1H, H-2_{cis}); 6.94-7.45(m, 2×5H, Ar-CH), 8.65(NH) ppm. ^{13}C-Nmr($CDCl_3$/δ): 15.82, 16.42, 19.00, 19.49[2×$CH(\underline{C}H_3)_2$]; 20.05, 23.26, 24.88, 25.21(2×C5-$\underline{C}H_3$); 31.28, 31.65[2×$\underline{C}H(CH_3)_2$]; 36.63, 37.03(2×C5); 52.41, 53.05(2×C6); 54.44(OCH_3); 62.65(C4); 68.57, 69.05(2×C2); 118.84, 119.22, 122.16, 122.48, 128.45, 128.72, 129.04, 133.32, 139.46(2×Ar-C); 157.31, 167.50, 168.21, 174.76(2×C=O) ppm. Anal. Calcd for $C_{18}H_{26}N_2O_3S$: C, 61.68; H, 7.48; N, 8.00. Found: C, 61.49; H, 7.23; N, 7.87. Ms (CI, Isobutane): *m/z* (%) = 351(100)[MH^+].

3-(3,4-Dichlorophenylcarbamoyl)-5,5-dimethyl-2-isopropylthiazolidine-4-acetic acid methyl ester (**7k**): mp: 113°C (from ether/petroleum ether). Yield: 90% (diastereomeric ratio *dr* = 75: 25).^{1}H-Nmr($CDCl_3$/δ): 0.89, 0.94[2d, ^3J = 6.7 Hz, 2×6H, 2×$CH(C\underline{H}_3)_2$]; 1.34, 1.36 and 1.40, 1.44(4s, 2×6H, 2×C5-CH_3); 1.94, 2.54[m 2×1H, $C\underline{H}(CH_3)_2$]; 2.71-2.83, 2.94-3.08(m, 2×2H, H_{6a}, H_{6b}); 3.75(s, 3H, OCH_3); 4.31, 4.34 (m, 2×1H, 2×H-4); 5.32(d, ^3J = 6.3 Hz, 1H, H-2_{trans}); 5.50(d, ^3J = 8.4 Hz, 1H, H-2_{cis}); 6.99-7.66(m, 3H, Ar-H); 8.89(s, 1H, NH) ppm. ^{13}C-Nmr($CDCl_3$/δ): 16.39, 18.92, 19.52, 20.10 [2×$CH(\underline{C}H_3)_2$]; 23.32, 24.88, 25.24(2×C5-$\underline{C}H_3$); 31.27, 31.52[2×$\underline{C}H(CH_3)_2$]; 36.36, 37.00(2×C5); 52.70(C6); 52.91, 54.30(2×OCH_3); 62.69(C4); 68.48, 69.14 (2×C2); 118.49, 120.77, 125.37, 128.16, 130.16, 130.65, 130.83, 132.43, 132.93, 139.19(Ar-C); 155.43, 156.95, 167.34, 175.14(2×C=O) ppm. Anal. Calcd for $C_{18}H_{24}N_2O_3Cl_2S$: C, 51.66; H, 5.79; N, 6.70. Found: C, 51.43; H, 5.92; N, 6.49. Ms(CI, Isobutane): *m/z* (%) = 419(100)[MH^+].

3-(3-Chlorophenylcarbamoyl)-5,5-dimethyl-2-phenylthiazolidine-4-acetic acid methyl ester (**7l**): mp: 123°C (from ether/petroleum ether). Yield: 78% (diastereomeric ratio *dr* ≥95:5).^{1}H-Nmr ($CDCl_3$/δ): 1.40, 1.58(4s, 6H, C5-CH_3); 2.98, 3.08(2dd, $J_{6a,6b}$=16.8 Hz, $J_{4,6a}$ =3.8 Hz, $J_{4,6b}$ = 10.1 Hz, 2H, H_{6a}, H_{6b}); 3.78(s, 3H, OCH_3); 4.52 (dd, $J_{4,6b}$ = 10.1 Hz, $J_{4,6a}$ = 3.8 Hz, 1H, H-4); 6.59(s, 1H, H2); 6.96-7.52(m, 9H, Ar-CH); 8.43 (s, 1H, NH) ppm. ^{13}C-Nmr($CDCl_3$/δ): 22.98, 30.55(2×C5-CH_3); 37.66(C5); 52.55(C6), 55.14(OCH_3); 68.08(C4); 117.29(C2); 119.37, 122.73, 126.35, 128.11, 129.67, 134.45, 140.11, 140.52(Ar-C); 155.62, 174.47(2×C=O) ppm. Anal. Calcd for $C_{21}H_{23}N_2O_3ClS$: C, 60.27; H, 5.54; N, 6.70. Found: C, 60.12; H, 5.69; N, 6.83. Ms (CI, Isobutane): *m/z* (%) = 419(100)[MH^+].

General procedure for preparation of the homohydantoins 8a-j(GP2):
The carbamoyls (**7**) were dissolved in triethylamine(20 ml) and refluxed for 2 h after which the solvents were distilled off completely under reduced pressure. The reminded oils were crystallized from ether (5 ml) and petroleum ether 40/60 (1 ml).

(±)- 5-(3-Chlorophenyl)-1,1,3,3-tetramethyldihydro-2-thia-3a,5-diazaindene-4,6-dione (**8a**): mp: 205°C (from ether/petroleum ether). Yield: 63%. ^{1}H-Nmr ($CDCl_3$/δ): 1.40, 1.52(2s, 6H, C5-CH_3); 1.82, 1.96 (2s, 6H, C2-CH_3); 2.69, 2.78 (2dd, $J_{6a,6b}$ =15.8, $J_{4,6b}$ = 12.9, $J_{4,6a}$ = 4.6 Hz, 2H, H_{6a}, H_{6b}); 4.09 (dd, $J_{4,6b}$ =12.9 Hz, $J_{4,6a}$ =4.6 Hz, H-4); 7.06 -7.39(m, 4H, Ar-CH) ppm. ^{13}C-Nmr($CDCl_3$/δ): 25.69, 26.15 (C5-$\underline{C}H_3$); 29.12, 31.94(C2-$\underline{C}H_3$); 33.57 (C5); 50.04(C6); 65.04(C4); 72.64(C2); 127.20, 128.73, 129.30, 129.91, 134.54, 136.30(Ar-C); 150.82, 168.18 (2×C=O) ppm. Anal. Calcd for $C_{16}H_{19}N_2O_2ClS$: C, 56.79; H, 5.66; N, 8.28. Found: C, 56.55; H, 5.71; N, 8.07. Ms (CI, Isobutane): *m/z* (%) = 339(100)[MH^+].

(±)- 5-(4-Chlorophenyl)-1,1,3,3-tetramethyldihydro-2-thia-3a,5-diazaindene-4,6-dione (**8b**): mp: 141°C (from ether/petroleum ether). Yield: 95%. ^{1}H-Nmr($CDCl_3$/δ): 1.40, 1.51(2s, 6H, C5-CH_3); 1.80, 1.95(2s, 6H, C2-CH_3); 2.68, 2.79(2dd, $J_{6a,6b}$ = 15.8 Hz, $J_{4,6b}$ = 11.6 Hz, $J_{4,6a}$ =4.6 Hz, 2H, H_{6a}, H_{6b}); 4.09(dd, $J_{4,6b}$ =11.6 Hz, $J_{4,6a}$ = 4.6 Hz, H-4); 7.09-7.43(m, 4H, Ar-CH) ppm. ^{13}C-Nmr($CDCl_3$/δ): 25.64, 26.12(C5-$\underline{C}H_3$); 29.06, 31.90(C2-$\underline{C}H_3$); 33.52(C5); 52.79(C6); 64.94(C4); 72.57(C2); 129.28, 130.12, 133.65, 134.31(Ar-C); 150.87, 168.28 (2×C=O) ppm. Anal. Calcd for $C_{16}H_{19}N_2O_2ClS$: C, 56.79; H, 5.66; N, 8.28. Found: C, 56.93; H, 5.80; N, 8.11. Ms (CI, Isobutane): *m/z* (%) = 339(100)[MH^+].

1,1,3,3-Tetramethyl-6-(3-trifluoromethylphenyl)-dihydrothiazolo[3,4-a]pyridine-5,7-dione (**8c**): mp: 121°C (from ether/petroleum ether). Yield: 93%. ^{1}H-Nmr($CDCl_3$/δ): 1.41, 1.45(2s, 6H, C5-CH_3); 1.82, 1.95(2s , 6H, C2-CH_3); 2.68, 2.77(2xdd , $J_{6a,6b}$ = 15.8 Hz, $J_{4,6b}$ = 12.7 Hz, $J_{4,6a}$ =4.7 Hz, 2H, H_{6a}, H_{6b}); 4.10(dd, $J_{4,6b}$ = 12.7 Hz, $J_{4,6a}$ = 4.7 Hz, 1H, H-4); 7.27-7.67(m, 4H, Ar-H) ppm. ^{13}C-Nmr($CDCl_3$/δ): 25.68, 26.14(C5-CH_3); 29.12, 31.92(C2-CH_3); 33.55(C5); 52.86(C6); 65.01(C4); 72.65(C2); 121.74, 125.29, 126.11, 129.57, 131.74, 132.45, 135.72(Ar-C, CF_3); 150.74, 168.27(2×C=O) ppm. Anal. Calcd for $C_{17}H_{19}N_2O_2F_3S$: C, 54.82; H, 5.15; N, 7.53. Found: C, 54.71; H, 5.39; N, 7.44. Ms (CI, Isobutane): *m/z* (%) = 373(100)[MH^+].

1,1,3,3-Tetramethyl-6-(3,4-dichlorophenyl)-dihydrothiazolo[3,4-a]pyridine-5,7-dione (**8d**): mp: 197°C (from ether/petroleum ether). Yield: 90% .^{1}H-Nmr ($CDCl_3$/δ): 1.40, 1.51, 1.80, 1.95(4s, 12H, 4×CH_3); 2.69, 2.79(2xdd , $J_{6a,6b}$ = 15.9 Hz, $J_{4,6b}$ = 13.0 Hz, $J_{4,6a}$ =4.4 Hz, 2H, H_{6a}, H_{6b}); 4.10(dd, $J_{4,6b}$ = 13.0 Hz, $J_{4,6a}$ = 4.4 Hz, 1H, H-4); 7.01-7.53(m, 4H, Ar-H) ppm. ^{13}C-Nmr ($CDCl_3$/δ): 25.66, 26.15, 29.13, 31.90(4×CH_3); 33.51(C5); 52.91(C6); 64.99(C4); 72.66(C2); 128.41, 130.65, 131.05, 132.93, 134.41(Ar-C); 150.59, 168.17 (2×C=O) ppm. Anal. Calcd for $C_{16}H_{18}N_2O_2Cl_2S$: C, 51.61; H, 4.88; N, 7.53. Found: C, 51.75; H, 5.12; N, 7.36. Ms (CI, Isobutane): *m/z* (%) = 373(100)[MH^+], 374(20)[MH^++1], 375(80)[MH^++2].

The homohydantoin (**8e**): mp: 131°C (from ether/petroleum ether). Yield: 52% . ^{1}H-Nmr($CDCl_3$/δ): 1.40, 1.48(2s, 6H, 2×CH_3); 1.12-1.88, 2.67-2.93 (m, 12H, 6×CH_2); 4.12(dd, $J_{4,6b}$ = 12.4 Hz, $J_{4,6a}$ = 5.0 Hz,

1H, H-4); 7.26-7.66(m, 4H, Ar-CH) ppm. ^{13}C-Nmr($CDCl_3$/δ): 25.89, 26.37(2×CH_3); 24.38, 24.80, 25.32, 33.53, 36.43, 38.03, 49.40(6×CH_2 and C5); 64.94(C4); 80.32(C2); 121.78, 125.28, 126.11, 129.55, 132.47, 135.97(Ar-C); 150.92, 167.97(2×C=O) ppm. Anal. Calcd for $C_{20}H_{23}N_2O_2F_3S$: C, 58.23; H, 5.62; N, 7.76. Found: C, 58.18; H, 5.44; N, 7.85. Ms (CI, Isobutane): *m/z* (%) = 413(100)[MH^+].

The homohydantoin (**8f**): mp: 142°C (from ether/petroleum ether). Yield: 69%. ^{1}H-Nmr ($CDCl_3$/δ): 1.39, 1.47(2s, 6H, 2×CH_3); 1.10-1.86, 2.17, 2.65-2.93, 3.64 (m, 12H, 6×CH_2); 4.10(dd, $J_{4,6b}$ = 12.7 Hz, $J_{4,6a}$ = 4.8 Hz, 1H, H-4); 7.07-7.43(m, 4H , Ar-CH) ppm. ^{13}C-Nmr ($CDCl_3$/δ): 25.87, 26.37(2×CH_3); 21.54, 24.39, 25.32, 33.52, 35.33, 36.38, 38.02(6×CH_2 and C5); 64.90(C4); 80.28(C2); 121.18, 128.93, 129.32, 130.14, 133.88, 137.71(Ar-C); 151.08, 168.09(2×C=O) ppm. Anal. Calcd for $C_{19}H_{23}N_2O_2ClS$: C, 60.30; H, 6.13; N, 7.41. Found: C, 60.12; H, 6.23; N, 7.66. Ms (CI, Isobutane): *m/z* (%) = 379(100) [MH^+].

(±)- 5-(3-Chlorophenyl)-3-isopropyl-1,1-dimethyldihydro-2-thia-3a,5-diazaindene-4,6-dione (**8g**): mp: 138°C (from ether/petroleum ether). Yield: 83% (diastereomeric ratio *dr* ≥95:5). ^{1}H-Nmr($CDCl_3$/δ): 0.95[d, ^{3}J = 6.7 Hz, 6H, CH(C<u>H</u>$_3$)$_2$]; 1.37, 1.43(2s, 6H, C5-CH_3); 2.55[m, 1H, C<u>H</u>(CH_3)$_2$]; 2.75, 2.98(2xdd, $J_{6a,6b}$ =16.8 Hz, $J_{4,6a}$ = $J_{4,6b}$ =7.5 Hz, 2H, H_{6a}, H_{6b}); 3.81(dd, $J_{4,6b}$ = $J_{4,6a}$ = 7.5 Hz, H-4); 5.33(d, ^{3}J =6.7 Hz, H-2); 7.03-7.08, 7.15-7.17, 7.36-7.39(m, 4H, Ar-CH) ppm. ^{13}C-Nmr ($CDCl_3$/δ): 16.42, 19.52[CH(<u>C</u>H_3)$_2$]; 24.87, 25.23(C5-<u>C</u>H_3); 31.29(C5); 31.59[<u>C</u>H(CH_3)$_2$]; 52.98(C6); 62.65(C4); 69.08(C2); 126.96, 128.80, 129.05, 129.95, 134.51, 136.14(Ar-C); 151.46, 167.38(2×C=O) ppm. Anal. Calcd for $C_{17}H_{21}N_2O_2ClS$: C, 57.86 ; H, 6.01; N, 7.95. Found: C, 57.55; H, 6.14; N, 7.72. Ms (CI, Isobutane): *m/z* (%) = 353(100)[MH^+].

(±)- 5-(4-Chlorophenyl)-3-isopropyl-1,1-dimethyldihydro-2-thia-3a,5-diazaindene-4,6-dione (**8h**): mp: 146°C (from ether/petroleum ether). Yield: 89% (diastereomeric ratio *dr* ≥95:5). ^{1}H-Nmr ($CDCl_3$/δ): 0.95[d, ^{3}J = 6.7 Hz, 6H, CH(C<u>H</u>$_3$)$_2$]; 1.37, 1.43(2s, 6H, C5-CH_3); 2.55[m, ^{3}J =6.7 Hz, 1H, C<u>H</u>(CH_3)$_2$]; 2.75, 2.98(2xdd, $J_{6a,6b}$=16.8 Hz, $J_{4,6a}$ = $J_{4,6b}$=7.7 Hz, 2H, H_{6a}, H_{6b}); 3.82 (dd, $J_{4,6b}$ = $J_{4,6a}$ = 7.7 Hz, H-4); 5.33(d, ^{3}J = 6.40 Hz, H-2); 7.03-7.08, 7.15-7.17, 7.36-7.39(m, 4H, Ar-CH) ppm. ^{13}C-Nmr ($CDCl_3$/δ): 16.39, 19.51[CH(<u>C</u>H_3)$_2$]; 24.89, 25.24(C5-CH_3); 31.37(C5); 31.56[<u>C</u>H(CH_3)$_2$]; 52.96(C6); 62.72(C4); 69.13 (C2); 129.31, 129.93, 133.61, 134.38(Ar-C); 151.57, 167.45(2×C=O) ppm. Anal. Calcd for $C_{17}H_{21}N_2O_2ClS$: C, 57.86; H, 6.01; N, 7.95. Found: C, 57.62; H, 6.23; N, 7.80. Ms(CI, Isobutane): *m/z* (%) = 353(100)[MH^+].

3-Isopropyl-1,1-dimethyl-5-(3-trifluoromethylphenyl)dihydro-2-thia-3a,5-diazaindene-4,6-dione (**8i**): mp: 193°C (from ether/petroleum ether). Yield: 85% (diastereomeric ratio *dr* ≥95:5).^{1}H-Nmr ($CDCl_3$/δ): 0.95 [d, ^{3}J = 6.7 Hz, 6H, CH(C<u>H</u>$_3$)$_2$]; 1.38, 1.44(2s, 6H, C5-CH_3); 2.55[m, ^{3}J = 6.7 Hz, C<u>H</u>(CH_3)$_2$]; 2.77, 3.00(2xdd, $J_{6a,6b}$ = 16.8 Hz, $J_{4,6b}$ = $J_{4,6a}$ = 7.8 Hz, 2H, H_{6a}, H_{6b}); 3.84(dd , $J_{4,6b}$ = $J_{4,6a}$ = 7.8 Hz, 1H, H-4); 5.34(d, ^{3}J = 6.3 Hz, 1H, H-2); 7.26-7.66(m, 4H, Ar-CH) ppm. ^{13}C-Nmr($CDCl_3$/δ): 17.21, 20.32, 25.71, 26.073(4×CH_3); 32.19[<u>C</u>(CH_3)$_2$]; 32.41(C5); 53.11(C6); 63.55 (C4); 69.97(C2); 126.16, 126.72,

130.01, 136.43 (Ar-C); 152.23, 168.19(2×C=O) ppm. Anal. Calcd for $C_{18}H_{21}N_2O_2F_3S$: C, 55.94; H, 5.48; N, 7.25. Found: C, 56.10; H, 5.33; N, 7.49. Ms(CI, Isobutane): *m/z* (%) = 387(100)[MH^+].

3-Isopropyl-1,1-dimethyl-6-phenyldihydro-thiazolo[3,4-a]pyridine-5,7-dione (**8j**): mp: 134°C (from ether/petroleum ether). Yield: 54% (dr≥95:5). ^{1}H-Nmr($CDCl_3$/δ) : 0.95[d, ^3J = 6.8 Hz, 6H, $CH(C\underline{H}_3)_2$]; 1.39, 1.44(2s, 6H, C5-CH_3); 2.56 [m, 1H, $C\underline{H}(CH_3)_2$]; 2.77, 3.00(2xdd, $J_{6a,6b}$=16.8 Hz, $J_{4,6a}$ = $J_{4,6b}$ = 7.6 Hz, 2H, H_{6a}, H_{6b}); 3.81(dd, $J_{4,6b}$ = $J_{4,6a}$ = 7.6 Hz, 1H, H-4); 5.35(d, ^3J = 6.4 Hz, 1H, H-2); 7.12-7.16, 7.40-7.49(m, 4H, Ar-CH) ppm. ^{13}C-Nmr($CDCl_3$/δ): 16.41, 19.52[$CH(\underline{C}H_3)_2$]; 24.89, 25.24(C5-CH_3); 31.35 (C5); 31.59[$\underline{C}H(CH_3)_2$]; 53.02(C6); 62.67(C4); 69.08(C2); 128.45, 128.84, 129.10, 135.11(Ar-C); 151.87, 167.59(2×C=O) ppm. Anal. Calcd for $C_{17}H_{22}N_2O_2S$: C, 64.12; H, 6.97; N, 8.80. Found: C, 64.30; H, 7.11; N, 8.93. Ms (CI, Isobutane): *m/z* (%) = 319(100)[MH^+].

ACKNOWLEDGEMENT

This research was supported, in part, by the *Fonds der Chemischen Industrie, Deutsche Forschungsgemeinschaft* , *Degussa AG* and *Hans-Böckler-Stiftung*.

REFERENCES

1. H. T. Nagasawa and D. J. W. Goon, *J. Med. Chem.*, 1978, **21**, 1274; H. T. Nagasawa, D. J. W. Goon, R. T. Zera, and D. I. Yuzon *J. Med. Chem.*, 1984, **27**, 591.
2. H. T. Nagasawa, D. J. W. Goon, R. T. Zera, and D. I. Yuzon, *J. Med. Chem.*, 1982, **25**, 489.
3. M. Györgydeak, J. Kajtar, and M. Kaitar, *Liebigs Ann. Chem.* , 1987, 927.
4. B. Refouvelet, J. F. Robert, J. Couquelet, and P. Tronche, *J. Heterocycl. Chem.*, 1994, **31**, 77; T. A. Crabb, M. J. Hall, and R. O. Williams, *Tetrahedron* , 1973, **29**, 3389.
5. Analgesic activity: M. H. Papon, B. Refouvelet, P. Bastide, J. Bastide, P. Troche, and A. M. Privat, *Eur. J. Med. Chem. Chim. Ther.*, 1986, **21**, 355; Immunomodulatory agents: B. Refouvelet, S. Harraga, L. Nicod, J. F. Robert, E. Seilles, J. Couquelet, and P. Tronche, *Chem. Pharm. Bull.* 1994, **42**, 1076; PAF-receptor antagonist: S. K. Davidsen, J. B. Summers, R. G. Conway, D. A. Rhein, and G. W. Carter, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 2729; Antibacterial activity: S. H. Cho, Y. J. Shin, and S. H. An, *Korean J. Med. Chem.*, 1993, **3** , 162.
6. Y. Saotome, T. Miyazawa, and T. Endo, *J. Polym. Sci., Part C: Polym. Lett.*, 1989, **27**, 507; Y. Saotome, T. Miyazawa, and T. Endo, Japan Patent: JP 87-115485 [*Chem. Abstr.*, 1989, **111**, 97923].
7. D. J. Hart, and D. C. Ha, *Chem. Rev.*, 1989, **89**, 1447; S. Kobayashi, T. Imori, T. Izawa, and M. Ohno, *J. Am. Chem. Soc.*, 1981, **103**, 2405.
8. Drey, C. N. C. '*Chemistry and Biochemistry of Amino Acids*' ed. by G. C. Barret, Chapman and Hall, London, 1985, 25.

9. Cytotoxic antineoplastic activities: K. Ogawva, I. Yamawaki, Y. I. Matsushita, N. Nomura, P. F. Kador, and J. H. Kinoshita, *Eur. J. Med. Chem. Chim. Ther.*, 1993, **28**, 769; Antimontagenic effects on biochemical strains of *Eschericha coli* : M. A. Kaldrikyan, V. A. Geboyan, and G. M.Stepanyon, *Pharm. Chem J.(Engl. Transl.)* , 1983, **17**, 727; Effects on spontaneous locomotor activity, antagonistic effects on resperine, induced hypothermia and pentobarbital anesthesia: M. Suzuki, H. Sugano, K. Matsumoto, M. Yamamura, and R. Ishida, *J. Med. Chem.*, 1990, **33**, 2130; Cytotoxic activity against the mouse L1210 leukemia cells, antineoplastic activity against P 388 cells: I. Antonini, D. Cola, S. Martelli, W. M. Cholody, and J. Konopa, *Farmco*, 1992, **47**, 1035.
10. M. Hatam and J. Martens, *Synth. Commun.*, 1995, **25**, 2553; H. Gröger, M. Hatam, and J. Martens, *Tetraherdron* , 1995, **51**, 7173; M. Hatam, D. Tehranfar and J. Martens, *Synth. Commun.*, 1995, **25**, 1677; M. Hatam, D. Tehranfar, and J. Martens, *Synthesis* , 1994, 619.
11. J. Martens, J. Kintscher, and W. Arnold, *Synthesis* , 1991, 497.
12. J. Martens, J. Kintscher, and W. Arnold, *Tetrahedron* , 1991, **47**, 7029.
13. M. D. Armstrong, *J. Am. Chem. Soc.*, 1955, **77**, 6049.
14. I. Lalezari, S. Seifter, and A. Thein, *J. Heterocycl. Chem.*, 1983, **20**, 483.
15. E. M. Jensen and E. P. Papadopoulos, *Heterocycles* , 1983, **20**, 2233.
16. G. W. Stacy, P. A. Craig, and R. I. Day, *J. Org. Chem.*, 1958, **23**, 1760.
17. S. Lieberman P. Brazeau, and B. Hariton, *J. Am. Chem. Soc.*, 1948, **70**, 3094.
18. W. Arnold, *Ph. D. Thesis*, University of Oldenburg, Oldenburg, Germany, 1992.
19. E. Arte, B. Tinant, J. P. Declerca, G. Germain, and M. van Meerssche, *Bull. Soc. Chim. Belg.*, 1980, **89**, 117; *ibid.*, 1980, **89**, 379.
20. F. M. Borremans, M. Budesinsky, R. E. A. Callens, and M. J. O. Anteunis, *Org. Magn. Reson.*, 1983, **21**, 328.
21. According to "*the low- and high field rules* " applied for determination of the relative configuration in C2-monosubstituted thiazolidine-4-acetic acids: δC4-H*(cis)* < δC4-H*(trans)* and δC2-H*(cis)* > δC2-H*(trans)* ; δC2*(cis)* > δC4*(trans)* ; I. McMillan and R. I. Stoodley, *Chem. Comm.*, 1968, 11; Z. Györgydeak, J. Kajtat, M. Kajtar, and M. Kajtar-Peredy, *Liebigs Ann. Chem.*, 1990, 281; D. Barby, G. Ricart, and D. Couturier, *J. Chem. Soc., Perkin Trans. 2* , 1990, 133; Ref.12 .

Received, 22nd March, 1996