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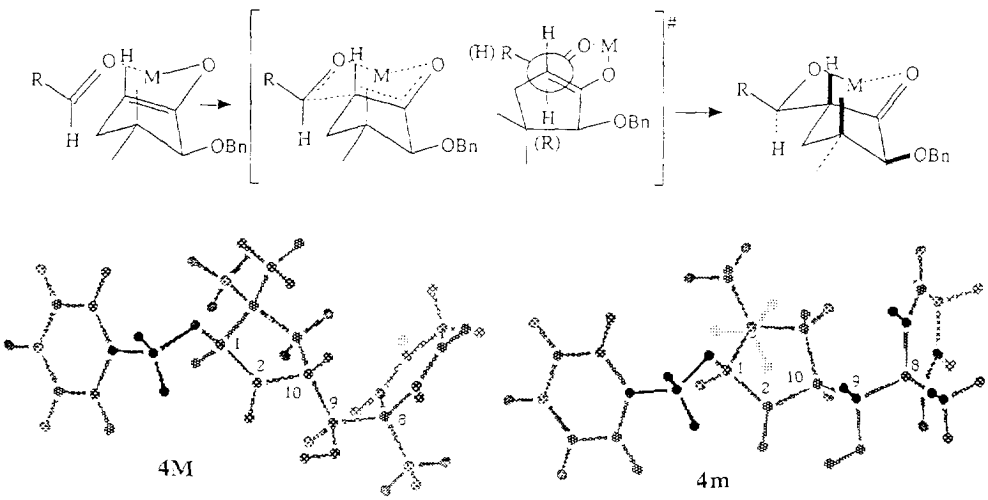
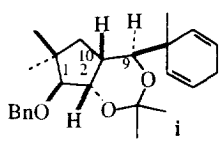


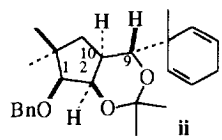
21. As the only use of of the magnitude of vicinal coupling constants is subject to care, the stereochemistry of aldols **4M** and **4m** was ascertained by conversion to the acetonides **i** (from **4M**) and **ii, iii** from **4m**, using literature conditions, as follows: To a solution of 60 mg (0.176 mmol) of **4M** in a mixture of ethanol (0.5 mL) and dichloromethane (3.0 mL) was added 34 mg (0.91 mmol) of sodium borohydride. The mixture was stirred at room temperature for 1 h, diluted with water, and extracted with dichloromethane. The combined extracts were washed with 1 M hydrochloric acid, saturated sodium bicarbonate, and worked up as usual. The resulting diol was disolved in acetone (2.0 mL) and 2,2-dimethoxypropane (0.5 mL) and 5 mg of TsOH was added. The mixture was stirred at room temperature for 10 min, filtered through aluminum oxide with ethyl acetate, and concentrated under reduced pressure to give 57 mg (79%) of **i: ^{1}H-NMR:** 1.00 (3H, s), 1.03 (3H, s), 1.05 (3H, s), 1.42 and 1.44 (6 H, s, Me-acetonide), 0.90 - 1.50 (2 H, m, H-11), 2.06 (1 H, m, H-10), 2.58 (2 H, m, H-5), 3.37 (1 H, d, J = 10.3, H-9), 3.38 (1 H, d, J = 3.9, H-1), 3.59 (1 H, dd, J = 3.9, 11.5, H-2), 4.52 and 4.92 (ABq, J= 12.5, OCH_2Ph), 5.35 - 5.75 (4 H, m, H-3,4,6,7), 7.15 - 7.45 (5 H, m, Ph). **CIMS:** *m /z* 383 (M+H, 5), 325 (M+H-Me_2CO, 94), 307 (61), 217 (20), 201 (21), 57 (100). Starting from the minor aldol **4m** and proceeding as described above the corresponding acetonides **ii** and **iii** (in nearly 1:1 ratio) were obtained. **ii: ^{1}H-NMR** (C_6D_6)**:** 1.08 (3H, s, Me-15α); 1.28 (3H, s, Me-15β); 1.33 (3H, s, Me-8); 1.42 (3H, s, Me); 1.66 (3H, s, Me);

1.25 (1H, m, H-11β); 1.61 (1H, dd, J= 6.7, 12.7, H-11α); 1.78 (1H, m, H-10); 2.55 (2H, m, 2 H-5); 3.43 (1H, d, J= 9.9, H-9); 3.58 (1H, d, J= 8.4, H-1); 3.82 (1H, dd, J= 8.4, 11.0 H-2); 4.79 and 4.99 (2H, ABq, J gem= 12.4, $PhCH_2O$); 5.45-6.05 (4H, m, H-3, 4, 6, 7); 7.15-7.30 (5H, m). **iii : ^{1}H-NMR:** 0.93 (3H, s, Me-15α); 1.10 (3H, s, Me); 1.19 (3H, s, Me-15β); 1.35 (3H, s, Me-8); 1.38 (3H, s, Me); 1.41 (2H, m, 2 H-11); 2.11 (1H, m, H-10); 2.57 (2H, m, 2 H-5); 3.23 (1H, d, J= 9.1, H-9); 3.28 (1H, d, J= 4.9, H-1); 4.05 (1H, dd, J= 4.9, 5.8, H-2); 4.50 and 4.73 (2H, ABq, J= 12.7, $PhCH_2O$); 5.30-5.80 (4H, m, H-3, 4, 6, 7); 7.25-7.40 (5H, m). **CIMS:** 383 [$(M+H)^+$, 5), 325 [$(M+H-CH_3COCH_3)+$, 94], 307 (61), 217 (20), 201 (21).

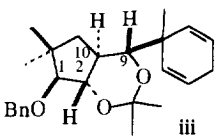
The structures of **i, ii, iii** were established by diagnostic n.O.e. experiments as depicted below:



i



ii



iii

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25. The desired enone **5** initially obtained in 67% yield was accompanied with its corresponding allylic alcohol which was reoxidized with PDC in dichloromethane to give an additional 8% recovery of **5**.

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Synthesis and Characterization of Thiourea Derivatives of α-Aminoacids. Crystal Structure of Methyl L-valinate and L-leucinate Derivatives.

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Abstract.- The synthesis of methyl 2-[(3,3-diethylthioureido)phenylmethylamino]-3-methylbutyrate and -4-methylpentenoate **3** have been achieved from 3-(chlorophenylmethylene)-1,1-diethylthiourea and the methyl esters of L-valine and L-leucine. From the latter, a *bis*-derivative **4** was also obtained as minor reaction product. Other compounds with morpholine residues and the glycine derivatives **5** have also been prepared. The X-ray diffraction showed an extended conformation for these compounds. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

The study of N-benzoyl-N'-alkylthioureides has attracted the attention of several research groups, due to their high interest as selective ligands for the concentration and separation of metal cations of Pt group.[1] The introduction of residues derived from α-aminoacids in this kind of compounds can produce an increase in their selectivities towards these cations and can make feasible their recognition by living organisms, because they incorporate essential aminoacids.[2,3] A specific use of these substances is the coordination of harmful compounds, that can be achieved in the organism by one or several ligands of adequate structure. This aspect is of importance and more attention had to be dedicated to the design and synthesis of new agents, able to coordinate these toxic metal ions to produce complexes that can be easy to eliminate.[4,5]

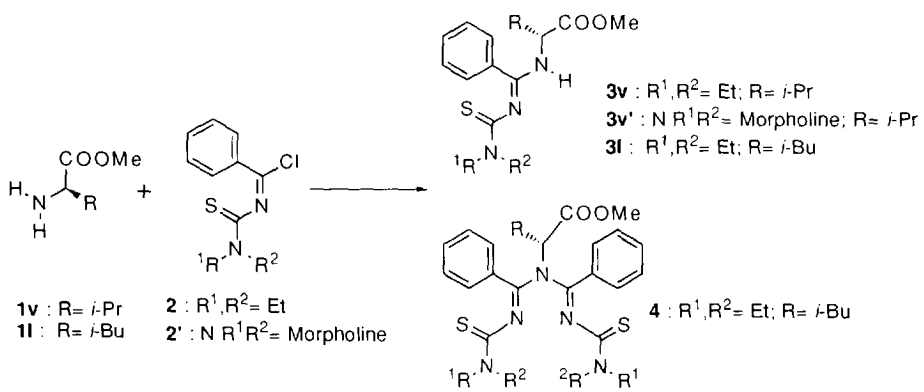
The reactivity and toxicity of a metal complex mainly depends on the structure of the ligands. These new ligands could compete with essential complexes producing metallic deficiency, that would produce adverse side effects more important than the therapeutic benefit. By these reasons it is necessary to choose carefully the substituents for these interesting ligands.[6,7]

With these aims in mind, we have prepared compounds type **3**, whose structure varies in the nature of R, depending on the structure of the starting α-aminoacid methyl ester (valine, leucine). The aminoacid derived residue of these thioureides introduces an ester group, that can modify the chelating capability of metallic cations and the hydrophobic/hydrophilic character of the ligand and the complex. Other

functional groups on the R residue: amino, carboxylate, hydroxy, sulfide, etc...., and latter modifications of their structures could also affect the properties of these ligands and increase the interest of their therapeutic applications.

RESULTS AND DISCUSSION

Following the methodology previously described for the synthesis of aminothiocarbonylbenzamidines[1], we have used methyl esters of α-aminoacids (**1**) in order to prepare derivatives containing this moiety. Thus, 3-(chlorophenylmethylene)-1,1-diethylthiourea (**2**) was treated with methyl esters of L-valine (**1v**) and L-leucine (**1l**), and morpholine-4-carbothioic acid chloro-phenyl-methyleneamide (**2'**) with **1v**, in the presence of triethylamine (Scheme 1). By this methodology, crystalline products **3** were directly obtained from the reaction mixtures and characterized by spectroscopic methods. From the reaction between methyl leucinate (**1l**) and **2**, the *bis*-derivative **4** crystallized previously to the appearance of the expected product type **3**. The main difference between compounds **3** and **4**, is the presence of N-H bond absorptions in the IR of **3**, which are not present in that of the *bis*-derivative **4**. The *bis*-derivative **4** was characterized in the MS by the M^++1 at 582 m/z, and other spectroscopic data. In the ^{1}H-NMR spectra the major difference corresponds to the α-proton, which appears at 4.23 (d) ppm in compound **3v** and 4.42 (dd) ppm in **3l**, while in derivative **4** it is shifted to 5.71 (dd) ppm due to the stronger electron withdrawing effect of two benzimido groups. Some differences are also observed in the ^{13}C-NMR spectra, showing the α-carbon at 62.0 ppm in **3v**, at 54.9 ppm in **3l** and 60.9 ppm in **4**.



Scheme.1. Synthesis of compounds **3** and **4**, thiourea derivatives of α-aminoacids methyl esters.

Compound **4** is formed by the reaction of the initial product **3l** with a second molecule of the reagent **2**, which is present in a 5:1 excess. The appearance of *bis*-derivative **4** in only one of the studied reactions is not easy to explain, because there is not enough difference between reagents **1v** and **1l** or their reaction products **3v** (**3v'**) and **3l**. Probably, *bis*-derivatives are also produced in the reaction of other aminoacid methyl esters, but they are not isolated by the crystallization methodology employed. Slight differences in their solubility and yield can avoid the crystallization of the *bis*-derivatives type **4** in other cases.

The X-ray structure determinations were carried out on the valine derivatives **3v**, **3v'** and leucine derivatives **3l** and **4**. The molecular structures (Figure 1: (a) **3v**; (b) **3v'**; (c) **3l** and (d) **4**) allowed us to have a better knowledge of the structural features of these interesting ligands. Selected bond lengths, angles and torsion angles are given in Table 1. Compounds **3** have the enamine form, with no hydrogen atom bonded to the nitrogen atom N1. In these compounds there are no intramolecular interactions, that can be responsible for the conformational disposition, so it must derive from the higher overlap along the N-C(Ph)=NH-C(S)-NR_2 fragment. In fact, the C2-N1 bonds (1.295; 1.304; 1.293 Å) are double bonds, whereas the C1-N1 (1.379; 1.378; 1.371 Å) are clearly shortened in comparison with a C-N single bond. Partial double bond character can be observed for the bonds C1-N2 to the diethylamino and morpholino groups (1.326; 1.330; 1.326 Å) too. The lengths of bonds C1-S1 (1.700; 1.689; 1.680 Å) are between the values for C-S single and double bonds. The bonds C2-N3 (1.343; 1.342; 1.351 Å) which are formally single bonds are remarkably shortened.

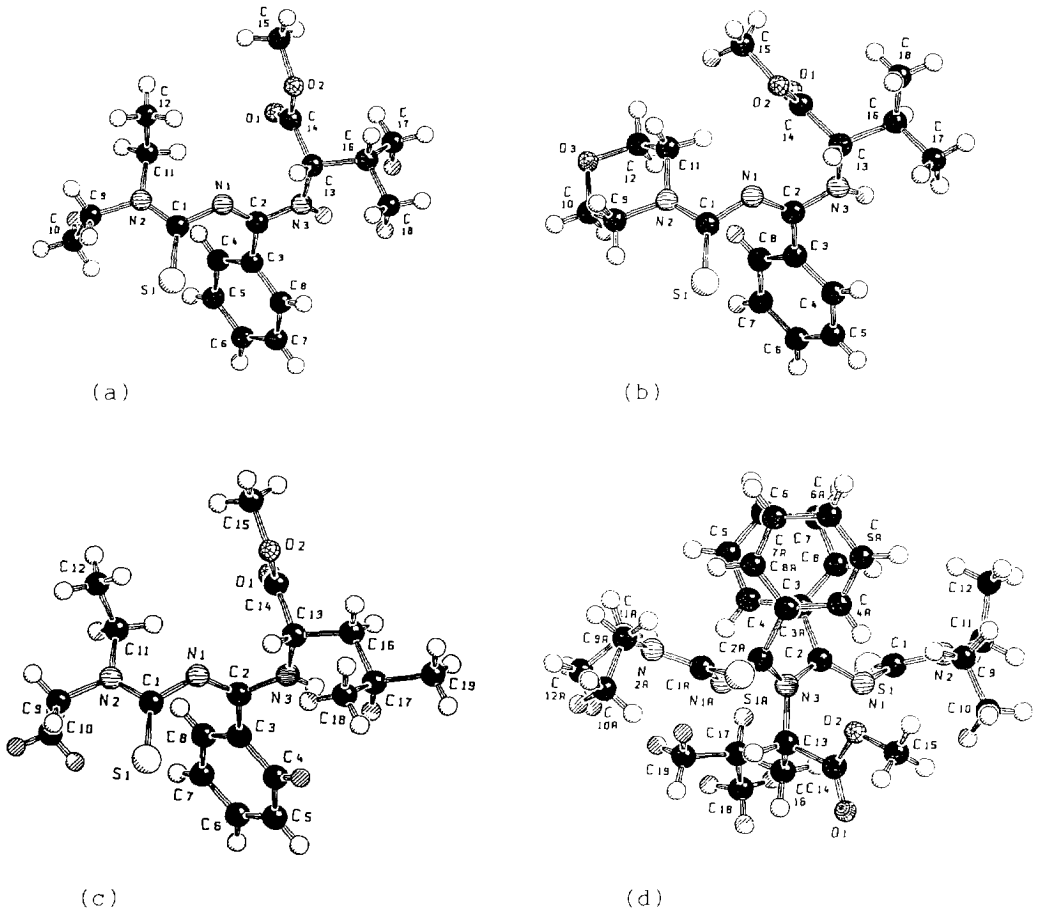
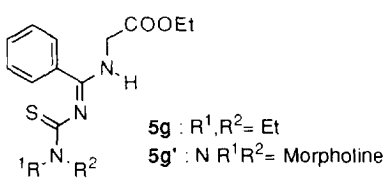


Figure 1. X-ray structure of compounds **3v** (a); **3v'** (b); **3l** (c) and **4** (d)

The benzimidoyl thiourea moiety is nearest to a Z,E' disposition (ω(S1-C1-N1-C2)= 63.0° and 61.7°;68.8°; ω(N3-C2-N1-C1)= -170.1°,-170.0° and-164.4°, respectively). This disposition is in accordance with the comparable N,N-diethyl-N'-(N"-phenylbenzimidoyl)thiourea,[8] without the formation of intramolecular N-H···S bond that would produce steric hindrances between the phenyl and the N-3 substituent. The intramolecular H-bond is found for the unhindered N,N-diethyl-benzimidoyl-thiourea.[9] In the crystal structures the molecules are connected by intermolecular NH···S hydrogen bonds (**3v** N3···S1' 3.53Å, H3···S1' 2.75Å; N3-H3···S1' 152°; **3v'** N3···S1' 3.51Å, H3···S1' 2.67Å, N3-H3···S1'165°; **3l** N3···S1' 3.41Å, H3···S1' 2.63Å; N3-H3···S1' 152°). There is also another short intermolecular contact in **3v** (H111···S1' 2.78Å).

In the *bis*-derivative **4**, as in the former cases, the disposition of both benzimidoyl thiourea moieties are also nearest to Z,E'. The torsion angles (ω(S1-C1-N1-C2)= -68.6° and -66.8°; ω(N3-C2-N1-C1=170.2° and 164.1°) have almost identical absolute values, have opposite sign in comparison with the monosubstituted derivatives **3**. No H-bond is possible in the *bis*-derivative **4**, but in this case the extended conformation is also favoured by the presence of two benzene rings, which are maintained spatially close and nearly parallel (dihedral angle 28°) by the stabilizing effect of π-stacking interactions.

This procedure was also employed to prepare the most simple analog of the series: **5g** and **5g'**. They are the diethylamino and the morpholino derivatives obtained from ethyl glycinate. The major difference with the other compound is the absence of substituent in the α-carbon atom.



5g : R^1,R^2= Et
5g' : N R^1R^2= Morpholine

These results confirm the utility of this methodology for the synthesis of thioureido derivatives of aminoacids for the complexation of metallic cations. The presence of an additional carboxylic group in this kind of chelating agents, in comparison with other ligands previously obtained, introduces a new point of attachment to the metal cation. This possibility and the chirality introduced by the aminoacid residue, are new interesting modifications for the use of these ligands as complexant of metal cation of biological and pharmaceutical relevance.

EXPERIMENTAL

Equipment and reagents. The aminoacids (methyl or ethyl ester hydrochlorides) and triethylamine were obtained from Aldrich. C, H and N analyses were performed using a Perkin-Elmer 2400 elemental analyzer. Fourier transform infra-red (FT-IR) spectra were recorded using KBr pellets on a Perkin-Elmer M1700 apparatus. The electronic spectra were recorded on a Varian-Techtron spectrophotometer, Model 635. NMR measurements (^{1}H: 200.13 MHz, ^{13}C: 50.3 MHz) were performed on a Bruker WP 200SY instrument. Electron impact (EI) mass spectra were recorded with a VG TS250 spectrometer; positive-ion fast atom bombardment (FAB+) mass spectra were recorded on a VG AutoSpec spectrometer with 3-nitrobenzylalcohol (m-NBA), as the matrix solvent.

Synthetic methodology. The synthesis was achieved by reaction between chloroderivatives (**2**: 3-(chlorophenylmethylene)1,1-diethylthiourea or **2'**: morpholine-4-carbothioic acid chlorophenylmethyleneamide) and the hydrochloride of aminoacid methyl or ethyl ester (**1**). Triethylamine (4 mmol) was added to a solution of **2** (10 mmol) in acetone (20 mL), followed by the addition of a solution of **1** (2 mmol) in EtOH (30 mL). The mixture was refluxed for one hour and cooled to 5°C. Crystals of $Et_3N{\cdot}HCl$ were filtered and the filtrate allowed to stand in a dessicator until the appearance of white crystals of derivatives **3**. From the reaction of **2** and **1l** yellow crystals of the *bis*-derivative **4** appeared previous to the crystallization of **3l**. All the compounds so obtained were recrystallized in EtOH.

2{[(3,3-Diethylthioureido)phenylmethyl]amino}-3-methylbutyric acid methyl ester (3v). Yield 72%. Mp: 123°C. FT-IR υ: 3246, 1748, 1622, 1601, 1530, 1497 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.94 (3H,d,J=6.8Hz), 1.00 (3H,d,J=6.8Hz), 1.06 (3H,t,J=7.2Hz), 1.10 (3H,t,J=7.2Hz), 2.09 (1H,m), 3.52 (2H,m), 3.63 (3H,s), 3.82 (2H,m), 4.23 (1H,d,J=7.2), 7.29 (5H,m) ppm. ^{13}C-NMR (CD_3OD) δ: 12.3(q), 13.3(q), 19.7(q), 19.7(q), 31.6(d), 45.6 (t), 47.3(t), 52.4(q), 62.3(d), 129.2(d), 129.2 (d), 129.3(d), 129.3(d), 131.5(d), 135.0(s), 160.2(s), 174.3(s), 190.4(s) ppm. EA: Calc.for $C_{18}H_{27}N_3O_2S$: C%, 61.86; H%, 7.79; N%, 12.02. Obs.: C%, 61.3; H%, 7.8; N%, 11.8. MS-FAB$^+$(m/z): 350 [M+1], 317 [M^+-MeOH]. MS-EI: 349 [M^+].

Table 1. Selected bond lengths, angles and torsion angles.

	3v	3v'	3l	4
Bond lengths (Å)				
S1-C1	1.700(3)	1.689(3)	1.680(7)	1.722(12);1.676(12)
O1-C14	1.186(4)	1.192(4)	1.178(7)	1.177(12)
O2-C14	1.327(4)	1.323(5)	1.337(8)	1.310(12)
O2-C15	1.443(5)	1.452(5)	1.438(6)	1.429(9)
N1-C1	1.379(4)	1.378(4)	1.371(8)	1.357(13);1.366(12)
N1-C2	1.295(4)	1.304(4)	1.293(8)	1.289(11);1.250(12)
N2-C1	1.326(4)	1.330(4)	1.326(7)	1.292(12);1.330(12)
N3-C2	1.343(4)	1.342(3)	1.351(7)	1.399(11);1.413(11)
N3-C13	1.446(4)	1.461(4)	1.433(6)	1.457(12)
C2-C3	1.486(5)	1.489(4)	1.494(8)	1.525(14);1.513(13)
Angles (°)				
C1-N1-C2	122.5(3)	122.5(3)	120.4(7)	122.8(10);124.5(10)
C2-N3-C13	122.1(3)	121.0(2)	120.3(6)	118.3(10);1173(9)
C14-O2-C15	116.9(3)	117.2(3)	114.7(6)	114.6(9)
S1-C1-N1	121.3(3)	122.1(2)	119.7(6)	119.3(9);119.3(9)
S1-C1-N2	123.9(3)	122.8(2)	123.9(6)	122.1(11);124.5(10)
N1-C1-N2	114.6(3)	114.8(3)	115.9(7)	117.9(12);116.1(11)
N1-C2-N3	119.7(3)	118.5(3)	120.4(7)	118.4(11);118.9(11)
N1-C2-C3	125.0(3)	125.0(2)	126.3(7)	125.1(10);126.0(11)
N3-C2-C3	115.3(3)	116.4(2)	113.4(7)	116.4(11);114.8(10)
O1-C14-O2	124.3(3)	124.3(3)	125.1(7)	126.9(12)
C2-N3-C2A	---	---	---	123.4(11)
Torsion Angles (°)				
S1-C1-N1-C2	63.0(4)	61.7(4)	68.8(9)	-68.6(13);-66.8(15)
N3-C2-N1-C1	-170.1(3)	-170.0(3)	-164.4(6)	170.2(10);164.1(9)
C1-N1-C2-C3	11.1(5)	13.4(5)	17.4(12)	-6.3(16);-9.1(18)

2{[(3,3-Diethylthioureido)phenylmethyl]amino}-4-methylpentanoic acid methyl ester (3l). Yield 68%. Mp: 96°C. FT-IR υ: 3203, 1752, 1613, 1600, 1531, 1499 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.98 (3H,d,J=7.5Hz), 0.98 (3H,d,J=7.5Hz), 1.06 (3H,t,J=7.0Hz), 1.11 (3H,t,J=7.0Hz), 1.6-1.8 (3H,m), 3.6-3.9 (4H,m), 3.65 (3H,s), 4.42 (1H,dd,J=12.0, 4.9), 7.25 (5H,m) ppm. ^{13}C-NMR (CD_3OD) δ: 12.3(q), 13.3(q), 22.2(q), 23.2(q), 26.3(d), 41.5(t), 45.8 (t), 47.3(t), 52.6(q), 54.9(d), 129.2(d), 129.2 (d), 129.2(d), 129.2(d), 131.4(d), 135.0(s), 160.2(s), 175.2(s), 190.5(s) ppm. EA: Calc.for $C_{19}H_{29}N_3O_2S$: C%, 62.78; H%, 8.04; N%, 11.56. Obs.: C%, 62.8; H%, 8.1; N%, 11.8. MS-FAB+(m/z): 364 [M+1], 332 [M^+-MeOH].

2-{*bis*-[(3,3-Diethylthioureido)phenylmethyl]amino}-4-methylpentanoic acid methyl ester (4). Yield 28%. Mp: 170°C. FT-IR υ: 1731, 1597, 1496 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H,d,J=6.8Hz), 1.14 (3H,d,J=6.8Hz), 1.20 (2x3H,t,J=7.2Hz), 1.26 (2x3H,t,J=7.2Hz), 1.6-1.9 (3H,m), 3.6-3.9 (8H,m), 3.85 (3H,s), 5.71 (1H,dd,J=12.0, 5.0), 7.05 2x(5H,m) ppm. ^{13}C-NMR ($CDCl_3$) δ: 11.9x2(q), 13.4x2(q), 21.6(q), 23.4(q), 25.4(d), 37.7(t), 44.7x2(t), 45.8x2(t), 52.3(q), 60.9(d), 127.9x4(d), 128.0x4(d), 129.9x2(d), 135.2x2(s), 157.1x2(s), 171.7(s), 188.2x2(s) ppm. Calc. for $C_{31}H_{43}N_5O_2S_2$: C%, 63.99; H%, 7.45; N%, 12.03. Obs.: C%, 63.7; H%, 7.6; N%, 12.0. MS-FAB+(m/z): 582 [M^++1], 363 [M^+-$C_{12}H_{15}N_2S$=**3l**]. MS-EI: 581 [M^+].

3-Methyl-2-{[(morpholine-4-carbothioylimino)phenylmethyl]amino}-butyric acid methyl ester (3v'). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (2x3H,d,J=6.8Hz), 2.25 (1H,m), 3.6-3.7 (8H,m), 3.74 (3H,s), 4.12 (1H,d,J=7.0), 7.42 (5H,m) ppm. ^{13}C-NMR ($CDCl_3$) δ: 18.0(q), 18.7(q), 30.7(d), 47.3x2(t), 51.6(q), 59.7(d), 65.6(t), 66.1(d), 127.2x2(d), 128.2x2(d), 130.3(d), 135.4(s), 158.7(s), 172.3(s), 188.2(s) ppm.

2-{[(3,3-Diethylthioureido)phenylmethyl]amino}-acetic acid ethyl ester (5g). Yield 65.5%. Mp: 95-97°C. FT-IR υ: 3240, 1745, 1620, 1530, 1480 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.12 (2x3H,t,J=7.2Hz), 1.24 (3H,t,J=7.1Hz), 3.54 (2H,q,J=7.1Hz), 3.77 (2H,q,J=7.1Hz), 4.00 (2H,d,J=5.9Hz), 4.14 (2H,q,J=7.1), 7.40 (5H,m) ppm. ^{13}C-NMR (DMSO-d_6) δ: 12.0(q), 13.1(q), 14.3(q), 43.6 (t), 44.2(t), 45.7(t), 60.7(t), 128.0x2(d), 128.3x2(d), 130.4(d), 133.8(s), 157.4(s), 170.1(s), 189.1(s) ppm. Calc. for $C_{16}H_{23}N_3O_2S$: C%, 59.79; H%, 7.21; N%, 13.07. Obs.: C%, 59.66; H%, 6.95; N%, 12.72. MS-EI (m/z): 321 [M^+].

2-{[(morpholine-4-carbothioylimino)phenylmethyl]amino}-acetic acid ethyl ester (5g'). Yield 66.0%. Mp: 91-92°C. FT-IR υ : 3260, 1745, 1615, 1550, 1480 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.24 (3H,t,J=7.1Hz), 3.5-4.0 (8H,m), 4.01 (2H,d,J=5.8Hz), 4.14 (2H,q,J=7.1), 7.45 (5H,m) ppm. ^{13}C-NMR (DMSO-d_6) δ: 14.4(q), 45.8(t), 47.4 (t), 48.8(t), 60.9(t), 65.8(t), 66.1(t), 128.1x2(d), 128.5x2(d), 130.4(d), 133.6(s), 158.2(s), 170.1(s), 189.5(s) ppm. Calc. for $C_{16}H_{21}N_3O_3S$: C%, 57.29; H%, 6.31; N%, 12.53. Obs.: C%, 56.96; H%, 6.55; N%, 12.28. MS-EI (m/z): 335 [M^+].

X-ray diffraction. The X-ray diffraction data were collected on a Stoe Stadi 4 diffractometer (MoKα, λ=0.71069 Å, graphite monochromator, room temperature, ω-2θ scan). The structures were solved by direct methods and refined with anisotropic temperature factors for the non-hydrogen atoms (SHELXS-86[10], SHELXL-93[11]).Crystal data and some details of the structure determinations are given in Table 2. The hydrogen positions were calculated in accordance with the results of difference maps but not refined. Complete lists with atomic coordinates and bond lenghts have been deposited.