2-Thioxo-1,3-thiazepan-4-ones, a Novel Class of Cyclic Dithiourethanes with a 7-Membered Ring System

Wolfgang Hanefeld* and Harald Schütz

Institut für Pharmazeutische Chemie, Marbacher Weg 6, D-35037 Marburg/Lahn, Federal Republic of Germany

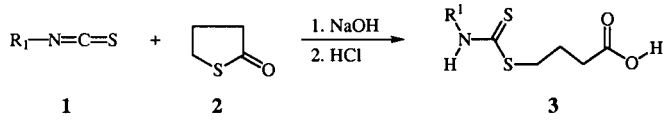
Received March 8, 1999

Reaction of isothiocyanates **1** with γ-thiobutyrolactone (**2**) in alkaline medium yielded 4-thiocarbamoylthiobutyric acids **3** after acidification, which could be cyclized to the 2-thioxo-1,3-thiazepan-4-ones **6**. Additional reactions were observed with the formation of **6t** from *p*-phenylenediisothiocyanate (**1s**) and with the formation of **6w** from benzyl isothiocyanate (**1t**). 3-Acetylamino-γ-thiobutyrolactone (**7**) could also be used in this reaction yielding the butyric acid derivatives **3u-3w.** Cyclization yielded the 1,3-thiazepane derivatives **6x, y** which rearranged under ring contraction to the 1,3-thiazinanes **8a, b**.

J. Heterocyclic Chem., **36**, 1167 (1999).

Cyclic dithiourethanes with 5- and 6-membered ring systems corresponding to the title compounds, the 2-thioxothiazolidin-4-ones **I** and the 2-thioxo-1,3-thiazinan-4-ones **II**, are well known and show considerable biological and pharmacological effects. Derivatives of **I**, also called rhodanines, were mainly described as bacteriostatic [1] and fungistatic [2-6], while derivatives of **II** were described as fungicide [7-9], thyreostatic [10] and antiarthritic [11]. In order to investigate the influence of ring size of structurally related cyclic dithiourethanes on biological or pharmacological effects we decided to prepare a series of the so far unknown 2-thioxo-1,3-thiazepan-4-ones **6**. The convenient method for the synthesis of **I** and **II**, reaction of sodium or ammonium dithiocarbamates with chloroacetic acid or β-chloropropionic acid respectively, followed by cyclization with acetic anhydride, could not be applied to the synthesis of **3** and **6** because our attempts to react sodium 4-bromobutyrate with sodium or ammonium dithiocarbamates to yield **3** failed. As Garraway [12] and Cherbuliez *et al.* [13] had successfully reacted isothiocyanates with salts of β-mercaptopropionic acid in aqueous solutions to yield 3-thiocarbamoylthiopropionic acids, starting materials for the cyclization to the 1,3-thiazine derivatives **II**, we used this method in a modified version for the synthesis of **3**. Isothiocyanates **1** and γ-thiobutyrolactone (**2**) were gently heated with sodium hydroxide in a dioxane/water system and on acidification yielded the 4-thiocarbamoylthiobutyric acids **3**. Seven acids have been fully characterized, the other have been cyclized as crude materials. Compound **3** could not be cyclized so easily as the corresponding thiocarbamoylthioacetic acids or thiocarbamoylthiopropionic acids, which could be cyclized to the thiazolidines **I** or 1,3-thiazinanes **II** respectively by the following methods: A: acetic anhydride with a catalytic amount of sulphuric acid; B: thionyl chloride; C: 4-toluenesulfonic acid/phosphorus pentaoxide; D: *N,N'*-dicyclohexylcarbodiimide; E: phosphorus trichloride. All these methods failed to cyclize **3** to **6**. In a search for an appropriate system for the cyclization of **3** to **6** we found a publication by Scriven [14], wherein the combination of *N,N'*-dicyclohexylcarbodiimide and 4-pyrrolidinopyridine or 4-dimethylaminopyridine was pointed out as an excellent cyclizing system. Ondetti [15] synthesized 1,4-thi-

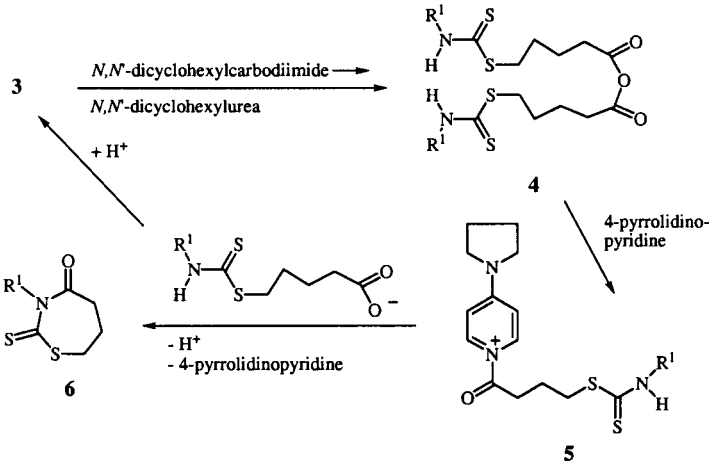
Scheme 1



1 **2** **3**

3/6	R^1	3/6	R^1
a	CH_3	j*	4-CH_3O-C_6H_4
b	C_2H_5	k*	3-CF_3-C_6H_4
c*	CH_2=CH-CH_2	l*	4-F-C_6H_4
d**	Cyclohexyl	m*	4-Cl-C_6H_4
e	C_6H_5-CH_2	n*	4-Br-C_6H_4
f	C_6H_5	o*	4-NO_2-C_6H_4
g	2-CH_3-C_6H_4	p*	4-$(CH_3)_2N$-C_6H_4
h*	3-CH_3-C_6H_4	q	2-[CH_3O-C(O)]-C_6H_4
i*	4-CH_3-C_6H_4	r*	1-Naphthyl

*Acids **3** not isolated. **No product **6d** isolated.

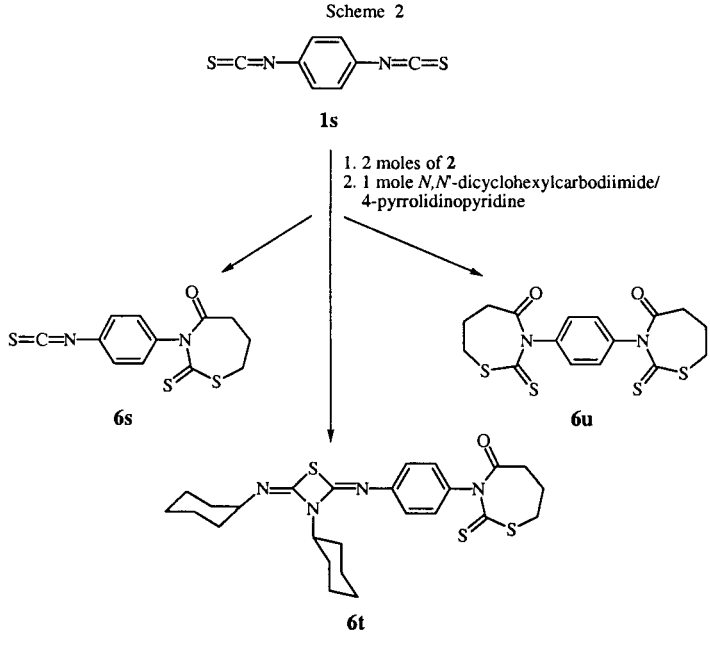


3 **4** **5** **6**

azepane-2,5-diones by this method using *N,N'*-dicyclohexylcarbodiimide and 4-dimethylaminopyridine. The *N,N'*-dicyclohexylcarbodiimide/4-pyrrolidinopyridine method proved best for the cyclization of **3** to **6**. The reaction pathway is shown in Scheme 1. *N,N'*-dicyclohexylcarbodiimide and 4-pyrrolidinopyridine were used in the relation 10:1; *N,N'*-dicyclohexylurea could easily be removed by filtration.

From the reaction of *p*-phenylenediisothiocyanate (**1s**) with **2**, followed by cyclization, three compounds could be isolated by column chromatography: compound **6s** with one free isothiocyanate group, compound **6t**, where this group was involved in a 2+2 cycloaddition with *N,N'*-dicyclohexylcarbodiimide forming a 1,3-thiazetidine system and **6u** where both isothiocyanate groups had reacted.

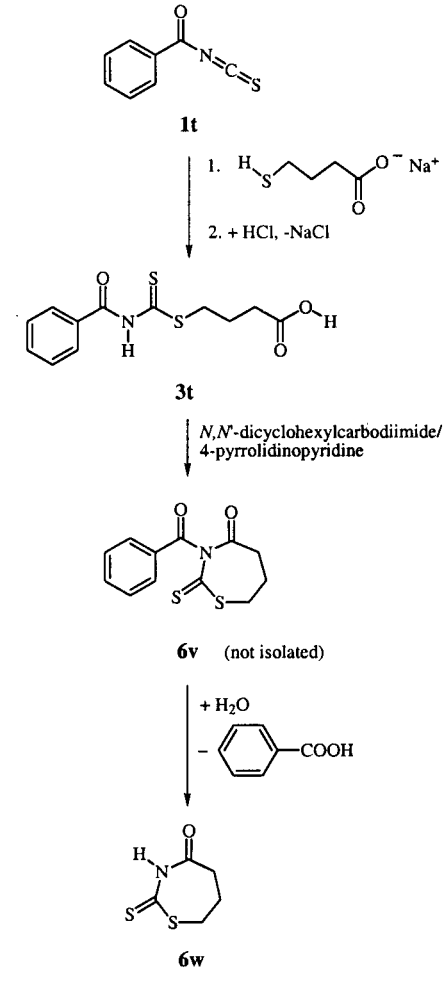
Scheme 2



It is known from the reaction of aryl-substituted isothiocyanates with *N,N'*-dicyclohexylcarbodiimide that the 2+2 cycloaddition always yields 2,4-diimino-1,3-thiazetidines, never 4-imino-1,3-diazetidine-2-thiones [16]. This rule was also followed by compound **6t**, demonstrated by the ^{13}C nmr spectrum, which showed only one thiocarbonyl signal of the 1,3-thiazepane ring at 210.1 ppm, not a second one of a 1,3-diazetidine-2-thione.

In order to synthesize *N*-benzoyl-2-thioxo-1,3-thiazepan-4-one (**6v**), *N*-benzoylisothiocyanate (**1t**) was reacted with sodium 4-mercaptobutyrate in dichloromethane to yield a crystalline solid (from toluene) after acidification. The crude 4-(*N*-benzoylthiocarbamoylthio)-butyric acid (**3t**) was treated with *N,N'*-dicyclohexylcarbodiimide/4-pyrrolidinopyridine as usual. Within a few minutes, dc-control (SiF-microcards, Riedel -de-Häen, dichloromethane) showed a yellow product with rf-value 0.7. Thirty minutes later another yellow spot appeared with rf-value 0.4. With preceding reaction time the rf 0.7 compound, probably **6v**, more and more disappeared and the rf 0.4 compound increased. This compound was isolated by column chromatography and identified as the *N*-unsubstituted 2-thioxo-1,3-thiazepan-4-one (**6w**), the hydrolysis product of **6v**.

Scheme 3

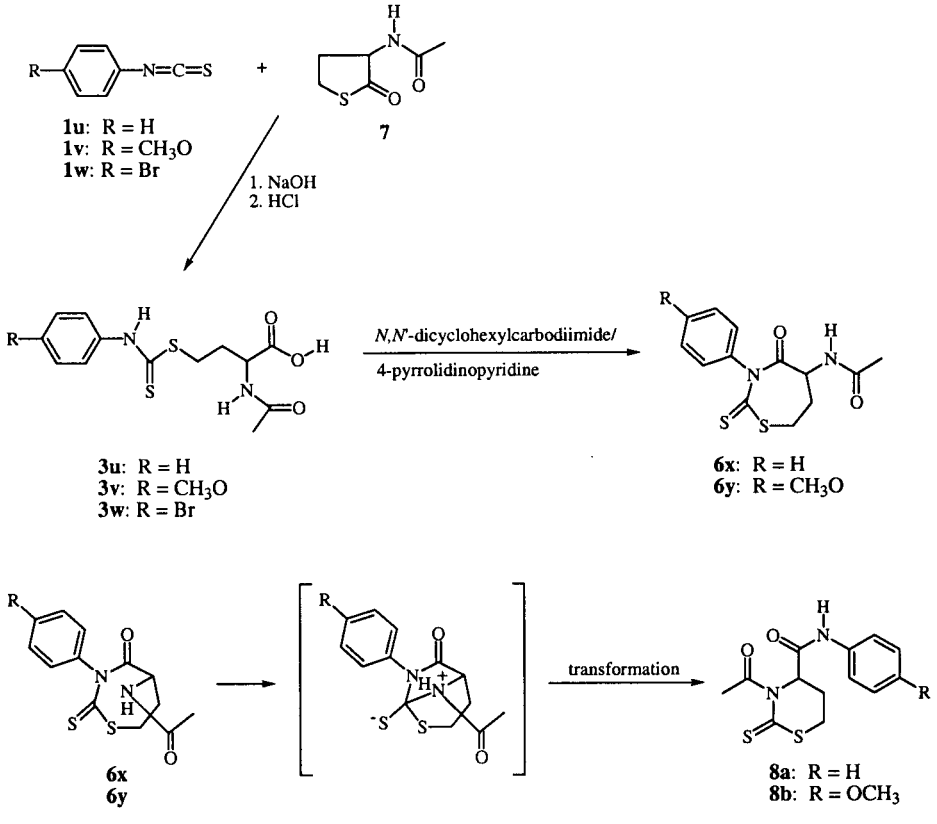


This ease of hydrolysation at the exocyclic amide bond had also been observed with *N*-acyl-2-thioxo-1,3-thiazinan-4-ones [17]. Attempts to synthesize **6w** by reaction of sodium thiocyanate with sodium 4-mercaptobutyrate failed at the first step, because after acidification no 4-thiocarbamoylthiobutyric acid could be isolated.

The reactions of some aromatic isothiocyanates **1u,v,w** with 2-acetylamino γ-thiobutyrolactone (**7**) yielded 2-acetylamino-4-(*N*-arylthiocarbamoylthio)butyric acids. **3u** and **3v** were cyclized as crude compounds; **3w** was completely characterized. From the cyclization of **3u** two compounds could be separated by column chromatography: the yellow 1,3-thiazepane **6x** and the colorless *R,S*-3-

acetyl-4-(*N*-phenylcarbamoyl)-1,3-thiazinane-2-thione (**8a**). This can also be generated by treatment of pure **6x** within one hour on the silica gel disc of a chromatotron or mentioned above. The right conditions were found by chance observing the behaviour of **6y** while determining the melting point: the yellow color changed to colorless

Scheme 4



by stirring **6x** with silica gel in dichloromethane for 70 hours. The rearrangement with ring contraction from the 7- to the 6-membered ring is demonstrated in Scheme 4.

The structure of the 1,3-thiazinane-2-thione (**8a**) was derived from the following significant spectroscopic data: The ^{13}C nmr spectrum shows a signal at 196.8 ppm for the C=S group. Such a value around or below 200 ppm is typical for 1,3-thiazinane-2-thiones [18,19], the C=S signal of the 1,3-thiazepane **6x** shows a value of 207.5 ppm. The acetyl group of **8a** gives a signal at very low field with 183.8 ppm, the carbamoyl C=O a signal at 173.3 ppm. The two C=O groups of **6x** for comparison show signals at 171.9 and 169.6 ppm. The most significant feature of the ^1H nmr spectrum of **8a** is the singlet of the carbamoyl-NH instead of the doublet of the NH of the parent compound **6x**. The ir spectrum also contributes to the structural confirmation. The acetyl group at 3-position of **8a** absorbs at 1760 cm^{-1}; this value is typical for *N*-acylated 1,3-thiazinane-2-thiones [19]. The two C=O groups of **6x** absorb at 1720 and 1640 cm^{-1}.

Compound **6y** did not so easily rearrange as **6x**, because no rearrangement occurred under the conditions near the melting point. Repeating the experiment on a preparative scale by heating **6y** to 160° for 20 minutes yielded **8b**.

EXPERIMENTAL

Instrumental equipment and chromatographic conditions were those already described [20]. For preparative chromatography on a rotating disc a "Chromatotron" from Harrison Research, Palo Alto, California was used.

General Procedure for the Preparation of the *N*-Substituted 4-Thiocarbamoylthiobutyric Acids **3a**, **b**, **d**, **e**, **f**, **g**, **q**.

Equimolar quantities of the appropriate isothiocyanate **1** and γ-thiobutyrolactone (**2**) were dissolved in 50 ml of dioxane and heated to 60°. An equimolar amount of sodium hydroxide, dissolved in the minimum amount of water was added with stirring. The reaction started spontaneously and was stopped after 20 minutes of stirring by pouring the solution onto crushed ice. After acidification to *p*H 2 by addition of concentrated hydrochloric acid the acid **3** in some cases separated in crystalline form, could be filtered with suction, washed with a small amount of water, dried and recrystallized. If **3** did not crystal-

lize, the whole solution was evaporated to dryness. Acetone was added to the residue and after 1 hour of cooling in ice the precipitated sodium chloride was filtered. The acetone solution was dried over sodium sulfate, filtered and evaporated *in vacuo* to yield **3**, purified by recrystallization.

4-(*N*-Methylthiocarbamoylthio)butyric Acid (**3a**).

This compound was obtained from 3.58 g (0.049 mole) of methyl isothiocyanate (**1a**), 5.0 g (0.049 mole) of **2** and 2.0 g (0.049 mole) of sodium hydroxide as colorless crystals (water), 3.8 g (40%), mp 91°; ir: ν NH 3220, CO 1690 cm^{-1}; ^1H nmr (deuteriomethanol): δ 1.76-2.16 (m, 2H, H-3), 2.30-2.43 (m, 2H, H-2), 3.10 (s, 3H, CH_3), 3.26 (t, 2H, H-4), no signals for NH and COOH because of deuterium exchange; ^{13}C nmr (deuteriomethanol): δ 26.0 (C-3), 33.6 (C-2), 34.0 (CH_3), 34.7 (C-4), 176.8 (CO), 199.1 (CS); ms: m/z 193 (47, M^+), 107 (75), 74 (100).

Anal. Calcd. for $C_6H_{11}NO_2S_2$ (193.29): C, 37.28; H, 5.74; N, 7.25; S, 33.18. Found: C, 37.22; H, 5.55; N, 7.25; S, 33.19.

4-(*N*-Ethylthiocarbamoylthio)butyric Acid (**3b**).

This compound was obtained from 4.26 g (0.049 mole) of ethyl isothiocyanate (**1b**), 5.0 g (0.049 mole) of **2** and 2.0 g (0.049 mole) of sodium hydroxide as colorless crystals (water), 6.4 g (63%), mp 79°; ir: ν NH 3040, CO 1690 cm^{-1}; ^1H nmr (deuteriomethanol): δ 1.03 (t, 3H, CH_3-CH_2), 1.80-2.56 (m, 4H, H-2, H-3), 3.25 (t, 2H, H-4), 3.66 (q, 2H, CH_3-CH_2), no signals for NH and COOH because of deuterium exchange; ^{13}C nmr (deuteriomethanol): δ 13.5 (CH_3), 26.0 (C-3), 33.6 (C-2), 34.6 (C-4), 42.9 (CH_2N), 176.8 (CO), 198.1 (CS); ms: m/z 207 (42, M^+), 121 (69), 102 (31), 88 (100), 87 (57), 60 (76).

Anal. Calcd. for $C_7H_{13}NO_2S_2$ (207.32): C, 40.65; H, 6.32; N, 6.76; S, 30.93. Found: C, 40.63; H, 6.08; N, 6.65; S, 30.76.

4-(*N*-Cyclohexylthiocarbamoylthio)butyric Acid (**3d**).

This compound was obtained from 13.8 g (0.098 mole) of cyclohexyl isothiocyanate (**1d**), 10.0 g (0.098 mole) of **2** and 3.9 g (0.098 mole) of sodium hydroxide as a white powder, 21 g (82%), mp 97° (cyclohexane/toluene); ir: ν NH 3180, CO 1705 cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 0.63-2.1 (m, 12H, H-3, cyclohexyl-protons H-2 to H-6), 2.31 (m, 2H, H-2), 3.20 (t, 2H, H-4), 4.00-4.57 (m, 1H, H-1-cyclohexyl), 9.65, 9.70 (2s, NH, COOH); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 26.2, 26.6, 32.5 (C-3 acid, C-2, C-6 cyclohexyl), 33.6 (C-2 acid), 34.5 (C-4 acid), 57.2 (C-1 cyclohexyl), 176.8 (CO), 197.0 (CS); ms: m/z 261 (16, M^+), 175 (38), 142 (29), 141 (100), 102 (41), 83 (87).

Anal. Calcd. for $C_{11}H_{19}NO_2S_2$ (261.41): C, 50.54; H, 7.33; N, 5.36; S, 24.53. Found: C, 50.62; H, 7.14; N, 5.16; S, 24.30.

4-(*N*-Benzylthiocarbamoylthio)butyric Acid (**3e**).

This compound was obtained ftom 7.3 g (0.049 mole) of benzyl isothiocyanate (**1e**), 5.0 g (0.049 mole) of **2** and 2.0 g (0.049 mole) of sodium hydroxide as a white powder (water), 8.1 g (62%), mp 89°; ir: ν NH 3300, CO 1680 cm^{-1}, ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.68-2.10 (m, 2H, H-3), 2.3-2.6 (m, 2H, H-2), 3.21 (t, 2H, H-4), 4.81 (d, 2H, CH_2-C_6H_5), 7.21 (m, 5H, phenyl), 10.76 (s, 1H, NH), 12.38 (s, 1H, COOH); ^{13}C nmr (deuteriochloroform): δ 26.0 (C-3), 33.6 (C-2), 34.8 (C-4), 51.2 (CH_2-C_6H_5), 128.3, 128.9, 129.4, 138.6 (phenyl carbons), 176.8 (CO), 199.2 (CS); ms: m/z 269 (4, M^+), 149 (28), 91 (100).

Anal. Calcd. for $C_{12}H_{15}NO_2S_2$ (269.38): C, 53.53; H, 5.57; N, 5.20; S, 23.79. Found: C, 53.47; H, 5.37; N, 5.32; S, 23.80.

4-(*N*-Phenylthiocarbamoylthio)butyric Acid (**3f**).

This compound was obtained from 6.6 g (0.049 mole) of phenyl isothiocyanate (**1f**), 5.0 g (0.049 mole) of **2** and 2.0 g (0.049 mole) of sodium hydroxide as a white powder, 7.9 g (63%), mp 116° (toluene); ir: ν NH 3320, CO 1700 cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.7-2.1 (m, 2H, H-3), 2.22-2.50 (m, 2H, H-2), 3.27 (t, 2H, H-4), 7.25-7.50 (m, 5H, phenyl protons), 11.78 (s, 1H, NH), 11.96 (s, 1H, COOH); ^{13}C nmr (deuteriochloroform): δ 25.8 (C-3), 33.7 (C-2), 35.2 (C-4), 125.3, 127.3, 129.7, 140.9 (phenyl carbons), 176.7 (CO), 200.4 (CS).

Anal. Calcd. for $C_{11}H_{13}NO_2S_2$ (255.36): C, 51.74; H, 5.13; N, 5.49; S, 25.11. Found: C, 51.87; H, 5,15; N, 5.43; S, 24.98.

4-[*N*-(2-Tolyl)thiocarbamoylthio]butyric Acid (**3g**).

This compound was obtained from 5.0 g (0.034 mole) of 2-tolyl isothiocyanate (**1g**), 3.5 g (0.034 mole) of **2** and 3.5 g (0.034 mole) of sodium hydroxide as a white powder, 4.6 g (50%), mp 97° (toluene); ir: ν NH 3190, CO 1690 cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.61-2.30 (m, 4H, H-2, H-3), 2.18 (s, 3H, CH_3), 3.20 (t, 2H, H-4), 7.20 (m, 4H, phenyl protons), 9.83-10.3 (broad, 2H, NH, COOH); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 17.4 (CH_3), 24.2 (C-3), 32.5 (C-2), 34.1 (C-4), 126.4, 127.7, 130.6, 134.9, 138.1 (phenyl carbons), 173.8 (CO), 198.0 (CS); ms: m/z 269 (1, M^+), 149 (100).

Anal. Calcd. for $C_{12}H_{15}NO_2S_2$ (269.39): C, 53.50; H, 5.61; N, 5.20; S, 23.81. Found: C, 53.78; H, 5.45; N, 5.10; S, 23.66.

4-[*N*-(2-Methoxycarbonylphenyl)thiocarbamoylthio]butyric Acid (**3q**).

This compound was obtained from 4.8 g (0.025 mole) of methyl 2-isothiocyanatobenzoate (**1q**), 2.5 g (0.025 mole) of **2** and 1.0 g (0.025 mole) of sodium hydroxide as pale yellow crystals, 2.1 g (27%), mp 115° (acetone/water); ir: ν NH 3250, CO 1700 cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.7-2.1 (m, 2H, H-3), 2.33 (m, 2H, H-2), 3.23 (t, 2H, H-4), 3.76 (s, 3H, CH_3), 7.06-7.90 (m, 4H, phenyl protons), 11.33-12.17 (br, 2H, NH, COOH); ^{13}C nmr (deuteriochloroform): δ 24.2 (C-3), 32.5 (C-2), 34.0 (C-4), 52.4 (CH_3), 126.0, 127.0, 127.5, 130.5, 132.9, 138.9 (phenyl carbons), 165.9 ($COOCH_3$), 173.8 (COOH), 197.8 (CS); ms: m/z 313 (2, M^+), 193 (80), 162 (100).

Anal. Calcd. for $C_{13}H_{15}NO_4S_2$ (313.40): C, 49.82; H, 4.82; N, 4.74; S, 20.46. Found: C, 49.81; H, 4.65; N, 4.53; S, 20.29.

General Procedure for the Cyclization of Compounds **3** to the 2-Thioxo-1,3-thiazepan-4-ones **6**.

The isolated 4-thiocarbamoylthiobutyric acid **3** (0.02 mole) or the crude product were suspended in 100 ml of dichloromethane and 0.022 mole of *N,N'*-dicyclohexylcarbodiimide and 0.002 mole of 4-pyrrolidinopyridine were added. After stirring for 15-20 hours the precipitated *N,N*-dicyclohexylurea was separated by filtration. The yellow solution was concentrated to 20 ml and purified by column chromatography mostly with dichloromethane.

3-Methyl-2-thioxo-1,3-thiazepan-4-one (**6a**).

This compound was obtained from **3a** as yellow needles, 2.1 g (92%), mp 62° (ether/light petroleum); ir: ν CO 1670 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.26 (q, 2H, H-6), 2.86-3.20 (m, 4H, H-5, H-7), 3.55 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 26.8 (C-6), 35.2, 35.4 (C-5, C-7), 38.8 (CH_3), 172.5 (CO), 210.7 (CS); ms: m/z 175 (100, M^+), 103 (50), 102 (38).

Anal. Calcd. for $C_6H_9NOS_2$ (175.27): C, 41.12; H, 5.18; N, 7.99; S, 36.59. Found: C, 41.26; H, 4.99; N, 7.83; S, 36.49.

3-Ethyl-2-thioxo-1,3-thiazepan-4-one (**6b**).

This compound was obtained from **3b** as a yellow oil, 2.0 g (74%); ir: ν CO 1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.24 (t, CH_3), 2.33 (quint, 2H, H-6), 2.86-3.18 (m, 4H, H-5, H-7), 4.32 (q, 2H, CH_2-CH_3); ^{13}C nmr (deuteriochloroform): δ 13.5 (CH_3), 26.8 (C-6), 35.4 (C-5, C-7), 46.9 (CH_2-CH_3), 172.1 (CO), 210.4 (CS); ms: m/z 189 (91, M^+), 103 (100), 102 (37), 87 (35), 55 (48).

Anal. Calcd. for $C_7H_{11}NOS_2$ (189.30): C, 44.42; H, 5.86; N, 7.40; S, 33.88. Found: C, 44.58; H, 5.67; N, 7.27; S, 33.86.

3-Allyl-2-thioxo-1,3-thiazepan-4-one (**6c**).

This compound was obtained from 4.85 g (0.049 mole) of freshly distilled allyl isothiocyanate (**1c**) and 5.0 g of **2** dissolved in 50 ml of dioxane by heating to 50°. After the addition of 2.0 g (0.05 mole) of sodium hydroxide in 30 ml of water the mixture was stirred until clear. After cooling with ice, concentrated hydrochloric acid was added until the *p*H was 2. The solvent was evaporated completely, the residue dissolved in acetone and the remaining sodium chloride filtered. The acetone phase was dried over sodium sulfate and evaporated to yield 2.0 g of crude **3c** as a brown powder, which was cyclized without further purification; **6c** resulted as a yellow oil, 1.37 g (74%); ir: ν CO 1690 cm^{-1}; ^1H nmr: (deuteriochloroform): δ 2.28 (quin, 2H, H-6), 2.89-3.25 (m, 4H, H-5, H-7), 4.81 (d, 2H, CH_2-CH=CH_2), 5.01-5.33 (m, 2H, CH_2-CH=CH_2), 5.56-6.21 (m, 1H, CH_2-CH=); ^{13}C nmr (deuteriochloroform): δ 26.7 (C-6), 35.2 (C-5, C-7), 52.9 (CH_2-CH=CH_2), 118.5 (CH_2-CH=CH_2), 131.8 (CH_2-CH=), 172.0 (CO), 209.7 (CS).

Anal. Calcd. for $C_8H_{11}NOS_2$ (201.31): C, 47.73; H, 5.51; N, 6.96; S, 31.86. Found: 47.94; H, 5.39; N, 6.80; S, 31.53.

3-Benzyl-2-thioxo-1,3-thiazepan-4-one (**6e**).

This compound was obtained from **3e** as yellow crystals, 2.2 g (59%), mp 95° (ether); ir: ν CO 1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.27 (quin, 2H, H-6), 2.97, 2.99 (2 t, 4H, H-5, H-7), 5.47 (s, 2H, CH_2-C_6H_5), 7.23-7.34 (m, 5H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 26.9 (C-6), 35.1 (C-5, C-7), 53.5 (CH_2-C_6H_5), 127.6, 128.2, 128.4, 136.7 (phenyl carbons), 172.4 (CO), 210.4 (CS); ms: m/z 251 (47, M^+), 149 (58), 148 (48), 103 (100), 91 (88).

Anal. Calcd. for $C_{12}H_{13}NOS_2$ (251.37): C, 57.34; H, 5.21; N, 5.57; S, 25.51. Found: C, 57.18; H, 5.06; N, 5.60; S, 25.37.

3-Phenyl-2-thioxo-1,3-thiazepan-4-one (**6f**).

This compound was obtained from **3f** as yellow crystals, 1.27 g (35%), mp 84° (methanol); ir: ν CO 1705 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.36 (quin, 2H, H-6), 3.06 (t, 2H, H-5), 3.25 (t, 2H, H-7), 7.13-7.16, 7.35-7.44 (2 m, 5H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 26.5 (C-6), 35.0 (C-5), 35.5 (C-7), 128.1, 128.9, 129.1, 142.2 (phenyl carbons), 172.1 (CO), 209.9 (CS); ms: m/z 237 (20, M^+), 135 (100).

Anal. Calcd. for $C_{11}H_{11}NOS_2$ (234.34): C, 55.67; H, 4.67; N, 5.90; S, 27.02. Found: C, 55.57; H, 4.64; N, 5.81; S, 27.30.

3-(2-Methylphenyl)-2-thioxo-1,3-thiazepan-4-one (**6g**).

This compound was obtained from **3g** as yellow crystals, 1.35 g (58%), mp 90° (methanol), ir: ν CO 1690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.18 (s, 3H, CH_3), 2.32-2.46 (m, 2H, H-6), 3.09-3.21, 3.24-3.37 (2 m, 4H, H-5, H-7), 7.02-7.32 (m, 4H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 17.9 (CH_3), 26.7 (C-6), 35.3 (C-5), 35.7 (C-7), 127.1, 128.7, 128.9, 131.2, 135.7, 141.6 (phenyl carbons), 172.7 (CO), 208.2 (CS); ms: m/z 251 (17, M^+), 149 (100).

Anal. Calcd. for $C_{12}H_{13}NOS_2$ (251.37): C, 57.34; H, 5.21; N, 5.57; S, 25.51. Found: C, 57.25; H, 5.10; N, 5.49; S, 25.36.

3-(3-Methylphenyl)-2-thioxo-1,3-thiazepan-4-one (**6h**).

This compound was obtained from 5.0 g (0.034 mole) of 3-methylphenyl isothiocyanate (**1h**) and **2** following the procedure described for **6c**. Yellow crystals, 0.35 (15%), were obtained, mp 84° (dichloromethane); ir: ν CO 1700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.36 (quin, 2H, H-6), 2.38 (s, 3H, CH_3), 3.09 (t, 2H, H-5), 3.29 (t, 2H, H-7), 6.94-6.95, 7.18-7.19, 7.28-7.33 (3 m, 4H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 21.3 (CH_3), 26.7 (C-6), 35.2, 35.7 (C-5, C-7), 125.7, 129.1, 129.2, 129.3, 139.4, 142.1 (phenyl carbons), 173.0 (CO), 210.0 (CS); ms: m/z 251 (22, M^+), 149 (100).

Anal. Calcd. for $C_{12}H_{13}NOS_2$ (251.37): C, 57.34; H, 5.21; N, 5.57; S, 25.51. Found: C, 57.55; H, 5.17; N, 5.52; S, 25.25.

3-(4-Methylphenyl)-2-thioxo-1,3-thiazepan-4-one (**6i**).

This compound was obtained from 2.5 g (0.0167 mole) 4-methylphenyl isothiocyanate (**1i**) and **2** following the procedure described for **6c**. Yellow crystals, 1.2 g (29%), mp 148° (toluene); ir: ν CO 1700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.37 (quin, 2H, H-6), 2.37 (s, 3H, CH_3), 3.10 (t, 2H, H-5), 3.29 (t, 2H, H-7), 7.01-7.04, 7.25-7.33 (2 m, 4H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 21.2 (CH_3), 26.7 (C-6), 35.1 (C-5), 35.6 (C-7), 128.3, 130.0, 138.4, 139.6 (phenyl carbons), 172.4 (CO), 210.1 (CS); ms: m/z 251 (23, M^+), 149 (100).

Anal. Calcd. for $C_{12}H_{13}NOS_2$ (251.37): C, 57.37; H, 5.21; N, 5.57; S, 25.51. Found: C, 57.36; H, 5.06; N, 5.53; S, 25.63.

3-(4-Methoxyphenyl)-2-thioxo-1,3-thiazepan-4-one (**6j**).

This compound was obtained from 2.5 g (0.015 mole) of 4-methoxyphenyl isothiocyanate (**1j**) and **2** following the procedure described for **6c**. Yellow crystals, 1.73 g (42%) were obtained, mp 119° (dichloromethane); ir: ν CO 1690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.04-2.60 (m, 2H, H-6), 2.95-3.42 (m, 4H, H-5, H-7), 3.81 (s, 3H, CH_3), 6.87-7.27 (m, 4H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 26.6 (C-6), 35.1 (C-5), 35.6 (C-7), 55.3 (CH_3), 114.4, 134.8, 139.6, 159.2 (phenyl carbons), 172.5 (CO), 210.3 (CS); ms: m/z 276 (11, M^+), 165 (100).

Anal. Calcd. for $C_{12}H_{13}NO_2S_2$ (267.37): C, 53.91; H, 4.90; N, 5.24; S, 23.98. Found: C, 53.86; H, 4.91; N, 5.24; S, 24.02.

3-(3-Trifluoromethylphenyl)-2-thioxo-1,3-thiazepan-4-one (**6k**).

This compound was obtained from 4.0 g (0.019 mole) of 3-trifluoromethylphenyl isothiocyanate (**1k**) and **2** following the procedure described for **6c**. Yellow crystals, 1.3 g (23%), mp 125° (methanol); ir: ν CO 1690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.39 (quin, 2H, H-6), 3.12 (t, 2H, H-5), 3.33 (t, 2H, H-7), 7.34-7.40, 7.52-7.64 (2 m, 4H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 25.6 (C-6), 35.1 (C-5), 35.7 (C-7), 123.5 (CF_3), 125.4, 126.0, 129.8, 131.9, 132.6, 142.4 (phenyl carbons), 172.1 (CO), 209.6 (CS); ms: m/z 305 (15, M^+), 203 (100).

Anal. Calcd. for $C_{12}H_{10}F_3NOS_2$ (305.34): C, 47.20; H, 3.30; N, 4.59; S, 21.00. Found: C, 47.13; H, 3.26; N, 4.61; S, 21.14.

3-(4-Fluorophenyl)-2-thioxo-1,3-thiazepan-4-one (**6l**).

This compound was obtained from 5.0 g (0.032 mole) of 4-fluorophenyl isothiocyanate (**1l**) and **2** following the proce-

dure described for **6c**. Yellow crystals, 1.8 g (22%) were obtained, mp 127° (dichloromethane); ir: ν CO 1700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.30 (quin, 2H, H-6), 2.97-3.37 (m, 4H, H-5, H-7), 7.05-7.27 (m, 4H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 26.6 (C-6), 35.0 (C-5), 35.6 (C-7), 115.8, 116.7, 130.3, 130.7, 137.7, 162.7 (phenyl carbons), 172.3 (CO), 209.9 (CS); ms: m/z 255 (17, M^+), 153 (100).

Anal. Calcd. for $C_{11}H_{10}FNOS_2$ (255.33): C, 51.74; H, 3.95; N, 5.49; S, 25.15. Found: C, 51.72; H, 3.78; N, 5.38; S, 25.15.

3-(4-Chlorophenyl)-2-thioxo-1,3-thiazepan-4-one (**6m**).

This compound was obtained from 5.0 g (0.029 mole) of 4-chlorophenyl isothiocyanate (**1m**) and **2** following the procedure described for **6c**. Yellow crystals, 1.1 g (14%) were obtained, mp 153° (dichloromethane); ir: ν CO 1700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.35 (quin, 2H, H-6), 3.08 (t, 2H, H-5), 3.28 (t, 2H, H-7), 7.06-7.09, 7.37-7.40 (2 m, 4H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 26.6 (C-6), 35.1 (C-5), 35.7 (C-7), 129.6, 130.2, 134.4, 140.6 (phenyl carbons), 172.2 (CO), 209.7 (CS), ms: m/z 271 (7, M^+), 169 (100).

Anal. Calcd. for $C_{11}H_{10}ClNOS_2$ (271.79): C, 48.61; H, 3.71; N, 5.15; S, 23.59. Found: C, 48.57; H, 3.70; N, 5.19; S, 23.73.

3-(4-Bromophenyl)-2-thioxo-1,3-thiazepan-4-one (**6n**).

This compound was obtained from 5.0 g (0.023 mole) of 4-bromophenyl isothiocyanate (**1n**) and **2** following the procedure described for **6c**. Yellow crystals, 1.5 g (21%) were obtained, mp 151° (dichloromethane); ir: ν CO 1690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.36 (quin, 2H, H-6), 3.00-3.40 (m, 4H, H-5, H-7), 6.90-7.60 (m, 4H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 26.6 (C-6), 35.1 (C-5), 35.7 (C-7), 122.5, 130.4, 132.6, 141.0 (phenyl carbons), 172.1 (CO), 209.6 (CS); ms: m/z 316 (2, M^+), 215 (100), 213 (96).

Anal. Calcd. for $C_{11}H_{10}BrNOS_2$ (316.24): C, 41.78; H, 3.19; N, 4.43; S, 20.28. Found: C, 42.04; H, 3.19; N, 4.35; S, 20.08.

3-(4-Nitrophenyl)-2-thioxo-1,3-thiazepan-4-one (**6o**).

This compound was obtained from 3.5 g (0.019 mole) of 4-nitrophenyl isothiocyanate (**1o**) and **2** following the procedure described for **6c**. Yellow crystals, 0.16 g (3%) were obtained, mp 166° (dichloromethane); ir: ν CO 1700 cm^{-1}, ms: m/z 282 (11, M^+), 180 (100).

Anal. Calcd. for $C_{11}H_{10}N_2O_3S_2$ (282.34): C, 46.80; H, 3.57; N, 9.92; S, 22.71. Found: C, 47.03; H, 3.50; N, 9.96; S, 22.47.

3-(4-Dimethylamino)-2-thioxo-1,3-thiazepan-4-one (**6p**).

This compound was obtained from 10.0 g (0.056 mole) of 4-dimethylaminophenyl isothiocyanate (**1p**) and **2** following the procedure described for **6c**. Orange-yellow crystals, 0.5 g (3%) were obtained, mp 161° (dichloromethane); ir: ν CO 1700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.35 (quin, 2H, H-6), 2.97 (s, 6H, 2 CH_3), 3.09 (t, 2H, H-5), 3.27 (t, 2H, H-7), 6.67-6.71, 6.95-6.98 (2 m, 4H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 26.8 (C-6), 35.2 (C-5), 35.7 (C-7), 40.4 (CH_3), 112.2, 129.0, 131.0, 150.0 (phenyl carbons), 172.8 (CO), 210.7 (CS); ms: m/z 280 (10, M^+), 178 (100).

Anal. Calcd. for $C_{13}H_{16}N_2OS_2$ (280.41): C, 55.68; H, 5.75; N, 9.99; S, 22.87. Found: C, 55.72; H, 5.62; N, 9.97; S, 22.72.

Methyl 2-(4-Oxo-2-thioxo-1,3-thiazepan-3-yl)benzoate (**6q**).

This compound was obtained from **3q** as yellow crystals, 0.06 g (6%), mp 126° (chloroform); ir: ν 2 CO 1710, 1690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.28-2.49 (m, 2H, H-6), 3.09-3.15, 3.29-3.47 (2 m, 4H, H-5, H-7), 3.84 (s, 3H, CH_3), 7.14-8.09 (m, 4H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 26.7 (C-6), 35.8, 35.9 (C-5, C-7), 52.4 (CH_3), 128.0, 128.8, 130.7, 131.6, 133.7, 142.5 (phenyl carbons), 164.8 (*C*OOCH$_3$), 174.1 (CO), 207.8 (CS); ms: m/z 295 (33, M^+), 193 (100), 162 (92).

Anal. Calcd. for $C_{13}H_{13}NO_3S_2$ (295.38): C, 52.86; H, 4.44; N, 4.74; S, 21.71. Found: C, 52.78; H, 4.44; N, 4.66; S, 21.58.

3-(1-Naphthyl)-2-thioxo-1,3-thiazepan-4-one (**6r**).

This compound was obtained from 2.6 g (0.014 mole) of 1-naphthyl isothiocyanate (**1r**) and **2** following the procedure described for **6c**. Yellow crystals, 0.3 g (15%), were obtained, mp 145° (dichloromethane); ir: ν CO 1700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.27-2.62 (m, 2H, H-6), 3.13-3.53 (m, 4H, H-5, H-7), 7.22-8.02 (m, 7H, naphthyl protons); ^{13}C nmr (deuteriochloroform): δ 26.8 (C-6), 35.5 (C-5), 36.0 (C-7), 122.1, 125.4, 126.3, 127.0, 127.2, 128.7, 129.3, 130.0, 134.4, 139.2 (naphthyl carbons), 173.0 (CO), 208.5 (CS); ms: m/z 287 (12, M^+), 185 (100).

Anal. Calcd. for $C_{15}H_{13}NOS_2$ (287.40): C, 62.69; H, 4.56; N, 4.87; S, 22.31. Found: C, 62.80; H, 4.56; N, 4.79; S, 22.04.

Reaction of 1,4-Phenylene Diisothiocyanate with **2**.

Compound **2** (2.65 g, 0.026 mole) and an equimolar amount of sodium hydroxide were heated in 50 ml of water to 70° for 30 minutes. 1,4-Phenylendiisothiocyanate (**1s**) (2.5 g, 0.013 mole) in 50 ml of dioxane was added and the mixture was stirred for 20 hours initially, then for 3 hours at 70°. The solution was cooled on ice, acidified with concentrated hydrochloric acid and filtered from 2.9 g of the precipitated material. This crude product was allowed to reacted with 2.7 g (0.0134 mole) of *N,N'*-dicyclohexylcarbodiimide and 0.20 g (0.00134 mole) of 4-pyrrolidinopyridine in 50 ml of dichloromethane for 20 hours at room temperature. The precipitate was filtered, the yellow filtrate was concentrated to 20 ml and separated by column chromatography with toluene/dioxane 15/1 to yield two yellow fractions. Additional column chromatography with dichloromethane yields a first fraction A and a second fraction B. By changing the solvent mixture to toluene/dioxane 1/1 a third yellow fraction C could be isolated.

Fraction A: 3-(4-Isothiocyanatophenyl)-2-thioxo-1,3-thiazepan-4-one (**6s**).

This compound was isolated as yellow crystals, 0.95 g (25%), mp 141°; ir: ν N=C=S 2120, CO 1690 cm^{-1}, ^1H nmr (deuteriochloroform): δ 2.31-2.63 (m, 2H, H-6), 2.97-3.38 (m, 4H, H-5, H-7), 7.13 (s, 4H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 26.6 (C-6), 35.1 (C-5), 35.7 (C-7), 126.5, 130.2 (C-2, C-6 and C-3, C-5 phenyl), 131.4 (C-1 phenyl), 136.2 (S=C=N), 140.7 (C-4 phenyl), 172.1 (CO), 209.5 (C=S); ms: m/z 294 (9, M^+), 192 (100).

Anal. Calcd. for $C_{12}H_{10}N_2OS_3$ (294.42): C, 48.96; H, 3.42; N, 9.51; S, 32.67. Found: C, 48.90; H, 3.32; N, 9.38; S, 32.45.

Fraction B: 3-[4-(3-Cyclohexyl-4-cyclohexylimino-1,3-thiazetidine-2-ylidenamino)phenyl]-2-thioxo-1,3-thiazepan-4-one (**6t**).

This compound was obtained as yellow crystals, 0.15 g (2.3%), mp 125°; ir: ν CO 1690, C=N 1650-1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.14-2.14 (m, 20H, 2 cyclohexyl), 2.33-2.41 (m, 2H, H-6), 2.73-2.80 (m, 1H, C-1 cyclohexyl), 3.07-3.11

(m, 2H, H-5), 3.27-3.31 (m, 2H, H-7), 3.86 (m, 1H, H-1 cyclohexylimino), 7.07 (s, 4H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 24.5, 25.1, 25.5, 25.6, 30.2, 34.2 (2x C-2 to C-6 cyclohexyl), 26.7 (C-6 thiazepane), 35.1 (C-5 thiazepane), 35.7 (C-7 thiazepane), 55.2 (C-1 cyclohexylimino), 64.1 (C-1 cyclohexyl), 122.3, 129.5, 138.5, 139.5, 144.1, 147.0 (phenyl carbons, C-2, C-4 thiazetidine), 172.3 (CO), 210.1 (CS); ms: m/z 294 (6), 206 (26), 192 (100), 163 (52).

Anal. Calcd. for $C_{25}H_{32}N_4OS_3$ (500.75): C, 59.97; H, 6.44; N, 11.19; S, 19.21. Found: C, 59.93; H, 6.30; N, 11.24; S, 19.31.

Fraction C: 3,3'-(1,4-Phenylene)-di-(2-thioxo-1,3-thiazepan-4-one) (**6u**).

This compound was obtained as yellow crystals, 0.15 g (0.8%), mp 174°; ν CO 1680 cm^{-1}; ms: m/z 311 (2), 192 (100).

Anal. Calcd. for $C_{16}H_{16}N_2O_2S_4$ (396.57): C, 48.46; H, 4.07; N, 7.06; S, 32.34. Found: C, 48.68; H, 3.99; N, 7.24; S, 32.16.

2-Thioxo-1,3-thiazepan 4-one (**6w**).

This compound was obtained from an experiment to prepare 3-benzoyl-2-thioxo-1,3-thiazepan-4-one (**6v**). Thus 4.0 g (0.039 mole) of **2** were heated with 1.57 g (0.039 mole) of sodium hydroxide in 50 ml of water for 30 minutes at 70°. The water was evaporated and the resulting sodium 4-mercaptobutyrate washed with acetone. The dried salt (4.5 g, 0.032 mole) was stirred with 5.17 g (0.032 mole) of benzoyl isothiocyanate (**1t**) in 150 ml of dichloromethane for 20 hours at room temperature. The precipitate was filtered and dissolved in 100 ml of water. Concentrated hydrochloric acid was added and the crude 4-(*N*-benzoyl)thiocarbamoylthiobutyric acid (**3t**) precipitated, which was crystallized from toluene as a yellow powder, 2.5 g. This product was stirred with 2.0 g (0.01 mole) of *N,N'*-dicyclohexylcarbodiimide and 0.13 g (0.0009 mole) 4-pyrrolidinopyridine in 100 ml of dichloromethane for 6 hours at room temperature. Undissolved compounds were filtered, the dichloromethane phase concentrated to a small volume and this purified by column chromatography with dichloromethane/dioxane 5/1. Yellow needles, (0.20 g, 14%), mp 180°; ir: ν NH 3160, CO 1680 cm^{-1}; ^{1}H nmr (deuteriochloroform/dimethyl-d_6 sulfoxide 1:1): δ 2.27 (quin, 2H, H-6), 2.89 (t, 2H, H-5), 3.19 (t, 2H, H-7), 11.62 (s, 1H, NH); ^{13}C nmr (deuteriochloroform/dimethyl-d_6 sulfoxide 1:1): δ 25.4 (C-6), 34.4 (C-5), 35.0 (C-7), 172.0 (CO), 206.6 (CS); ms: m/z 161 (100, M$^+$), 102 (65).

Anal. Calcd. for $C_5H_7NOS_2$ (161.25): C, 37.24; H, 4.38; N, 8.69; S, 39.77. Found: C, 37.03; H, 4.17; N, 8.52; S, 39.88.

R,S-5-Acetylamino-3-phenyl-2-thioxo-1,3-thiazepan-4-one (**6x**).

R,S-3-Acetylaminotetrahydrothiophene-2-one (**7**) (4.0 g, 0.025 mole) and 3.4 g (0.025 mole) of phenyl isothiocyanate (**1f**) were dissolved in 50 ml of dioxane and heated to 50°. After addition of a solution of 1.0 g (0.025 mole) of sodium hydroxide in 20 ml of water the mixture was stirred for 10 minutes, cooled in ice and acidified with concentrated hydrochloric acid to *p*H 2. The solvent was completely evaporated and the residue treated with acetone. The precipitated sodium chloride was filtered and the filtrate evaporated to a viscous oil which crystallized on cooling to crude *R,S*-2-acetylamino-4-(*N*-phenylthiocarbamoylthio)butyric acid (**3u**), 6.4 g (82%), which was directly used for the cyclization. Thus **3u** (0.02 mole) was suspended with 4.3 g (0.02 mole) of *N,N'*-dicyclohexylcarbodiimide and 2.3 g (0.15 mole) of 4-pyrrolidinopyridine in 100 ml of dichloromethane and stirred for 6 hours at room temperature. Solid components were filtered, the filtrate was reduced to 15 ml and purified by column chromatography with dichloromethane/dioxane 5/1 to provide a yellow powder, 1.47 g (24%), mp 149°; ir: ν NH 3310, 2 CO 1710, 1660 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.04 (s, 3H, CH_3), 2.11-2.19 (m, 1H, H-6_{ax}), 2.69-2.79 (m, 1H, H-6_{eq}), 2.97 (m, 1H, H-7_{ax}), 3.59 (m, 1H, H-7_{eq}), 5.47 (m, 1H, H-5), 6.45 (d, 1H, NH), 7.15-7.19, 7.35-7.46 (2 m, 5H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 23.1 (CH_3), 32.9 (C-7), 33.5 (C-6), 52.0 (C-5), 128.7, 128.8, 129.5, 141.7 (phenyl carbons), 169.6, 171.9 (2 CO), 207.5 (CS); ms: m/z 294 (4, M$^+$), 224 (69), 143 (49), 99 (67), 56 (100).

Anal. Calcd. for $C_{13}H_{14}N_2O_2S_2$ (294.40): C, 53.04; H, 4.79; N, 9.52; S, 21.78. Found: C, 52.98; H, 4.85; N, 9.63; S, 21.60.

R,S-5-Acetylamino-3-(4-methoxyphenyl)-2-thioxo-1,3-thiazepan-4-one (**6y**).

This compound was obtained following the procedure described for **6x** from 4.0 g (0.024 mole) of 4-methoxyphenyl isothiocyanate (**1v**) and **7**. From 6.0 g (73%) of crude *R,S*-2-acetylamino-4-[*N*-(4-methoxyphenyl)thiocarbamoylthiobutyric acid (**3v**) (yellow powder) **6y** was obtained after 20 hours at room temperature, column chromatography and crystallization from methanol as yellow needles, 0.5 g (9%), mp 158-160°; ir: ν NH 3220, 2 CO 1720, 1640 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.04 (s, 3H, C(O)CH_3), 2.09-2.17 (m, 1H, H-6_{ax}), 2.68-2.78 (m, 1H, H-6_{eq}), 2.93-2.98 (m, 1H, H-7_{ax}), 3.58 (m, 1H, H-7_{eq}), 3.82 (s, 3H, OCH_3), 5.45 (m, 1H, H-5), 6.48 (d, 1H, NH), 6.94, 7.06-7.09 (2 m, 4H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 23.1 (C(O)-CH_3), 32.9 (C-7), 33.5 (C-6), 52.0 (C-5), 55.5 (OCH_3), 114.8, 130.0, 134.4, 159.6 (phenyl carbons), 169.6, 172.2 (2 CO), 207.8 (CS); ms: m/z 324 (68, M$^+$), 282 (50), 235 (100).

Anal. Calcd. for $C_{14}H_{16}N_2O_3S_2$ (324.42): C, 51.83; H, 4.97; N, 8.63; S, 19.77. Found: C, 51.70; H, 4.94; N, 8.55; S, 19.67.

R,S-2-Acetylamino-4-[*N*-(4-bromophenyl)thiocarbamolythio]-butyric Acid (**3w**).

4-Bromophenylisothiocyanate (**1w**) (5.6 g, 0.026 mole) was dissolved in 100 ml of dioxane and a solution of 4.1 g (0.026 mole) **7** and 1.0 g (0.026 mole) of sodium hydroxide in 50 ml of water was added. After stirring for 1 hour at 70° the solution was cooled in ice and acidified with concentrated hydrochloric acid to *p*H 2. After evaporation of the solvent acetone was added, the precipitated sodium chloride filtered and the filtrate concentrated to give a white powder, 4.3 g (42%), mp 144° (water); ir: ν 2 NH 3200, 3120, COOH 2960-2300, 2 CO 1700, 1610 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.87 (s, 3H, CH_3), 1.87-1.97 (m, 1H, H-3), 2.06-2.15 (m, 1H, H-3), 3.19-3.34 (m, 2H, H-4), 4.29 (m, 1H, H-2), 7.47-7.63 (m, 4H, phenyl protons), 8.20 (d, 1H, NH-C(O)-CH_3), 11.74 (s, 1H, NHC(S), 12.68 (s, 1H, COOH); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 22.3 (CH_3), 30.5, 31.1 (C-3, C-4), 50.9 (C-2), 118.0-138.7 (phenyl carbons), 169.3 (NHCO), 173.0 (COOH), 198.0 (CS); ms: m/z 215 (100), 213 (96).

Anal. Calcd. for $C_{13}H_{15}BrN_2O_3S_2$ (391.31): C, 39.90; H, 3.86; N, 7.16; S, 16.39. Found: C, 40.00; H, 3.85; N, 7.21; S, 16.19.

R,S-3-Acetyl-4-(*N*-phenylcarbamoyl)-1,3-thiazinane-2-thione (**8a**).

Compound **6x** (1.0 g, 0.0034 mole) was dissolved in 20 ml of dichloromethane and added dropwise onto a chromatography disc of a chromatotron, prepared with a 4 mm layer of silica gel 60

PF_{254} containing calcium sulfate (Merck). Dichloromethane was used for elution at a flow rate of 11 ml/minute under nitrogen. The deeply yellow **6x** only migrated a short distance on the disc and was discolored within 1 hour. The colorless eluate was evaporated to yield a white powder, which was recrystallized from toluene. The rearrangement could also be achieved with the same yield by stirring **6x** in a suspension of silica gel in dichloromethane for 70 hours. Colorless crystals, 0.78 g (78%) were obtained, mp 135°; ir: ν NH 3200, 2 CO 1760, 1670; ^{1}H nmr (deuteriochloroform): δ 2.09-2.28 (m, 2H, H-6), 2.39 (s, 3H, CH_3), 2.96-3.02, 3.17-3.25 (2 m, 2H, H-5), 4.27 (m, 1H, H-4), 7.29-7.32, 7.42-7.52 (2 m, 5H, phenyl protons), 8.34 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 25.0 (C-6), 30.7 (CH_3), 31.9 (C-5), 58.1 (C-4), 128.3, 129.2, 129.3, 132.6 (phenyl carbons), 173.3 (NHCO), 183.8 (CH_3CO), 196.8 (CS); ms: m/z 294 (57, M^+), 252 (52), 205 (100).

Anal. Calcd. for $C_{13}H_{14}N_2O_2S_2$ (294.40): C, 53.04; H, 4.79; N, 9.52; S, 21.78. Found: C, 52.82; H, 4.87; N, 9.48; S, 21.56.

R,S-3-Acetyl-4-(*N*-4-methoxyphenylcarbamoyl)-1,3-thiazinane-2-thione (**8b**).

Compound **6y** (0.14 g, 0.0043 mole) was heated in a small flask to 160° for 20 minutes. After cooling, the clear melt was dissolved in 2 ml of dichloromethane and purified with the chromatotron on a 2 mm silica gel layer with dichloromethane/dioxane 5/1, flow rate 3 ml/minute. A colorless oil remained after evaporation of the solvent, crystallizing after addition of methanol. Colorless crystals were obtained, 0.075 g (54%), mp 138°; ir: ν NH 3280, 2 CO 1720, 1680 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.09-2.27 (m, 2H, H-5), 2.39 (s, 3H, $C(O)CH_3$), 2.95-3.01, 3.17-3.25 (2 m, 2H, H-6), 3.83 (s, 3H, OCH_3), 4.24 (m, 1H, H-4), 6.98-7.01, 7.23 (2 m, 4H, phenyl protons), 8.23 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 24.8 (C-6), 30.7 ($C(O)CH_3$), 31.9 (C-5), 55.5 (OCH_3), 58.0 (C-4), 114.7, 125.2, 129.4, 160.0 (phenyl carbons), 173.5 (C(O)NH), 184.3 ($C(O)CH_3$), 196.8 (CS); ms: m/z 324 (70, M^+), 282 (57), 235 (100).

Anal. Calcd. for $C_{14}H_{16}N_2O_3S_2$ (324.42): C, 51.83; H, 4.97; N, 8.68; S, 19.77. Found: C, 51.79; H, 4.97; N, 8.92; S, 19.56.

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